Cost-effectiveness of mirabegron compared to tolterodine ER 4 mg for overactive bladder in Canada

Sender Herschorn, MD[1]; Jameel Nazir, MSc[2]; Barbara Ramos, PhD[3]; Zalmai Hakimi, PharmD[4]

[1]University of Toronto, Toronto, ON, Canada; [2]Astellas Pharma Europe Ltd, Chertsey, UK; [3]Astellas Pharma Canada, Markham, ON, Canada; [4]Astellas Pharma Europe B.V., Leiden, The Netherlands

Cite as: *Can Urol Assoc J* 2017;11(3-4):123-30. http://dx.doi.org/10.5489/cuaj.4114
Supplementary data available at *www.cuaj.ca*

Abstract

Introduction: This analysis compared the cost-effectiveness of once-daily regimens of mirabegron 50 mg and generic tolterodine ER 4 mg in a hypothetical cohort of previously treated patients with overactive bladder (OAB) in Canada.

Methods: A Markov model was developed to represent different health states according to OAB symptoms (frequency, incontinence), presence/absence of adverse events (AEs; dry mouth, constipation, blurred vision), and treatment status (on-treatment, discontinue treatment, restart previous treatment). The time horizon used was one year, with monthly transitions between health states. The model was populated using data from a phase 3, placebo-controlled trial of mirabegron that included tolterodine as an active comparator (SCORPIO), as well as other published literature and expert opinion. Cost-effectiveness was calculated from Canadian public payer (based on Quebec list prices) and societal perspectives.

Results: The incremental one-year cost per patient for mirabegron over tolterodine was $182 CAD and $157 CAD from the payer and societal perspectives, respectively. The incremental quality-adjusted life year (QALY) gain for mirabegron was 0.0066 when using EQ-5D health-state utilities. Mirabegron was cost-effective compared with tolterodine, from both payer and societal perspectives, and remained cost-effective vs. tolterodine across the majority of sensitivity analyses. The model was based on limited clinical trial evidence supplemented with expert opinion and assumptions; a select number of OAB symptoms, AEs, and direct and indirect medical costs associated with OAB; and a timeframe of only one year.

Conclusions: From the payer and societal perspectives, the health economic model indicates that in Canada, mirabegron is a cost-effective treatment strategy compared with tolterodine, leading to improved health outcomes (QALYs) at an acceptable incremental cost.

Introduction

Overactive bladder (OAB) is a bothersome condition with a relatively high prevalence in the general population. In a survey of over 16 500 subjects aged ≥40 years in six European countries, the prevalence of OAB was 16.6%.[1] In a subsequent survey of over 19 000 subjects aged ≥18 years in Canada and Europe, the prevalence of OAB was 11.8%.[2] Two large surveys have also been conducted in Canada, showing prevalence rates of 12–18%.[3,4]

OAB has a substantial negative impact on patients' health-related quality of life (HRQoL) and mental health.[5] The cardinal symptoms — urgency with or without incontinence, usually associated with frequency, and nocturia[6] — interfere with basic activities of daily living, such as work, travel, sleep, interpersonal activities, sexual function, and physical activities.[7,8] Studies have often focused specifically on the impact of incontinence, but it has been shown that frequency and urgency, which are more prevalent, are as bothersome as urgency incontinence.[1] In terms of mental health, it is estimated that approximately one-third of men and women with lower urinary tract symptoms may have comorbid clinical anxiety and/or depression.[9] In addition, it has been shown that the prevalence of depression in those with OAB is two-fold higher than in the general population (10.5% vs. 4.9%, respectively; $p<0.0001$).[10] At a societal level, OAB is associated with substantial healthcare costs. In Canada, the total excess cost attributed to OAB, excluding nursing care and lost productivity, was approximately $576 000 000 in 2009; this rose to over $640 000 000 when lost productivity was taken into account.[11,12]

Treatment options for OAB can be broadly divided into conservative, pharmacological, and surgical.[13,14] Antimuscarinic agents represent a common drug treatment option for OAB that has been used for over 30 years.[14] Meta-analyses of data from clinical trials comparing antimuscarinics with placebo report statistically significant improvements in favour of active treatment for the proportion of patients returning to continence; mean number of incontinence episodes and micturitions per day; and volume voided per micturition.[15,16] Antimuscarinic side effects are well-characterized and include dry mouth, constipation, and occasionally blurred vision, central nervous system (CNS) effects, and urinary retention.[17-20] Meta-analyses also indicate that antimuscarinics have different efficacy and tolerability profiles, which may help guide treatment choice.[21,22] However, it is also well-known that antimuscarinic agents might not be effective in all patients, and tolerability may be an issue.[23] Bothersome side effects, such as dry mouth, constipation, and blurred

vision may contribute to the low adherence rates reported with pharmaceutical database studies,[24] as well as treatment discontinuation.[23] In one study, which included 377 patients with OAB, the median time for persistence with first-line antimuscarinics was 6.5 months.[23] In addition, an analysis of prescription data from almost 5000 patients with OAB in the U.K. revealed 12-month adherence rates of 26% for oxybutynin extended-release (ER), 28% for tolterodine ER, 26% for trospium, 35% for solifenacin, and 17% for darifenacin.[25] A more recent study of prescription data from over 31 700 patients starting OAB medication in Canada showed that approximately 72% had discontinued treatment in the first year, while approximately 91% discontinued during the four-year followup.[26] Furthermore, of those who discontinued, only 12.5% were switched to an alternative medication.[26] Thus, there is clearly a need for alternative pharmacological treatments for first- and second-line use in OAB.

