CDEC FINAL RECOMMENDATION

MIRABEGRON
(Myrbetriq — Astellas Pharma Canada Inc.)
Indication: Overactive Bladder

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that mirabegron be listed for the treatment of overactive bladder (OAB) with symptoms of urgency, urgency incontinence, and urinary frequency, if the following clinical criteria and conditions are met:

Clinical Criteria:
- Intolerance or inadequate response to an adequate trial of an anticholinergic therapy.

Conditions:
- List in a manner similar to other pharmacological treatments for use after oxybutynin.
- Not to be used in combination with other pharmacological treatments for OAB.

Reason for the Recommendation:
1. Nine double-blind randomized controlled trials (RCTs) and a network meta-analysis demonstrated that mirabegron was superior to placebo and similar to other anticholinergic drugs for improving the symptoms of OAB. The incidence of dry mouth, a clinically important side effect to patient groups, appeared lower with mirabegron than with comparator anticholinergic drugs.

2. At the submitted price ($[redacted] per day), mirabegron is more costly than generic oxybutynin immediate release (IR) ($0.20 to $0.30 per day), but less costly than other anticholinergic drugs currently funded by most Common Drug Review (CDR)–participating drug plans as second-line options for the treatment of OAB ($1.50 to $2.28 per day).

Of Note:
CDEC noted that patients with OAB may benefit from behavioural training or lifestyle modification, and non-pharmacological approaches should be considered before initiating any drug therapy.

Background:
Mirabegron is indicated for the treatment of OAB with symptoms of urgency, urgency incontinence, and urinary frequency. Mirabegron is a selective beta 3-adrenoceptor agonist and is available as 25 mg and 50 mg tablets. The dosage recommended in the product monograph is 25 mg administered orally, once daily, to a maximum of 50 mg per day.

Summary of CDEC Considerations:
CDEC considered the following information prepared by CDR: a systematic review of RCTs for mirabegron, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to individuals living with OAB.

Patient Input Information
The following is a summary of the information provided by one patient group that responded to the CDR call for patient input:

- Those living with OAB report that they have persistent fears about urine leakage (or losing complete control) such as when going from a seated to standing position, that they have to identify the location of toilets along any routes they take, whether walking or biking, and that they frequently experience the associated feelings of embarrassment, reduced self-esteem, and a sense of loss of control over their lives. They may need to get up frequently at night to urinate, thus placing them at increased risk for reduced sleep quality, as well as falls and fractures.
- Symptoms of urinary urgency and urgency incontinence are the most important aspects of OAB to control.
- People living with OAB reported that anticholinergic medications were often discontinued due to poor tolerability (i.e., dry mouth, constipation, blurred vision, being unable to drive, cognitive impairment) or incomplete response to treatment. They also very much dislike having to wear pads, which, especially over the course of years, can be quite costly.
- Patients with OAB expect that a new drug would control their symptoms more effectively, have a lower risk of side effects compared with current treatments, improve their quality of life (including reducing their anxiety about urine leakage), improve their sleep quality, and be easier to take.

Clinical Trials
The systematic review included nine double-blind RCTs of adults with OAB: five were 12-week placebo and active-controlled efficacy studies (SCORPIO [N = 1,987], study 048 [N = 1,139], study 090 [N = 1,126], DRAGON [N = 928], and SYMPHONY [N = 1,306]), two were 12-week placebo-controlled studies (ARIES [N = 1,329] and CAPRICORN [N = 1,306]), one was a 12-week active-controlled non-inferiority study (BEYOND [N = 1,870]), and one was a 52-week active-controlled safety study (TAURUS [N = 2,452]). From 35% to 62% of patients enrolled in the trials had not previously used OAB drugs except in BEYOND, where all patients had been treated and showed lack of efficacy to prior OAB medications. Six of the 12-week trials compared mirabegron 25 mg and/or 50 mg daily with placebo; a tolterodine ER 4 mg daily treatment group was also included in four trials (SCORPIO, study 048, study 090, and DRAGON). One trial assessed the non-inferiority of mirabegron 50 mg daily versus solifenacin 5 mg daily (BEYOND), and one trial examined the efficacy of mirabegron 25 mg or 50 mg daily as add-on therapy to solifenacin (2.5 mg, 5 mg, or 10 mg daily), compared with solifenacin monotherapy (SYMPHONY). The 52-week trial (TAURUS) compared the safety of mirabegron 50 mg daily with tolterodine ER 4 mg daily.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following: change in the number of incontinence, micturition, and urgency episodes; quality of life; serious adverse events; total adverse events; and withdrawal due to adverse events. Symptoms and health-related quality of life (HRQoL) were measured using different scales in the trials, including the Patient Perception of Intensity of Urgency Scale (PPIUS), Patient Perception of Bladder Condition (PPBC), Overactive Bladder Questionnaire (OAB-q), and the King's Health Questionnaire (KHQ).

The primary outcome in seven 12-week trials was the change from baseline in the number of micturition episodes per 24 hours. SCORPIO, ARIES, and CAPRICORN included change from baseline in the number of incontinence episodes per 24 hours as a co-primary end point. The change from baseline in mean volume voided was the primary outcome in SYMPHONY. Safety was the primary outcome in the 52-week TAURUS study; however, no formal statistical analyses of between-treatment differences were planned for safety or efficacy outcomes.

