Common Drug Review
Pharmacoeconomic Review Report

July 2015

Drug	mirabegron extended-release tablets (Myrbetriq)
Indication	Treatment of overactive bladder (OAB) with symptoms of urgency, urgency incontinence and urinary frequency
Listing request	As a second-line treatment option, in a similar manner to other currently listed second-line drugs for OAB, i.e., for patients who have failed an adequate trial of oxybutynin due to lack of efficacy or unacceptable side effects
Manufacturer	Astellas

Mirabegron (Myrbetriq) Common Drug Review Pharmacoeconomic Report was prepared using PharmaStat data from IMS Health Canada Inc. The analyses, conclusions, opinions and statements expressed are those of the Canadian Agency for Drugs and Technologies in Health and not those of IMS Health Canada Inc.

This report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). Through the CADTH Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update — Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

CDR	CADTH Common Drug Review
CMA	cost-minimization analysis
CUA	cost-utility analysis
ER	extended release
IR	immediate release
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
OAB	overactive bladder
ODB	Ontario Drug Benefit

EXECUTIVE SUMMARY OF THE PHARMACOECONOMIC SUBMISSION

Mirabegron is a selective beta 3-adrenoceptor agonist for the treatment of overactive bladder (OAB) with symptoms of urgency, urgency incontinence, and urinary frequency.[1] Mirabegron is available as 25 mg and 50 mg extended-release (ER) tablets, taken once daily, at a confidential submitted price of [redacted] per tablet, or [redacted] per day ([redacted] per year).

Mirabegron was previously submitted to the CADTH Common Drug Review (CDR) for this indication in 2012, but the submission was withdrawn by the manufacturer. The current submission includes new clinical information and a lower confidential price ([redacted] per tablet versus [redacted] in the previous submission).

The manufacturer submitted a cost-minimization analysis comparing mirabegron with oxybutynin immediate release (IR), darifenacin ER, fesoterodine ER, solifenacin, tolterodine ER, and trospium chloride IR for a one-year time horizon. The choice of a cost-minimization analysis was based on results from systematic reviews and meta-analyses suggesting that, aside from oxybutynin IR, most anticholinergics have similar efficacy, safety, and tolerability profiles. Although not referenced in the manufacturer's pharmacoeconomic report, the submission's executive summary also refers to a published manufacturer-funded network meta-analysis (NMA) by Maman et al.,[2] as well as a reanalysis of the manufacturer's NMA performed by the National Institute for Health and Care Excellence (NICE) Evidence Review Group.[3]

In the general OAB population (treatment-naive and treatment-experienced patients) direct evidence suggests that mirabegron and tolterodine are relatively similar with regard to reductions in urgency, incontinence, or micturition. Results of the manufacturer's NMA as well as NICE reanalysis suggest similar efficacy between mirabegron and anticholinergics (darifenacin, fesoterodine ER, oxybutynin IR and ER, tolterodine IR and ER, and trospium chloride IR and ER) with regard to micturition and incontinence, with the exception of solifenacin, which was found to be significantly more effective than mirabegron 50 mg at reducing incontinence in the NICE reanalysis. Both direct and indirect evidence suggest that mirabegron is associated with a lower risk of dry mouth compared with anticholinergics. There is limited evidence on the comparative efficacy and safety of mirabegron in the subgroup of patients who have failed an adequate treatment with anticholinergics. The BEYOND trial, which enrolled OAB patients who were non-responders to anticholinergics, failed to demonstrate that mirabegron was non-inferior to solifenacin.[4]

At recommended doses, mirabegron is more expensive than generic oxybutynin IR ($0.20 to $0.30 per day), but less expensive than anticholinergics currently funded by most drug plans as second-line options for the treatment of OAB (cost ranging from $1.50 to $2.28 per day). Mirabegron could save between [redacted] and [redacted] per patient per year, if used as monotherapy, compared with second-line anticholinergic drugs. If mirabegron were used in combination with second-line anticholinergics reimbursed under public drug plans, this would substantially increase treatment costs.