Mirabegron is a potent, selective β_3-adrenoceptor agonist for the treatment of OAB. It is the first of a new class of compounds with a mechanism that differs from the antimuscarinic agents.[27] In a pre-specified pooled analysis of three 12-week, randomized, placebo-controlled studies (one of which also included a tolterodine ER 4 mg arm), mirabegron (50 mg and 100 mg once-daily) was associated with statistically significant reductions in incontinence episodes, frequency, and urgency compared with placebo.[28] The pooled analysis included an active-controlled study (SCORPIO), designed to compare the efficacy between mirabegron and placebo, as well as tolterodine ER (4 mg once-daily; included as an active control to placebo). The study, showed statistically significant reductions in incontinence episodes and micturition frequency (the co-primary endpoints) for mirabegron vs. placebo, but not for tolterodine ER 4 mg vs. placebo.[29] In addition, mirabegron significantly improved patients' perception of disease and HRQoL vs. placebo.[30] Furthermore, in a post-hoc analysis of the SCORPIO trial, designed to evaluate efficacy in treatment-naïve patients and in those previously treated with an antimuscarinic, mirabegron demonstrated significant reductions in frequency and incontinence in both subgroups, while the response to tolterodine ER 4 mg was similar to placebo.[31] The pooled analysis also demonstrated that the tolerability profile of mirabegron was similar to that of placebo and tolterodine ER 4 mg, with the exception of dry mouth, where the incidence was five times higher with tolterodine ER 4 mg than with mirabegron.[32] In a review of clinical trials of up to 12 months, the most common adverse events (AEs) observed with mirabegron were hypertension, nasopharyngitis, and urinary tract infection.[33] Real-world experience (based on data from >19 000 patients treated for OAB in Canada) indicates that mirabegron provides greater persistence and adherence than antimuscarinic agents.[34]

The objective of the current analysis was to evaluate the cost-effectiveness of mirabegron vs. generic tolterodine ER 4 mg in previously treated patients with OAB from Canadian healthcare and societal perspectives.

Methods

Model overview

A Markov model was developed to compare the cost-effectiveness of licensed doses of mirabegron (50 mg once-daily) and generic tolterodine ER (4 mg once-daily) in a hypothetical cohort of previously treated patients with OAB in Canada. Although 25 mg and 50 mg doses of mirabegron are licenced in Canada, the 50 mg dose only was used in this analysis, as the lower dose was not assessed in the SCORPIO trial. Tolterodine was chosen as the comparator because there is a phase 3, placebo-controlled trial of mirabegron in patients with OAB that includes tolterodine ER 4 mg as an active comparator (SCORPIO; ClinicalTrials.gov identifier, NCT00689104).[29] This decision was subsequently justified by data from the analysis by Wagg et al, which showed that tolterodine ER was the most commonly used second-line OAB medication for patients who were switched in Canada.[26] Generic tolterodine was used in the model based on the recent availability of this formulation in Canada; a cost-effectiveness analysis of mirabegron vs. branded tolterodine was previously conducted.[35]

The population (i.e., previously treated patients) was chosen to reflect current Canadian reimbursement guidelines, which recommend trial of antimuscarinic agents as first-line treatment for OAB.[14] The time horizon was one year, which was deemed sufficient to capture the health-state utilities and costs that accrue from management of OAB, including treatment discontinuation.

The structure of the model was based on that developed by Aballéa et al.[36] It included different health states, determined according to the symptoms of OAB, the presence or absence of AEs, and treatment status. Transitions between different health states were possible at one-month intervals. The symptoms were micturition frequency and incontinence episodes (the co-primary endpoints of the SCORPIO study), each of which had five levels of severity (Table 1). AEs considered in the model were dry mouth, blurred vision, and constipation. In terms of treatment status, patients could remain on current treatment, discontinue treatment, or restart previous treatment. The model was run in parallel for each symptom, generating a distribution of patients by severity level at monthly intervals over one year; average costs and health-state utilities were then calculated based on these distributions.

Quebec was selected for the basis of drug and physician visit costs, as it was the first Canadian province to include mirabegron on its reimbursement formulary. In addition, Quebec has a unique reimbursement system, i.e., it is the only Canadian province that adopts a single-payer system

Table 1. Symptom severity definitions and patient distribution at baseline

Severity level	Micturition		Incontinence	
	Mean no. of micturitions per day	Percentage of patients	Mean no. of incontinence episodes per day	Percentage of patients
1	≤8	6.25	0	29.92
2	>8–10	29.61	>0–1	18.65
3	>10–12	26.23	>1–2	16.29
4	>12–14	18.65	>2–3	10.45
5	>14	19.26	>3	24.69

Symptom severity cutoff points between different levels were roughly based on qui ntiles for each number in pooled data from three pivotal, randomized trials of mirabegron: SCORPIO,[29,31] ARIES,[28] and CAPRICORN.[37] Patient distribution was based on the SCORPIO study.[29,31] Patients could have differing severities for each symptom and were, therefore, described using the format (Mx, Iy); for example, a patient described as (M2, I3) has 8–10 micturitions per day and 1–2 incontinence episodes.

and includes societal perspectives within their health technology assessments.

Cost-effectiveness, presented as incremental cost savings, quality-adjusted life-years (QALYs) gained, and incremental cost-effectiveness ratios (ICER), was calculated from both public payer (Régie de l'assurance maladie du Québec) and societal perspectives.

Treatment pathway

The model compared treatment with mirabegron 50 mg once-daily and tolterodine ER 4 mg once-daily in previously treated patients. At the end of the first month, patients could: transition to a lower (L_{n-1}) or higher (L_{n+1}) symptom severity or stay at the same level (L_n); develop or not develop AEs; and discontinue treatment or stay on current treatment (Supplementary Fig. 1; available at *www.cuaj.ca*). On subsequent months, those who had discontinued treatment could remain without treatment or restart their previous treatment; it was assumed that they would not switch to another drug. Patients who experienced AEs had a higher probability of discontinuing treatment, but could stay on treatment and incur a disutility associated with the AE(s).

Probabilities of improvement or worsening of symptoms may differ in the short- and long-term and the model was designed to account for this. Thus, the probability of improvement was greatest in the first month following treatment initiation, but decreased progressively and was assumed to be constant after three months.