Efficacy

- All of the included studies reported reductions from baseline in OAB symptoms (incontinence, urgency incontinence, micturitions, urgency, and nocturia) for the placebo, mirabegron, solifenacin, mirabegron plus solifenacin, and tolterodine groups.
- The mean difference (95% confidence interval) for the change from baseline in the number of micturitions per 24 hours was reported as follows:
  - Mirabegron 25 mg versus placebo: −0.45 (−0.99 to 0.10) in DRAGON; −0.47 (−0.82 to −0.13) in CAPRICORN; and −0.05 (−0.87 to 0.77) in SYMPHONY.
  - Mirabegron 50 mg versus placebo: −0.60 (−0.90 to −0.29) in SCORPIO; −0.86 (−1.16 to −0.57) in study 048; −0.57 (−1.04 to −0.09) in study 090; −0.64 (−1.19 to −0.10) in DRAGON; −0.61 (−0.98 to −0.24) in ARIES; −0.42 (−0.76 to −0.08) in CAPRICORN; and −0.13 (−0.94 to 0.69) in SYMPHONY.
  - Mirabegron 50 mg versus tolterodine ER 4 mg: −0.34 (−0.64 to −0.04) in SCORPIO; −0.25 (−0.55 to 0.04) in study 048; −0.60 (−1.07 to −0.13) in study 090, and 0.12 (−0.11 to 0.35) in TAURUS.
  - Mirabegron 50 mg versus solifenacin 5 mg: 0.18 (−0.06 to 0.42) in BEYOND (non-inferiority not met); −0.02 (−0.73 to 0.69) in SYMPHONY.
  - Mirabegron 50 mg plus solifenacin 5 mg versus solifenacin 5 mg: −0.80 (−1.39 to −0.22) in SYMPHONY.
- Differences between mirabegron and tolterodine ER were not statistically significantly different for OAB symptom outcomes, with the exception of change in the number of micturition episodes per 24 hours in SCORPIO and study 090 (favoured mirabegron 50 mg), and change in the number of incontinence episodes per 24 hours in TAURUS (favoured tolterodine).
- No statistically significant differences were detected between mirabegron and solifenacin for OAB symptom outcomes. Non-inferiority was not met for mirabegron 50 mg versus solifenacin 5 mg for the primary outcome of micturition frequency in the BEYOND trial.
- Combination therapy (mirabegron plus solifenacin) showed statistically significant differences versus solifenacin monotherapy for the number of urgency episodes, micturition frequency, and the proportion of patients achieving continence in SYMPHONY.

- HRQoL was measured using validated OAB specific instruments. While all treatments reported improvement from baseline to end of treatment, the differences between groups were small and the clinical importance was unclear.

Harms (Safety and Tolerability)

- The incidence of serious adverse events, total adverse events, and withdrawals due to adverse events were similar between the mirabegron, placebo, solifenacin, mirabegron plus solifenacin, and tolterodine groups in the 12-week trials, and between mirabegron and tolterodine in the 52-week trial.
- The incidence of dry mouth was higher in the tolterodine (8% to 14%), solifenacin (6% to 30%), and mirabegron plus solifenacin (9% to 20%) groups than in the mirabegron (< 1% to 5%) or placebo (2% to 5%) groups, but the incidence of other anticholinergic adverse events was similar between treatments.
- No increased risk of cardiovascular adverse events was observed for mirabegron versus comparators.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis comparing mirabegron 25 mg and 50 mg with oxybutynin immediate release (IR), darifenacin ER, fesoterodine ER, solifenacin, tolterodine ER, and trospium chloride IR in a general population of adult OAB patients (including both treatment-naive and treatment-experienced patients) over a one-year time horizon. Similar efficacy and safety was supported by head-to-head trials comparing mirabegron with solifenacin and tolterodine, and a manufacturer-funded indirect comparison with the other anticholinergic drugs.

CDR noted that there is limited evidence on the comparative efficacy and safety of mirabegron in the subgroup of patients having failed an adequate treatment with anticholinergic drugs. In addition, the BEYOND trial, which enrolled OAB patients who were non-responders to anticholinergic drugs, failed to demonstrate that mirabegron was non-inferior to solifenacin.

At recommended doses, mirabegron ($[redacted] per day) is more costly than generic oxybutynin IR ($0.20 to $0.30 per day), but less costly than anticholinergic drugs currently funded by many drug plans as second-line options for the treatment of OAB (darifenacin ER, fesoterodine ER, solifenacin, tolterodine ER, trospium chloride IR, and oxybutynin ER, cost ranging from $1.50 to $2.28 per day). 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.

Other Discussion Points:

CDEC noted the following:

- Only one of the included RCTs (BEYOND) was designed to assess the non-inferiority of mirabegron against another drug commonly used as a second-line pharmacological treatment for OAB. This study failed to demonstrate non-inferiority of mirabegron versus solifenacin for the primary outcome of micturition frequency at the pre-set margin of 0.2 micturitions per 24 hours.
- The manufacturer's network meta-analysis suggested similar efficacy between mirabegron and anticholinergic drugs (darifenacin, fesoterodine, oxybutynin IR and ER, tolterodine IR

and ER, and trospium IR and ER) with regard to micturition and incontinence. This result was supported by the reanalyses conducted by the National Institute for Health and Care Excellence (NICE) Evidence Review Group, with the exception that solifenacin was found to be significantly more effective than mirabegron 50 mg at reducing incontinence.
- Patients reported that dry mouth is a difficult symptom to tolerate and mirabegron consistently demonstrated a lower incidence of this adverse effect.
- Oxybutynin IR (5 mg tablets) is covered by all CDR-participating drug plans; however, coverage of second-line anticholinergic drugs is variable.

Research Gaps:
CDEC noted that there is an absence of evidence regarding the following:
- Data regarding the comparative long-term safety and efficacy of mirabegron against other pharmacological treatments for OAB.

CDEC Members:
Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

October 15, 2014 Meeting

Regrets: None

Conflicts of Interest: None

About This Document:
CDEC provides formulary listing recommendations or advice to CDR-participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

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