REVIEW OF THE PHARMACOECONOMIC SUBMISSION

1. INTRODUCTION

Mirabegron (Myrbetriq) is a selective beta 3-adrenoceptor agonist indicated for the treatment of overactive bladder (OAB) with symptoms of urgency, urgency incontinence, and urinary frequency.[1] Mirabegron is available as 25 mg and 50 mg extended-release (ER) tablets taken once daily at a confidential price of [redacted] per tablet, or [redacted] per day ([redacted] per year).

1.1 Cost Comparison Table

Clinical experts have deemed the comparator treatments presented in Table 1 to be appropriate. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified.

TABLE 1: COST COMPARISON TABLE FOR DRUGS USED FOR THE MANAGEMENT OF OVERACTIVE BLADDER

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Annual Drug Cost ($)
Mirabegron (Myrbetriq)	**25 mg 50 mg**	**ER tab**	[redacted][a]	**25 mg to 50 mg once daily**	[redacted]	[redacted]
Fesoterodine fumarate (Toviaz)	4 mg 8 mg	ER tab	1.5000	4 mg to 8 mg daily	1.50	548
Darifenacin (Enablex)	7.5 mg 15 mg	ER tab	1.5800	initial dose 7.5 mg daily; final dose 7.5 mg to 15 mg daily	1.58	577
OnabotulinumtoxinA (Botox)[b]	50 units 100 units 200 units	vial	178.5000 357.0000 714.0000	100 units/dose every 3 months every 24 weeks	3.91 2.12	1,448 793
Oxybutynin chloride (generics)	5 mg	tab	0.0986	5 mg 2 to 3 times daily	0.20 to 0.30	72 to 108
Oxybutynin (Oxytrol)	36 mg	TD patch	7.3188[c]	one patch twice weekly	2.09	763
Oxybutynin chloride (Gelnique)	100 mg/g	topical gel	3.0380[c]	one 1 g sachet daily	3.04	1,109
Oxybutynin chloride ER (Ditropan XL)	5 mg 10 mg	ER tab	2.2780[d]	5 mg to 30 mg daily	2.28 to 6.83	902 to 2,707
Oxybutynin chloride (Uromax)	10 mg 15 mg	CR tab	1.4816[c] 1.5961[c]	10 mg to 20 mg daily	1.48 to 2.96	571 to 1,082
Solifenacin succinate (Vesicare)	5 mg 10 mg	tab	1.6892	5 mg to 10 mg daily	1.64	599
Tolterodine (Detrol LA)	2 mg 4 mg	ER cap	1.9466	4 mg daily	1.95	711

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Annual Drug Cost ($)
Tolterodine (Detrol)	1 mg 2 mg	tab	0.9733 0.9733	2 mg twice daily	1.95	711
Trospium chloride (Trosec)	20 mg	tab	0.7905	20 mg twice daily	1.58	577

CR = controlled release; ER = extended-release; LA = long acting; tab = tablet; TD = transdermal; XL = extended-release.
Note: All prices are from the Ontario Drug Benefit Formulary (accessed July 2014) unless otherwise indicated and do not include dispensing fees.
[a] Manufacturer's confidential submitted price.
[b] At the time the review was conducted, Botox was under review by the CADTH Common Drug Review for treatment of overactive bladder with symptoms of urinary incontinence, urgency, and frequency, in adult patients who have an inadequate response to or are intolerant of anticholinergic medication.
[c] McKesson Canada wholesale price (June 2014).
[d] Nova Scotia Formulary (October 2014).

2. SUMMARY OF PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-minimization analysis (CMA) comparing mirabegron 50 mg daily to anticholinergic treatments in a general population of OAB patients (including both treatment-naive and treatment-experienced patients) over a one-year time horizon from the perspective of a public payer (Table 2).[5] The manufacturer submitted a CMA based on the assumption of similar clinical efficacy (reduction in frequency of micturitions and incontinence episodes), safety, and tolerability with oxybutynin immediate release [IR], darifenacin ER, fesoterodine ER, solifenacin, tolterodine ER, and trospium chloride IR and ER. Oxybutynin is reimbursed as first-line therapy for OAB by all public drug plans in Canada, while other anticholinergic drugs are currently reimbursed by most public drug plans as second-line therapy. Only drug costs were considered, with prices obtained from the Ontario Drug Benefit (ODB) Formulary when possible and, alternatively, from IMS Health Canada Ltd. data. The ODB markup of 8% was assumed, with a dispensing fee of $8.40 assumed every 30 days.