Clinical model inputs

Clinical inputs were based on data from the published literature and/or expert opinion (Table 2). AE data were taken from the subgroup of previously treated patients in the SCORPIO study (49.6% of the total study population)[29,31] and transition probabilities between symptom levels were obtained by applying multinomial logistic regression models to the SCORPIO data. Three transition matrices were produced for each type of symptom: one for the transition between baseline and the first month; one between the first and second months; and one between the second and third months (Supplementary Table 1; available at *www.cuaj.ca*). For patients staying on treatment beyond three months, the transition between the second and third months was reapplied for the cycle from the third to fourth months and subsequent monthly cycles until discontinuation. For patients discontinuing treatment, severity distributions were assumed to be the same as baseline.

Probabilities for discontinuation of mirabegron and tolterodine ER 4 mg were based on the literature[34] and expert opinion. It was assumed that a small percentage of patients (5.6%) would restart treatment following discontinuation; this was based on the observation that 14% of patients stop treatment because their OAB symptoms improve[44] and the assumption that 50% annually would require retreatment for worsening symptoms after discontinuation. In this scenario, it was assumed that patients would always restart treatment with their original therapy, i.e., they would not switch treatments.

Health state utilities, resource use, and costs

Health state utility values were derived from the EQ-5D index scores (based on the U.K. time trade-off tariff[45]) and OAB-q, a five-dimensional health classification system derived from the validated Overactive Bladder Questionnaire (OAB-q),[46] which were collected as part of the SCORPIO study[29,30] using a mapping algorithm. Health state utilities according to symptom severity were derived by applying a linear regression model to the EQ-5D and OAB-5D scores, with adjustment for age, gender, and country.[38]

Resource use inputs included in the model were primary care and specialist consultations, and incontinence pad use. Consultation estimates were based on expert opinion, as these data are not available in the literature. Incontinence pad use was based on interpretation of data from the SCORPIO study[29,30] by the experts consulted for this analysis. Pad use began at severity level 3 (one pad/day), increasing to two pads/day at level 4 and three pads/day at level 5.

All costs were reported in 2015 Canadian dollars ($CAD).[47] Unit costs for primary care and specialist consultations were based on the Quebec schedule, while other unit costs were derived from official list prices for Quebec[39,41,42] and published literature in the Canadian setting.[40-42,48] Unit costs per incontin-

Table 2. Model inputs and sources

Parameter	Probability or value	Source
Monthly probability of discontinuation of OAB therapy		
Without AEs	6.4%	Base case and upper limit: Wagg et al 2012 Lower limit: assumption
With AEs	90%	Expert opinion
Monthly probability of restarting OAB therapy in patients without treatment		
Restarting treatment	5.6%	Assumption
Probability of AEs at 12 weeks		
Dry mouth	Mirabegron=2.8% Tolterodine ER=10.1% No treatment=0%	Khullar et al 2013[29]
Blurred vision	Both pharmacological treatments or no treatment=0%	Khullar et al 2013[29]
Constipation	Mirabegron=1.6% Tolterodine ER=2% No treatment=0%	Khullar et al 2013[29]
Utilities		
From EQ-5D index score	From 0.85 (best health state) to 0.73 (worst)	Khullar et al 2013;[29] Khullar et al 2013;[31] Desroziers et al 2013[38]
From OAB-q index score	From 0.92 (best health state) to 0.74 (worst)	Khullar et al 2013a;[29] Khullar et al 2013b;[31] Desroziers et al 2013[38]
Disutility associated with each AE	0.04	Khullar et al 2013;[29] Khullar et al 2013;[31] Desroziers 2013[38]
Resource use		
GP consultations	1 visit after restarting	Expert opinion
Specialist consultations	1 visit after restarting	Expert opinion
Incontinence pads	0–3/day, depending on incontinence severity	Expert opinion
Costs*		
Mirabegron	$1.46 CAD per 50 mg tablet	INESSS list of medications[39]
Tolterodine ER (generic)	$0.49 CAD per 4 mg tablet	INESSS list of medications[39]
Incontinence pads	$1.55 CAD per pad	Herschorn et al 2010[40] (adjusted to 2015 $CAD)
GP consultation	$40.05 CAD per visit	Manuel Des Médecins Omnipraticiens[41]
Specialist consultation (urology)	$62.50 CAD per visit	Manuel Des Médecins Spécialistes[42]
Loss of productivity		
Proportion of workers among OAB population	35.7%	Statistics Canada 2012[43] (≥55 years); age distribution from Nitti et al 2013[28]
Labour cost per month	$3380 CAD	Statistics Canada 2012[43] (average annual salary); age distribution from Nitti et al 2013[28]

*All prices are in Canadian dollars. CAD: Canadian dollar; EQ-5D: EuroQol five-dimensional health-related quality of life questionnaire; ER: extended release; GP: general/family practitioner; INESSS: Institute national d'excellence en santé et en services sociaux; OAB: overactive bladder; OAB-q: Overactive Bladder Questionnaire.

ence pad were taken from a Canadian pharmacoeconomic analysis investigating OAB.[40] No discounting was conducted, as the time horizon of the analysis was of a one-year duration.

For the payer perspective, only direct costs associated with the management of OAB were included (OAB medications, incontinence pads, and healthcare consultations). For the societal perspective, loss of productivity was also included, based on absenteeism for primary care or specialist visits, as well as the impact of daily number of micturition and incontinence episodes on the percentage work time missed, which was estimated using a linear regression model with adjustment on age, gender, and country. This monthly cost of absenteeism was calculated as the percentage of work time missed (using data from the Work Productivity and Activity Impairment questionnaire in SCORPIO) multiplied by Canadian gross monthly earnings[48] and the proportion of patients with OAB of working age. Based on an estimated mean age of 60 years,[28] it was estimated that approximately 34.7% of patients would still be employed.

Model assumptions

Key assumptions for the conduct of the model are summarized in Supplementary Table 2 (available at *www.cuaj.ca)*.

Sensitivity analyses

Deterministic and probabilistic sensitivity analyses (DSA and PSA) were undertaken to test the robustness of the model to changes in key parameters. The following parameters

were evaluated in the DSA: time horizon; monthly probability of having a dry mouth AE; monthly probability of discontinuation of mirabegron without AE; monthly probability of discontinuation of tolterodine ER 4 mg without AE; monthly probability of restarting treatment; monthly probability of switch after discontinuation; utilities by symptom levels (micturition and incontinence); and distribution across severity groups at baseline (micturition and incontinence). For the PSA, the following distributions were used: Dirichlet for baseline characteristics; lognormal for resource use; beta for compliance parameters and AEs; and normal for utilities.

Results

Base-case scenario (Table 3)

From the public payer perspective, the mean total annual direct cost associated with mirabegron 50 mg treatment was $1043 CAD per patient, compared with $860 CAD for generic tolterodine ER 4 mg, producing an incremental cost of $182 CAD with mirabegron 50 mg compared with tolterodine ER 4 mg. From a societal perspective, the costs of mirabegron 50 mg and generic tolterodine ER 4 mg over one year were $1389 CAD and $1232 CAD, respectively, resulting in an annual incremental cost of $157 CAD with mirabegron 50 mg.

When utilities were measured using EQ-5D, mirabegron 50 mg and tolterodine ER 4 mg were associated with gains of 0.7904 and 0.7838 QALYs, respectively, over one year. This represented an incremental QALY gain of 0.0066 for mirabegron 50 mg. The corresponding incremental QALY gain with mirabegron 50 mg was 0.0109 when utilities were measured using OAB-5D.

The ICER demonstrated that mirabegron 50 mg was cost-effective over generic tolterodine ER 4 mg from both Canadian public payer and societal perspectives, and irrespective of the utilities used (EQ-5D and OAB-5D).

One-way sensitivity analysis

ICERs were robust over a wide range of sensitivity analyses, but were most sensitive to the severity of micturition at baseline. Mirabegron was cost-effective (i.e., ICER below the $50 000 CAD threshold) compared with tolterodine ER 4 mg in 18 out of 22 one-way sensitivity analyses conducted using both high-end and low-end values. A tornado diagram is presented in Fig. 1.

Probabilistic sensitivity analysis (PSA)

Multivariate PSAs (1000 iterations) were carried out to determine the robustness of the results to variations in several parameters at once. Fig. 2 provides the cost-effectiveness acceptability curve of mirabegron compared with tolterodine ER 4 mg from the public payer perspective. In more than 80% of iterations, the ICER was below a willingness-to-pay threshold of $50 000 CAD per QALY vs. tolterodine ER 4 mg from the public payer perspective. Results were similar from a societal perspective.

Discussion

The results of the current analysis demonstrate that mirabegron 50 mg is a cost-effective strategy compared to generic tolterodine ER 4 mg in previously treated patients with OAB, both from public payer and societal perspectives in Canada. Mirabegron is associated with additional annual cost of $182 CAD (payer) and $157 CAD (societal), and QALYs gained of 0.0066 (EQ-5D) and 0.0109 (OAB-5D). The one-way sensitivity analysis showed that mirabegron remained cost effective in 18/22 scenarios and the PSA demonstrated the probability of it being cost-effective compared with tolterodine ER 4 mg was >80% at a willingness-to-pay threshold of $50 000 CAD per QALY. These results reflect differences in the efficacy and tolerability profiles of mirabegron and tolterodine ER 4 mg in the clinical trial on which the analyses are based,[29] as well as improvements in patient-reported outcomes with mirabegron.[30]

Table 3. Total costs, QALYs and cost-effectiveness of mirabegron 50 mg and tolterodine ER 4 mg using EQ-5D and OAB-5D as utility measures

Comparator			EQ-5D utilities			OAB-5D utilities		
	Total cost ($CAD)	Incremental cost ($CAD)	Total QALYs	Incremental QALYs	Incremental cost per QALY ($CAD)	Total QALYs	Incremental QALYs	Incremental cost per QALY ($CAD)
Ministry of Health								
Mirabegron	1042.66	182.39	0.7904	0.0066	27 443	0.8450	0.0109	16 663
Tolterodine ER 4mg	860.27		0.7838			0.8340		
Societal								
Mirabegron	1389.36	156.99	0.7904	0.0066	23 620	0.8450	0.0109	14 342
Tolterodine ER 4mg	1232.37		0.7838			0.8340		

CAD: Canadian dollar; EQ-5D: EuroQol five-dimensional health-related quality of life questionnaire; ER: extended release; QALY: quality-adjusted life-year.

Our data are consistent with those from a recent cost-effectiveness analysis of mirabegron vs. tolterodine ER 4 mg from a U.K. National Health Service perspective.[36] Using a model similar to that in the current analysis, the ICER over a five-year horizon for mirabegron was £4386 per QALY gained, well below the U.K. willingness-to-pay threshold of £20 000. The ICERs in the current analysis were slightly higher than those reported for the U.K.; this likely reflects the greater relative difference in acquisition costs of generic vs. branded tolterodine ER 4 mg in Canada compared with the U.K. Furthermore, mirabegron was dominant (i.e., both less costly and more effective) vs. tolterodine in the Canadian cost-effectiveness analysis (reported here) when the cost of branded tolterodine ER 4 mg was used in the model.[35]

The current analysis focused on previously treated patients with OAB, as current guidelines in Canada recommend first-line use of antimuscarinics.[14,49] The Canadian Agency for Drugs and Technologies in Health also recommended, based on their clinical and economic review, that mirabegron is listed as second-line treatment option for patients who have failed an adequate trial of oxybutynin due to lack of efficacy or unacceptable side effects.[50] However, mirabegron is also indicated for first-line use and antimuscarinic agents may not be suitable for all patients because of AEs or contraindications. The extent to which the results of the current analysis can be extrapolated to treatment-naïve patients is not clear. However, it is notable that in a post-hoc analysis of data from the SCORPIO study, the effect of mirabegron in treatment-naïve patients was greater than that observed with tolterodine ER 4 mg.[31]