The assumptions of similar efficacy, safety, and tolerability were based on the results of published systematic reviews and meta-analyses identified by the manufacturer.[6-8] Although not referenced in the manufacturer's pharmacoeconomic report, the submission's cover letter and executive summary also refer to a published manufacturer-funded network meta-analysis (NMA) by Maman et al.,[2] as well as a reanalysis of the manufacturer's NMA done by the National Institute for Health and Care Excellence (NICE) Evidence Review Group.[3] The NMA included studies in a general population of OAB patients (treatment-naive and treatment-experienced patients) treated with mirabegron 50 mg, darifenacin ER 7.5 mg and 10 mg, fesoterodine ER 4 mg and 8 mg, oxybutynin IR (10 and 15 mg) and ER (5 mg, 10 mg, and 15 mg), solifenacin 5 mg and 10 mg, tolterodine IR 4 mg and ER 4 mg, or trospium chloride 40 mg and 60 mg. The NICE reanalysis (which excluded some of the studies from the original NMA because of poor methodological quality, heterogeneous population, or outcomes reported at a time point other than 12 weeks) identified no significant difference between mirabegron 50 mg and other active treatments for the outcome of micturition. Solifenacin (5 mg and 10 mg) was found to be significantly more effective than mirabegron 50 mg at reducing incontinence. Mirabegron was associated with a lower risk of developing constipation compared with fesoterodine 8 mg, solifenacin (5 mg and 10 mg), and trospium chloride 60 mg, and was associated with a lower risk of developing dry mouth compared with the anticholinergic drugs evaluated.[3]

TABLE 2: MANUFACTURER'S BASE-CASE RESULTS, INCREMENTAL COSTS OF ANTICHOLINERGIC AGENTS REIMBURSED FOR OAB VERSUS MIRABEGRON

Comparator	Daily Dose	Daily Cost ($)	Annual Cost ($)	Annual Cost With Markup and Fees ($)	Incremental Cost (Savings) Relative to Mirabegron ($)
Oxybutynin IR	10 mg	0.1972	72	180	[redacted]
Mirabegron	**50 mg**	[redacted]	[redacted]	[redacted]	**Reference**
Darifenacin ER	7.5 mg	1.4600	533	678	[redacted]
	15 mg	1.4600	533	678	[redacted]
Fesoterodine fumarate ER	4 mg	1.5000	548	694	[redacted]
Solifenacin	5 mg	1.5000	548	694	[redacted]
	10 mg	1.5000	548	694	[redacted]
Trospium chloride	40 mg	1.5500	566	713	[redacted]
Tolterodine L-tartrate ER	4 mg	1.9465	710	870	[redacted]
Trospium chloride	60 mg[a]	2.3250	849	1,019	[redacted]

ER = extended-release; IR = immediate release; OAB = overactive bladder.
[a] The recommended daily dose of trospium chloride is 40 mg. The manufacturer used the cost of three 20 mg IR tablets in its analysis for the 60 mg dose. However, the 60 mg daily dose referenced in the manufacturer's NMA is based on the ER formulation of trospium chloride, which does not appear to be available in Canada and is therefore not included in the CADTH Common Drug Review's reanalyses.
Source: Manufacturer's pharmacoeconomic submission,[5] Tables 12, 19, and 20. Markup was assumed to be 8% and a dispensing fee of $8.40 was applied 12.17 times annually.

The manufacturer also submitted a cost-utility analysis (CUA) in the sub-population of treatment-experienced patients with OAB. As CADTH Common Drug Review (CDR) reviewers determined that a CMA was the most appropriate analysis, the CUA was not critiqued but was summarized in Appendix 2.

3. KEY LIMITATIONS

3.1 Assumption of Similar Efficacy and Safety

As stated in the clinical report, solifenacin, and tolterodine were used as active comparators in several mirabegron trials,[9-13] but only the BEYOND trial[4,13] was powered for head-to-head comparison. The BEYOND trial, which enrolled OAB patients who were non-responders to anticholinergic drugs, failed to demonstrate that mirabegron was non-inferior to solifenacin.[4] Assumption of similar efficacy and safety with other anticholinergic drugs relies primarily on the results of the manufacturer-funded indirect comparison. Although the NICE reanalyses were consistent with most of the manufacturer's results, heterogeneity remains in terms of population and quality of trials included in the NMA (Appendix VII of the CDR clinical report provides a summary and critical appraisal of the NMA).

3.2 Patient Population

With regard to the manufacturer's request that mirabegron be listed in a manner similar to other currently listed second-line OAB drugs, about 50% of patients in the trials included in the clinical report did not report previous use of OAB treatments. The only study conducted specifically in a non-responder population was the BEYOND study, in which mirabegron failed to demonstrate non-inferiority to solifenacin.[4]

4. ISSUES FOR CONSIDERATION

4.1 Place in Therapy

The 2012 update of the Canadian Urological Association guidelines on urinary incontinence states that, if patients fail to respond to two adequate treatments of anticholinergic drugs, recommended options include onabotulinumtoxinA (Botox, off-label at the time the guideline update was published, but since approved for the treatment of OAB), neuromodulation, or surgical intervention.[14] Mirabegron was not available at the time the guideline update was published. However, consultation by CDR with a clinical expert suggested that mirabegron would be considered in most patients who had failed adequate trials of one to two anticholinergic drugs before initiating onabotulinumtoxinA. OnabotulinumtoxinA was not included in the manufacturer's analysis. However, it was not listed on any public formulary for the treatment of OAB at the time of the CDR review.

4.2 Potential for Dual Therapy

Because mirabegron has a novel mechanism of action compared with available anticholinergic drugs used for the treatment of OAB, it may be used as an add-on to anticholinergic drugs. The clinical expert noted that using mirabegron with an anticholinergic drug simultaneously, rather than sequentially, could provide an added clinical benefit to some patients. This is supported by the SYMPHONY trial,[12,15] a 12-week long multi-group study, which showed statistically significant differences in micturition and urgency frequency favouring mirabegron 25 mg or 50 mg plus solifenacin 5 mg or 10 mg when compared with solifenacin 10 mg alone (CDR Clinical Report: Results and Interpretation, Efficacy). If mirabegron were used in combination with other second-line OAB drugs reimbursed under public drug plans, this would substantially increase treatment costs.

4.3 Potentially Improved Tolerability

In the NMA reanalysis performed by NICE,[3] mirabegron was reported to have a significantly lower risk of dry mouth than all anticholinergic comparators as well as a significantly lower incidence of constipation than fesoterodine 8 mg, solifenacin 5 mg and 10 mg and trospium chloride 60 mg. Both of these side effects were reported as difficult to tolerate in patient input submitted to CDR (CDR Clinical Report, Appendix II).

4.4 Variability in the Coverage of Second-Line Anticholinergic Drugs Across Drug Plans

While oxybutynin IR is covered by all public formularies, there is variation in the reimbursement of second-line anticholinergic drugs for OAB. Several provinces (e.g., Ontario, Alberta, Saskatchewan, and Nova Scotia), reimburse second-line anticholinergic drugs after failure or intolerance to oxybutynin IR, while others (e.g., British Columbia and Manitoba) do not regularly reimburse these drugs.

4.5 Price and Dispensing Fee Update

Since the manufacturer submitted mirabegron for consideration, ODB has increased the list prices of several of the comparators, making the confidentially submitted price of mirabegron somewhat more attractive in comparison (CDR reanalysis, Table 3). While the dispensing fee was also increased from $8.40 to $8.83 on April 1, 2014, most claims will likely be for a three-month or 100-day supply rather than 30 days assumed by the manufacturer; therefore, 3.65 dispensing fees per annum rather than 12.17 were included in CDR reanalysis.