A number of other antimuscarinic agents are available in Canada for treating OAB (oxybutynin, solifenacin, trospium, and fesoterodine). The cost-effectiveness of mirabegron vs. these agents in Canada is not known. However, a recent cost-effectiveness analysis of mirabegron vs. a range of antimuscarinic agents (conducted using a network meta-analysis) demonstrated that mirabegron was cost-effective in the U.K., with ICERs ranging from £367 (vs. solifenacin 10 mg) to £15 593 (vs. oxybutynin immediate release 10 mg) per QALY gained.[51]

One of the main strengths of the current model was the use of data from a phase 3 trial of mirabegron and tolterodine ER 4 mg, thus improving the reliability of the results. Other strengths include: data analysis from both payer and societal perspectives; use of both generic and disease-specific utilities; and inclusion of the indirect costs of reduced work productivity in the societal perspective analysis. Indeed, as well as affecting patients' HRQoL, OAB also has a substantial impact on work productivity. It has been estimated that compared with age-matched controls, employees with OAB lose 2.2 additional days per year for medical reasons and 3.4 additional days per year as a result of disability.[52] Indeed, the indirect cost of lost work days associated with OAB was 73% ($391) higher per year compared with controls, exceeding other chronic conditions, such as stress urinary incontinence and bipolar disorder.[52] Furthermore, it has been shown that increasing adherence to OAB medication could potentially provide economic benefits to employers, as employees with greater adherence had significantly lower medical, sick leave, and short-term disability costs.[53]

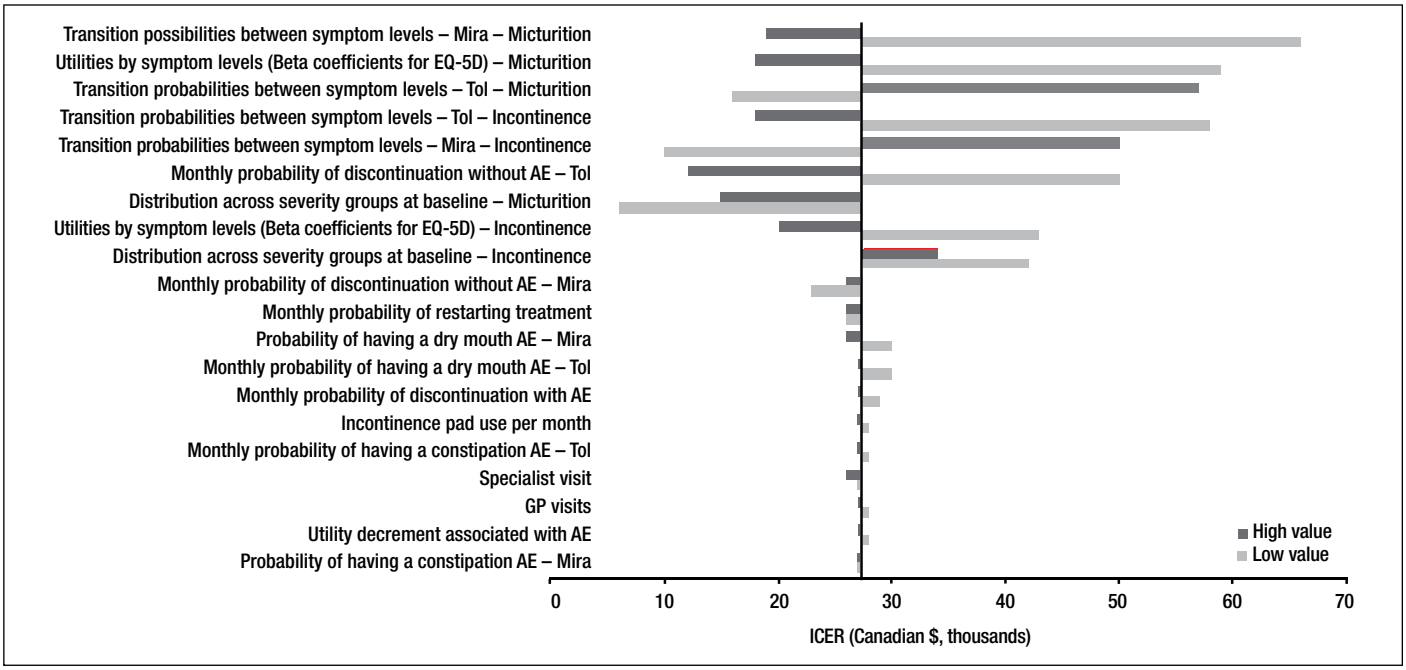

Fig. 1. Tornado diagram showing one-way sensitivity analysis from the societal payer perspective. AE: adverse events; EQ-5D: EuroQol five-dimensional health-related quality of life questionnaire; GP: general/family practitioner; Mira: mirabegron; Tol: tolterodine.

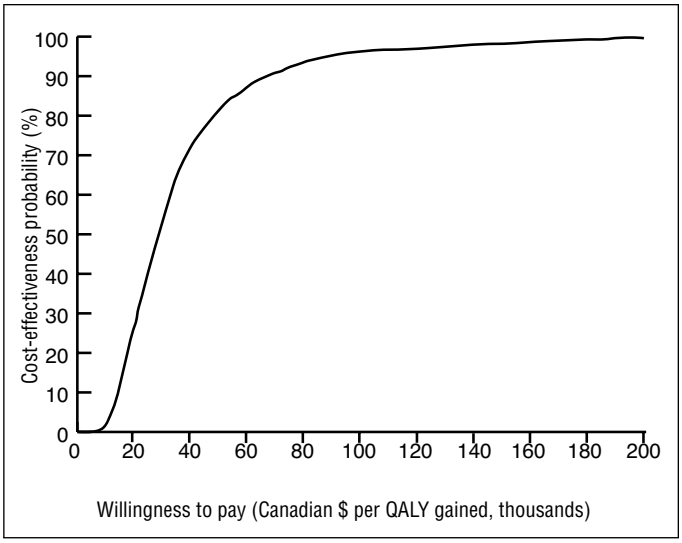

Fig. 2. Cost-effectiveness acceptability curve for mirabegron 50 mg vs. tolterodine ER 4 mg from the public payer perspective. ER: extended release; QALY: quality-adjusted life-year.

Mirabegron may provide a tolerability benefit compared with antimuscarinics, as it has placebo-like rates of bothersome anticholinergic-associated side effects, such as dry mouth a nd blurred vision. A 12-month study comparing mirabegron and tolterodine ER 4 mg in OAB reported that dry mouth, which contributed to the improved cost-effectiveness of mirabegron in the current analysis, was more frequently observed with tolterodine ER 4 mg.[54,55] Anticholinergic side effects are also likely to affect medication persistence and adherence, which are reported to decrease one month after treatment initiation with antimuscarinics.[24,56] Medication persistence and adherence are also reported to be important drivers of cost-effectiveness[57] and early real-world evidence in Canada suggests that median treatment persistence is greater with mirabegron (299 days or 196 days) compared to different antimuscarinics (96–242 days or 70–100 days) in previously treated and treatment-naïve patients, respectively.[34]

As well as the AEs included in the model (i.e., dry mouth, constipation, and blurred vision), antimuscarinic agents are associated with a number of other well-established bothersome anticholinergic AEs, including an increased risk of cognitive dysfunction.[58,59] Cognitive dysfunction was not included in the model, as there are no data on the comparative effects of mirabegron and tolterodine ER 4 mg.

Limitations to the model include the following: health states in the model were dependent upon micturition frequency and incontinence, the primary endpoints in the SCORPIO study, but not urgency. Nevertheless, mirabegron 50 mg significantly reduced the number of Grade 3 and 4 urgency episodes per day vs. placebo in SCORPIO and the mean change (-2.25) was similar to tolterodine ER 4 mg (-2.07).[29] Another assumption of the model was that OAB symptoms improve during the first three months of treatment and are stable thereafter; this is supported by data from the 12-month study comparing mirabegron and tolterodine ER 4 mg.[54,55] Another assumption was that patients who discontinued treatment would not switch to another drug. Although information on this aspect of patient management is limited, there are data indicating that the majority of patients discontinue drug therapy after their first treatment.[26]

Conclusion

The results of the current analysis indicate that in Canada, mirabegron 50 mg once-daily is a cost-effective treatment strategy compared to generic tolterodine ER 4 mg once-daily in previously treated patients with OAB, leading to improved QALYs.

Competing interests: Dr. Herschorn has received grants and personal fees from Allergan, Astellas, and Pfizer, and personal fees from Merus. Mr. Nazir, Ms. Ramos, and Dr. Hakimi are all full-time employees of Astellas Pharma. This study was sponsored by Astellas Pharma Canada.

Acknowledgements: Presented in part at the ISPOR 17th Annual European Congress, November 8–12, 2014, Amsterdam, The Netherlands. Medical writing assistance was provided by Nicky French and Tyrone Daniel of Bioscript Medical.

This paper has been peer-reviewed.

References

1. Milsom I, Abrams P, Cardozo L, et al. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. *BJU Int* 2001;87:760-6. https://doi.org/10.1046/j.1464-410x.2001.02228.x
2. Irwin DE, Milsom I, Hunskaar S, et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: Results of the EPIC study. *Eur Urol* 2006;50:1306-14. https://doi.org/10.1016/j.eururo.2006.09.019
3. Corcos J, Schick E. Prevalence of overactive bladder and incontinence in Canada. *Can J Urol* 2004;11:2278-84.
4. Herschorn S, Gajewski J, Schulz J, et al. A population-based study of urinary symptoms and incontinence: The Canadian Urinary Bladder Survey. *BJU Int* 2008;101:52-8. https://doi.org/10.1111/j.1464-410X.2007.07198.x
5. Stewart WF, Van Rooyen JB, Cundiff GW, et al. Prevalence and burden of overactive bladder in the United States. *World J Urol* 2003;20:327-36. http://dx.doi.org/10.1007/s00345-002-0301-4
6. Abrams P, Cardozo L, Fall M, et al. Standardization Sub-committee of the International Continence Society. The standardization of terminology of lower urinary tract function: Report from the Standardization Sub-committee of the International Continence Society. *Neurourol Urodyn* 2002;21:167-78. https://doi.org/10.1002/nau.10052
7. Abrams P, Kelleher CJ, Kerr LA, et al. Overactive bladder significantly affects quality of life. *Am J Manag Care* 2000;6:S580-90.
8. Nitti VW. Clinical impact of overactive bladder. *Rev Urol* 2002;4:S2-6.
9. Coyne KS, Wein AJ, Tubaro A, et al. The burden of lower urinary tract symptoms: Evaluating the effect of LUTS on health-related quality of life, anxiety, and depression: EpiLUTS. *BJU Int* 2009;103:4-11. https://doi.org/10.1111/j.1464-410X.2009.08371.x
10. Darkow T, Fontes CL, Williamson TE. Costs associated with the management of overactive bladder and related comorbidities. *Pharmacotherapy* 2005;25:511-9. https://doi.org/10.1592/phco.25.4.511.61033
11. Irwin DE, Mungapen L, Milsom I, et al. The economic impact of overactive bladder syndrome in six Western countries. *BJU Int* 2009;103:202-9. http://dx.doi.org/10.1111/j.1464-410X.2008.08036.x
12. Canadian Continence Foundation. Equity in access to pharmacological treatments for overactive bladder and urgency urinary incontinence in Canada; 2015. Available at: http://www.canadiancontinence.ca/pdfs/en-white-paper-equity-in-access-to-pharmaceutical-treatments-for-incontinence-in-canada.pdf. Accessed July 2016.