TABLE 3: CDR REANALYSIS, INCREMENTAL COSTS OF OTHER ANTICHOLINERGIC DRUGS REIMBURSED FOR OAB VERSUS MIRABEGRON

Comparator	Daily Dose	Daily Cost ($)	Without Markup and Fees		With Markup and Fees	
			Annual Cost ($)	Incremental Cost Relative to Mirabegron ($)	Annual Cost ($)	Incremental Cost Relative to Mirabegron ($)
Oxybutynin IR	10 mg	0.1972	72	[redacted]	110	[redacted]
Mirabegron	**50 mg**	[redacted]	[redacted]	**Reference**	[redacted]	**Reference**
Fesoterodine fumarate ER	4 mg	1.5000	548	[redacted]	623	[redacted]
Darifenacin ER	7.5 mg	1.5800	577	[redacted]	655	[redacted]
	15 mg	1.5800	577	[redacted]	655	[redacted]
Solifenacin	5 mg	1.6892	617	[redacted]	698	[redacted]
	10 mg	1.6892	617	[redacted]	698	[redacted]
Tolterodine L-tartrate ER	4 mg	1.9466	711	[redacted]	800	[redacted]
Trospium chloride	40 mg	1.5810	577	[redacted]	655	[redacted]
Oxybutynin ER[a]	10 mg	2.2780	831	[redacted]	930	[redacted]
Onabotulinumtoxin A[b]	100 units q24w	2.1726	793	[redacted]	876	[redacted]
	100 units q3m	3.9667	1,448	[redacted]	1,600	[redacted]

CDR = CADTH Common Drug Review; ER = extended-release; IR = immediate-release; OAB = overactive bladder; q24w = every 24 weeks; q3m = every 3 months (90 days).

[a] Nova Scotia formulary list price (Oct 2014).

[b] OnabotulinumtoxinA was not reimbursed for OAB by any public formulary at the time of this review.

Price Source: Ontario Drug Benefit Formulary (July 2014) unless otherwise indicated. Markup was assumed to be 8% and a dispensing fee of $8.83 was applied 3.65 times annually. Administration costs and other applicable resources for onabotulinumtoxinA treatment are not included but should be considered; dispensing fee for onabotulinumtoxinA applied at each administration.

To better appreciate the impact of potential changes or variability in pricing of second-line OAB drugs, Appendix 1 explores scenarios involving price reductions with tolterodine ER, the most commonly reimbursed second-line anticholinergic.

5. CONCLUSIONS

At the confidentially submitted price of [redacted] per tablet ([redacted] per day), mirabegron 25 mg or 50 mg is more expensive than generic oxybutynin IR ($0.20 to $0.30 per day), but less expensive than anticholinergic drugs currently funded by most drug plans as second-line options for the treatment of OAB (cost ranging from $1.50 to $2.28 per day).

In the general OAB population (treatment-naive and treatment-experienced patients), direct evidence suggests that mirabegron and tolterodine are relatively similar with regard to reductions in urgency, incontinence, or micturition. Results of the manufacturer's NMA as well as NICE reanalysis suggest similar efficacy between mirabegron and anticholinergic drugs (darifenacin, fesoterodine ER, oxybutynin IR and ER, tolterodine IR and ER, and trospium chloride IR and ER) with regard to micturition and incontinence, with the exception of solifenacin which was found to be significantly more effective than mirabegron 50 mg at reducing incontinence. Both direct and indirect evidence suggest that mirabegron is associated with a lower risk of developing dry mouth compared with anticholinergic drugs. There is limited evidence on the comparative efficacy and safety of mirabegron in the subgroup of patients who have failed an adequate treatment with anticholinergic drugs. The BEYOND trial, which enrolled OAB patients who were non-responders to anticholinergic drugs, failed to demonstrate that mirabegron was non-inferior to solifenacin.

Mirabegron could save between [redacted] and [redacted] dollars per patient per year, if used in monotherapy, compared with second-line anticholinergic drugs. If mirabegron were to be used in combination with second-line anticholinergic drugs reimbursed under public drug plans, this would substantially increase treatment costs.

APPENDIX 1: PRICE REDUCTION SCENARIOS

A CADTH Common Drug Review (CDR) analysis of utilization data from public plans reimbursing darifenacin, fesoterodine, tolterodine, solifenacin, and trospium chloride as second-line option for patients who have failed or who are intolerant to oxybutynin IR showed that, from the second quartile of 2013 to the first quartile of 2014, the majority of claims were for tolterodine ER, accounting for 51% to 65% of claims for second-line drugs (PharmaStat data from IMS Health Canada Inc., 2014).

In order to assess the impact of potential changes or variability in pricing, CDR conducted an additional analysis considering the relative cost per day of mirabegron compared with tolterodine ER in various price reduction scenarios for both products (Table 4).

TABLE 4: ADDITIONAL COST (SAVINGS) PER DAY WITH MIRABEGRON VERSUS TOLTERODINE AT VARIOUS PRICE REDUCTION SCENARIOS

	Mirabegron (Daily Drug Cost)			
	Submitted Price: [redacted]	25% Reduction: [redacted]	50% Reduction: [redacted]	75% Reduction: [redacted]
List price: $1.95	[redacted]	[redacted]	[redacted]	[redacted]
25% reduction: $1.46	[redacted]	[redacted]	[redacted]	[redacted]
50% reduction: $0.97	[redacted]	[redacted]	[redacted]	[redacted]
75% reduction: $0.49	[redacted]	[redacted]	[redacted]	[redacted]

Price Source: Ontario Drug Benefit Formulary (July 2014) for tolterodine ER and manufacturer's confidential price for mirabegron. Markups and dispensing fees not included.

APPENDIX 2: SUMMARY OF COST-UTILITY ANALYSIS

In addition to the cost-minimization analysis (CMA), the manufacturer submitted a cost-utility analysis (CUA) for a previously treated subgroup. Because a CMA was deemed by CADTH Common Drug Review (CDR) reviewers to be the most appropriate analysis, the manufacturer's CUA was not critiqued but is summarized below.

The manufacturer used data from the SCORPIO trial[10,16] to undertake a CUA for a previously treated subgroup of patients comparing mirabegron 50 mg with tolterodine 4 mg ER. The manufacturer states that tolterodine was the only comparator considered because of the dearth of data in the previously treated patient population for the other comparators; the model was not updated to include solifenacin, which was studied in treatment-experienced patients in the BEYOND trial.

The outcome considered in the analysis was the incremental cost per quality-adjusted life-year gained.

A Markov model was used to simulate therapeutic management including the course of disease and complications in hypothetical cohorts of patients with overactive bladder (OAB). The simulation accounted for changes in symptoms at monthly intervals and considered five health states for incontinence frequency levels. The model did not allow for changes in dosage over time. Incorporated costs included OAB medications, incontinence pad utilization, health care staff utilization, and, for the societal perspective, loss of productivity. Discontinuation probabilities were based on adverse events and other reasons, although discontinuation for other reasons was considered independent of symptom severity and the same between treatment groups.

From a Ministry of Health perspective, in the base-case analysis, mirabegron dominated tolterodine. Treating patients with mirabegron 50 mg versus tolterodine ER 4 mg for 12 months resulted in cost savings of $166.52 in one year ($1,010.72 versus $1,177.24). When the EuroQol Five-Dimension Health-Related Quality of Life Questionnaire (EQ-5D) was used as the utility measure, treatment with mirabegron compared with tolterodine resulted in an incremental quality-adjusted life-year gain of 0.0052 (0.7891 versus 0.7840 quality-adjusted life-years).

The manufacturer ran a number of deterministic sensitivity analyses which showed that the incremental cost-utility ratio was sensitive to many parameters. Some scenarios resulted in mirabegron being dominated by tolterodine.