13. Arnold J, McLeod N, Thani-Gasalam R, et al. Overactive bladder syndrome—management and treatment options. *Aust Fam Physician* 2012;41:878-83.
14. Geoffrion R. Treatments for overactive bladder: Focus on pharmacotherapy. *J Obstet Gynaecol Can* 2012;34:1092-101. https://doi.org/10.1016/S1701-2163(16)35440-8
15. Nabi G, Cody JD, Ellis G, et al. Anticholinergic drugs vs. placebo for overactive bladder syndrome in adults. *Cochrane Database Syst Rev* 2006;4:CD003781. https://doi.org/10.1002/14651858.CD003781.pub2
16. Chapple CR, Khullar V, Gabriel Z, et al. The effects of antimuscarinic treatments in overactive bladder: An update of a systematic review and meta-analysis. *Eur Urol* 2008;54:543-62. https://doi.org/10.1016/j.eururo.2008.06.047
17. Staskin DR, MacDiarmid SA. Using anticholinergics to treat overactive bladder: The issue of treatment tolerability. *Am J Med* 2006;119:9-15. https://doi.org/10.1016/j.amjmed.2005.12.011
18. Chancellor M, Boone T. Anticholinergics for overactive bladder therapy: Central nervous system effects. *CNS Neurosci Ther* 2012;18:167-74. https://doi.org/10.1111/j.1755-5949.2011.00248.x
19. Oefelein MG. Safety and tolerability profiles of anticholinergic agents used for the treatment of overactive bladder. *Drug Saf* 2011;34: 733-54. https://doi.org/10.2165/11592790-000000000-00000
20. Hollingsworth JM, Wilt TJ. Lower urinary tract symptoms in men. *BMJ* 2014;349:g4474. https://doi.org/10.1136/bmj.g4474
21. Buser N, Ivic S, Kessler TM, et al. Efficacy and adverse events of antimuscarinics for treating overactive bladder: Network meta-analyses. *Eur Urol* 2012;62:1040-60. https://doi.org/10.1016/j.eururo.2012.08.060
22. Madhuvrata P, Cody JD, Ellis G, et al. Which anticholinergic drug for overactive bladder symptoms in adults. *Cochrane Database Syst Rev* 2012;1:CD005429. https://doi.org/10.1002/14651858.CD005429.pub2
23. Krhut J, Gärtner M, Petzel M, et al. Persistence with first-line anticholinergic medication in treatment-naive overactive bladder patients. *Scand J Urol* 2014;48:79-83. https://doi.org/10.3109/21681805.2013.814707
24. Veenboer PW, Bosch JL. Long-term adherence to antimuscarinic therapy in everyday practice: A systematic review. *J Urol* 2014;191:1003-8. https://doi.org/10.1016/j.juro.2013.10.046
25. Wagg A, Compion G, Fahey A, et al. Persistence with prescribed antimuscarinic therapy for overactive bladder: A U.K. experience. *BJU Int* 2012;110: 1767-74. https://doi.org/10.1111/j.1464-410X.2012.11023.x
26. Wagg A, Diles D, Berner T. Treatment patterns for patients on overactive bladder therapy: A retrospective statistical analysis using Canadian claims data. *J Health Econ Outcomes Res* 2015;3:43-55.
27. Sacco E, Bientinesi R, Tienforti D, et al. Discovery history and clinical development of mirabegron for the treatment of overactive bladder and urinary incontinence. *Expert Opin Drug Discov* 2014;9:433-48. https://doi.org/10.1517/17460441.2014.892923
28. Nitti VW, Khullar V, van Kerrebroeck P, et al. Mirabegron for the treatment of overactive bladder: A prespecified pooled efficacy analysis and pooled safety analysis of three randomized, double-blind, placebo-controlled, phase 3 studies. *Int J Clin Pract* 2013;67:619-32. https://doi.org/10.1111/ijcp.12194
29. Khullar V, Amarenco G, Angulo JC, et al. Efficacy and tolerability of mirabegron, a β(3) adrenoceptor agonist, in patients with overactive bladder: Results from a randomized, European-Australian, phase 3 trial. *Eur Urol* 2013;63:283-95. https://doi.org/10.1016/j.eururo.2012.10.016
30. Khullar V, Amarenco G, Angulo JC, et al. Patient-reported outcomes with the β3-adrenoceptor agonist mirabegron in a phase 3 trial in patients with overactive bladder. *Neurourol Urodyn* 2016;35:987-94. https://doi.org/10.1002/nau.22844
31. Khullar V, Cambronero J, Angulo JC, et al. Efficacy of mirabegron in patients with and without prior antimuscarinic therapy for overactive bladder: A post-hoc analysis of a randomized, European-Australian, phase 3 trial. *BMC Urol* 2013;13:45. https://doi.org/10.1186/1471-2490-13-45
32. Nitti VW, Chapple CR, Walters C, et al. Safety and tolerability of the β3-adrenoceptor agonist mirabegron, for the treatment of overactive bladder: Results of a prospective pooled analysis of three 12-week, randomized, phase 3 trials and of a one-year, randomized, phase 3 trial. *Int J Clin Pract* 2014;68:972-85. https://doi.org/10.1111/ijcp.12433
33. Chapple CR, Cardozo L, Nitti VW, et al. Mirabegron in overactive bladder: A review of efficacy, safety, and tolerability. *Neurourol Urodyn* 2014;33:17-30. https://doi.org/10.1002/nau.22505
34. Wagg A, Franks B, Ramos B, et al. Persistence and adherence with the new beta-3 receptor agonist, mirabegron vs. antimuscarinics in overactive bladder: Early experience in Canada. *Can Urol Assoc J* 2015;9:343-50. https://doi.org/10.5489/cuaj.3098
35. Herschorn S, Vicente C, Nazir J, et al. Cost-effectiveness of mirabegron 50 mg compared to tolterodine ER 4mg in the treatment of patients with overactive bladder in Canada. *Value Health* 2014;17:A469. https://doi.org/10.1016/j.jval.2014.08.1325
36. Aballéa S, Maman K, Thokagevistk K, et al. Cost-effectiveness of mirabegron compared with tolterodine extended release for the treatment of adults with overactive bladder in the U.K. *Clin Drug Investig* 2015;35:83-93. https://doi.org/10.1007/s40261-014-0240-z