REFERENCES

1. Myrbetriq: mirabegron extended-release tablets 25 mg and 50 mg, selective beta 3-adrenoceptor agonist [product monograph]. Markham (ON): Astellas Pharma Canada; 2013.
2. Maman K, Aballea S, Nazir J, Desroziers K, Neine ME, Siddiqui E, et al. Comparative efficacy and safety of medical treatments for the management of overactive bladder: a systematic literature review and mixed treatment comparison. Eur Urol. 2014 Apr;65(4):755-65.
3. Edwards SJ, Karner C, Trevor N, Barton S, Nherera L. Mirabegron for the treatment of symptoms associated with overactive bladder [Internet]. London: BMJ Technology Assessment Group; 2013. [cited 2014 Aug 7]. Available from: http://www.nice.org.uk/guidance/ta290/resources/overactive-bladder-mirabegron-evidence-review-group-report2
4. Astellas Pharma Europe Ltd. Synopsis: a double-blind, randomized, parallel group, multi-centre study to evaluate the efficacy and safety of mirabegron compared to solifenacin in subjects with overactive bladder (oab) treated with antimuscarinics and dissatisfied due to lack of efficacy [Internet]. In: ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US); 2014 [cited 2014 Sep 25]. (ISN/Protocol 178-EC-001; EudraCT number: 2011-005713-37). Available from: http://www.clinicaltrials.jp/user/display/file/178-EC-001%20synopsis.pdf?fileId=1045.
5. Pharmacoeconomic evaluation. In: CDR submission: Myrbetriq (mirabegron) 25 mg and 50 mg extended-release tablets for the treatment of overactive bladder (OAB). Company: Astellas Pharma Canada Inc. [**CONFIDENTIAL** manufacturer's submission]. Markham (ON): Astellas Pharma Canada Inc.; 2013 Nov 27.
6. Novara G, Galfano A, Secco S, D'Elia C, Cavalleri S, Ficarra V, et al. A systematic review and meta-analysis of randomized controlled trials with antimuscarinic drugs for overactive bladder. Eur Urol. 2008;54(4):740-64.
7. Chapple CR, Khullar V, Gabriel Z, Muston D, Bitoun CE, Weinstein D. The effects of antimuscarinic treatments in overactive bladder: an update of a systematic review and meta-analysis. Eur Urol. 2008 Sep;54(3):543-62.
8. Khullar V, Chapple C, Gabriel Z, Dooley JA. The effects of antimuscarinics on health-related quality of life in overactive bladder: A systematic review and meta-analysis. Urology. 2006;68(2 Suppl 1):38-48.
9. Clinical study report (protocol no.178-CL-090): A phase 3, randomized, double-blind, parallel group, placebo and active controlled, multicenter study to assess the efficacy and safety of mirabegron (YM178) in Asian patients with symptoms of overactive bladder [**CONFIDENTIAL** internal manufacturer's report]. Tokyo: Astellas Pharma Inc.; 2012.
10. Clinical study report: A randomized, double-blind, parallel group, placebo and active controlled, multicenter study to assess the efficacy and safety of mirabegron in subjects with symptoms of overactive bladder (EU phase 3 pivotal study - SCORPIO, protocol no. 178-CL-046) [**CONFIDENTIAL** internal manufacturer's report]. Leiderdorp, The Netherlands: Astellas Pharma Europe B.V.; 2010.
11. Clinical study report: a randomized, double-blind, parallel group, active controlled, multi-center long-term study to assess the safety and efficacy of the beta-3 agonist mirabegron (YM178) 50 mg qd and 100 mg qd in subjects with symptoms of overactive bladder (protocol no. 178-CL-049) [**CONFIDENTIAL** internal manufacturer's report]. Leiderdorp, The Netherlands: Astellas Pharma Global Development; 2010.

12. Clinical Study Report: 178-CL-100. A randomized, double-blind, factorial, parallel-group, active and placebo-controlled, multicenter dose-ranging study to evaluate the efficacy, safety and tolerability of six dose combinations of solifenacin succinate and mirabegron compared to mirabegron and solifenacin succinate monotherapies in the treatment of overactive bladder (SYMPHONY) [**CONFIDENTIAL** internal manufacturer's report]. Leiden, The Netherlands: Astellas Pharma Europe B.V.; 2013.

13. Clinical Study Report: 178-EC-001. A double-blind, randomized, parallel group, multi-centre study to evaluate the efficacy and safety of mirabegron compared to solifenacin in subjects with overactive bladder (OAB) treated with antimuscarinics and dissatisfied due to lack of efficacy (BEYOND) [**CONFIDENTIAL** internal manufacturer's report]. Chertsey, United Kingdom: Astellas Pharma Europe Ltd.; 2014.

14. Bettez M, Tu LM, Carlson K, Corcos J, Gajewski J, Jolivet M, et al. 2012 update: guidelines for adult urinary incontinence collaborative consensus document for the Canadian Urological Association. Can Urol Assoc J. 2012 Oct;6(5):354-63.

15. Abrams P, Kelleher C, Staskin D, Rechberger T, Kay R, Martina R, et al. Combination Treatment with Mirabegron and Solifenacin in Patients with Overactive Bladder: Efficacy and Safety Results from a Randomised, Double-blind, Dose-ranging, Phase 2 Study (Symphony). Eur Urol. 2014 Feb 19.

16. Khullar V, Cambronero J, Angulo JC, Wooning M, Blauwet MB, Dorrepaal C, 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 [Internet]. 2013 [cited 2014 May 29];13:45. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3849064