37. Herschorn S, Barkin J, Castro-Diaz D, et al. A phase 3, randomized, double-blind, parallel-group, placebo-controlled, multicentre study to assess the efficacy and safety of the β_3 adrenoceptor agonist, mirabegron, in patients with symptoms of overactive bladder. *Urology* 2013;82:313-20. https://doi.org/10.1016/j.urology.2013.02.077
38. Desroziers K, Aballéa S, Maman K, et al. Estimating EQ-5D and OAB-5D health state utilities for patients with overactive bladder. *Health Qual Life Outcomes* 2013;11:200. https://doi.org/10.1186/1477-7525-11-200
39. List of Medications, effective March 15, 2016. Available at: http://www.ramq.gouv.qc.ca/SiteCollectionDocuments/liste_med/liste_med_2016_07_15_en.pdf . Accessed July 2016.
40. Herschorn S, Vicente C, Piwko C. Canadian cost-effectiveness analysis of solifenacin compared to oxybutynin immediate-release in patients with overactive bladder. *J Med Econ* 2010;13:508-15. https://doi.org/10.3111/13696998.2010.509244
41. Manuel Des Médecins Omnipraticiens 2013. Available at: http://www.ramq.gouv.qc.ca/SiteCollectionDocuments/professionnels/manuels/100-facturation-omnipraticiens/000_complet_acte_omni.pdf . Accessed July 2016
42. Manuel Des Médecins Spécialistes 2013. Available at: http://www.ramq.gouv.qc.ca/SiteCollectionDocuments/professionnels/manuels/150-facturation-specialistes/000_complet_acte_spec.pdf . Accessed July 2016.
43. Statistics Canada 2012. Available at: http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/labor20a-eng.htm. Accessed July 2016.
44. Benner JS, Nichol MB, Rovner ES, et al. Patient-reported reasons for discontinuing overactive bladder medication. *BJU Int* 2010;105:1276-82. https://doi.org/10.1111/j.1464-410X.2009.09036.x
45. Dolan P. Modeling valuations for EuroQol health states. *Med Care* 1997;35:1095-108. https://doi.org/10.1097/00005650-199711000-00002
46. Yang Y BJ, Tsuchiya A, Coyne K. Estimating a preference-based single index from the Overactive Bladder Questionnaire. *Value Health* 2009;12:159-66. https://doi.org/10.1111/j.1524-4733.2008.00413.x
47. Bank of Canada. Rates & Statistics. Consumer Price Index, 2000 to Present. Available at: http://www.bankofcanada.ca/rates/price-indexes/cpi/. Accessed July 2016.
48. Institut de la statistique Québec. Average income, total income, individuals (16 and older), Québec, 1996–2010. Available at: http://www.stat.gouv.qc.ca/statistiques/conditions-vie-societe/portrait-social2010.pdf. Accessed July 2016.
49. Gormley EA, Lightner DJ, Faraday M, et al. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline amendment. *J Urol* 2015; pii:S0022-5347(15)00177-9. https://doi.org/10.1016/j.juro.2015.01.087
50. Canadian Agency for Drugs and Technologies in Health. Mirabegron, July 2015. Available at: https://www.cadth.ca/sites/default/files/cdr/clinical/SR0363_Myrbetriq_CL_Report_e.pdf. Accessed July 2016.
51. Nazir J, Maman K, Neine ME, et al. Cost-effectiveness of mirabegron compared with antimuscarinic agents for the treatment of adults with overactive bladder in the U.K. *Value Health* 2015;18:783-90. https://doi.org/10.1016/j.jval.2015.05.011
52. Wu EQ, Birnbaum H, Marynchenko M, et al. Employees with overactive bladder: Work loss burden. *J Occup Environ Med* 2005;47:439-46. https://doi.org/10.1097/01.jom.0000161744.21780.c1
53. Kleinman NL, Odell K, Chen C-I, et al. Persistence and adherence with urinary antispasmodic medications among employees and the impact of adherence on costs and absenteeism. *J Manag Care Spec Pharm* 2014;20:1047-56. https://doi.org/10.18553/jmcp.2014.20.10.1047
54. Sacco E, Bientinesi R. Mirabegron: A review of recent data and its prospects in the management of overactive bladder. *Ther Adv Urol* 2012;4:315-24. https://doi.org/10.1177/1756287212457114
55. Chapple CR, Kaplan SA, Mitcheson D, et al. Randomized, double-blind, active-controlled, phase 3 study to assess 12-month safety and efficacy of mirabegron, a β(3)-adrenoceptor agonist, in overactive bladder. *Eur Urol* 2013; 63:296-305. https://doi.org/10.1016/j.eururo.2012.10.048
56. Sexton CC, Notte SM, Maroulis C, et al. Persistence and adherence in the treatment of overactive bladder syndrome with anticholinergic therapy: A systematic review of the literature. *Int J Clin Pract* 2011;65:567-85. https://doi.org/10.1111/j.1742-1241.2010.02626.x
57. Hiligsmann M, Boonen A, Rabenda V, et al. The importance of integrating medication adherence into pharmacoeconomic analyses: The example of osteoporosis. *Expert Rev Pharmacoecon Outcomes Res* 2012;12:159-66. https://doi.org/10.1586/erp.12.8
58. Wagg A, Verdejo C, Molander U. Review of cognitive impairment with antimuscarinic agents in elderly patients with overactive bladder. *Int J Clin Pract* 2010;64:1279-86. https://doi.org/10.1111/j.1742-1241.2010.02449.x
59. Ruxton K, Woodman RJ, Mangoni AA. Drugs with anticholinergic effects and cognitive impairment, falls and all-cause mortality in older adults: A systematic review and meta-analysis. *Br J Clin Pharmacol* 2015;80:209-20. https://doi.org/10.1111/bcp.12617

Correspondence: Dr. Sender Herschorn, University of Toronto, Toronto, ON, Canada; s.herschorn@utoronto.ca