CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

PROPIVERINE HYDROCHLORIDE
(Mictoryl/Mictoryl Pediatric — Duchesnay Inc.)
Indication: Overactive bladder

This document was originally issued on April 19, 2017 and was revised on June 23, 2017 to correct an error in the Cost and Cost-Effectiveness section.

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that propiverine hydrochloride be reimbursed for the symptomatic treatment of urinary incontinence and/or increased urinary frequency and urgency in patients with overactive bladder, if the following condition is met:

Condition:
- The drug plan cost for propiverine should not exceed the drug plan cost of oxybutynin immediate release (IR) tablets for adult patients or oxybutynin syrup for pediatric patients.

Reasons for the Recommendation:
1. Two randomized controlled trials (RCTs) demonstrated that propiverine modified release (MR) was noninferior to tolterodine in change from baseline in daily micturition frequency (Study 1300; N = 324) and statistically significantly superior to placebo in reducing daily incontinence and micturition frequency (Study 659,1; N = 988) in adults with overactive bladder (OAB). Propiverine MR was statistically significantly superior to tolterodine in reducing incontinence frequency; however, the numerical difference and 95% confidence interval (CI) were not reported. One RCT in pediatric patients with OAB demonstrated that propiverine-pediatric was statistically significantly superior to placebo in reducing daily incontinence and micturition frequency (Study 1169; N = 171). There was no other currently available evidence to suggest that there are any statistically significant or clinically meaningful differences between propiverine MR and oxybutynin.
2. At the submitted price, the daily cost of propiverine 30 mg and 45 mg MR ($1.39 per day) is more than that of oxybutynin IR ($0.20 to $0.30 per day) and would need to be reduced by 79% to be considered cost-neutral to oxybutynin IR in the adult population. In the pediatric population, at the submitted price ($0.74 to $2.22 per day), the estimated weighted-average daily cost of propiverine 5 mg IR ($1.48 per day) would need to be reduced by 70% to be considered cost-neutral to oxybutynin syrup ($0.44 per day).

Of Note:

- CDEC noted that oxybutynin is considered the first-line treatment for adult and pediatric patients with OAB and is currently reimbursed by most CADTH Common Drug Review (CDR) participating drug plans. There was no evidence in the three RCTs reviewed by CDR to assess the effectiveness of propiverine as a second-line treatment to other antimuscarinics including oxybutynin.

Discussion Points:

- On the basis of pharmacokinetic studies demonstrating that the 15 mg IR form of propiverine (two times daily or three times daily) was bioequivalent to the propiverine MR form (30 mg and 45 mg once daily), CDEC considered the results of three double-blind RCTs that evaluated the efficacy of propiverine IR compared with tolterodine, oxybutynin, or placebo in adult patients with OAB. The results demonstrated that compared with placebo, treatment with propiverine IR was associated with a reduction in micturition frequency, fewer incontinence episodes, and improved OAB symptoms. Propiverine IR 15 mg (three times daily) had a similar clinical effect compared with oxybutynin, and propiverine IR 15 mg (two times daily) was noninferior to tolterodine based on change in cystometric capacity from baseline.

Background:

Propiverine has a Health Canada indication for the symptomatic treatment of urinary incontinence and/or increased urinary frequency and urgency in patients with OAB. Propiverine is a detrusor relaxant drug with antimuscarinic and calcium-modulating properties. It is available as 30 mg and 45 mg MR capsules for adult use, and as propiverine-pediatric which is available in 5 mg tablets. The Health Canada–approved dose is propiverine MR 30 mg or 45 mg once daily for adults. A standard daily average of 0.8 mg/kg body weight administered in two doses for children with body weight up to 35 kg (achievable with propiverine-pediatric 5 mg tablets); for children or adolescents with a body weight over 35 kg, the maximum recommended dose is 30 mg administered in two daily doses.

Summary of CDEC Considerations:

CDEC considered the following information prepared by CDR: a systematic review of RCTs of propiverine and propiverine-pediatric, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients with OAB.

Patient Input Information:

One patient group (The Canadian Continence Foundation) responded to the CDR Call for Patient Input. Information was obtained through online surveys, one-on-one telephone interviews, and informal discussions with patients. The following is a summary of key information provided by the patient group:

- All respondents experienced symptoms and problems related to OAB, most of which required limiting or modifying daily activities, such as not leaving the house as often as preferred, modifying diet and limiting beverages, planning trips to the bathroom, getting up during the night, and wearing continence pads. Many of these modifications lead to a sense of isolation

and depression and subsequently have a strong impact on patients' and caregivers' quality of life.
- Many (but not most) patients who have received anticholinergic medications for OAB reported that there was some difference in symptom control between medications in the same drug class, and most patients said their treatments were ineffective. The treatment-related side effects (i.e., dry mouth and dizziness) led to concerns of tolerability and influenced patients' willingness to continue with the prescribed medications.
- None of the patients who directly informed the submission had experience with propiverine. The submission's authors noted that the efficacy, safety, and tolerability of propiverine have been evaluated in clinical trials enrolling adults and children with OAB and/or urinary incontinence. The MR formulation of propiverine and its once daily administration are expected to have benefits for patients in terms of their ability to adhere to the medication.

Clinical Trials

The CDR systematic review included three randomized, multi-centre, double-blind placebo and/or active controlled trials in adult or pediatric patients with OAB:
- Study 659,1 (Junemann et al., N = 988): included adult patients randomized to one of the following: propiverine MR, propiverine IR or placebo for a treatment period of 32 days.
- Study 1300 (Leng et al., N = 324): included adult patients randomized to either propiverine MR or tolterodine for a treatment period of 56 days.
- Study 1169 (Marschall-Kehrel et al., N = 171): included pediatric patients randomized to either propiverine-pediatric or placebo for a treatment period of 56 days.

Study 659,1 and Study 1300 assessed the non-inferiority of propiverine MR 30 mg once daily to propiverine IR 15 mg twice daily or tolterodine 4 mg once daily, respectively. Study 1169 evaluated the superiority of propiverine-pediatric 5 mg (weight-dependent dose) compared with placebo. The study discontinuation rates ranged from 3.4% to 11.4% across studies.

The included studies were limited by their short duration (four to eight weeks), high placebo response that is characteristic of trials in patients with OAB, and difficulty interpreting the clinical significance of the results. There were no trials available to assess the 45 mg dose of propiverine MR.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:
- Incontinence episodes: the number of incontinence episodes per 24 hours was documented in the micturition diary for three consecutive days during the screening period and at the end of treatment period; "change from baseline in the number of incontinence episodes per 24 hours" was calculated by subtracting an arithmetic mean for incontinence episodes at end of treatment from the mean for incontinence episodes at baseline.
- Micturition frequency: the number of micturitions per 24 hours was documented in the micturition diary for three consecutive days during the screening period and at the end of treatment period; "change from baseline in micturition frequency per 24 hours" was calculated by subtracting micturition frequency per 24 hours at end of treatment from the frequency recorded at baseline.
- Urgency episodes: the number of urgency episodes per 24 hours was documented in the micturition diary for three consecutive days during the screening period and at the end of

treatment period; "change from baseline in urgency episodes per 24 hours" was calculated by subtracting urgency episodes per 24 hours at end of treatment from the episodes recorded at baseline.
- Health-related quality of life (HRQoL): as measured by the King's Health Questionnaire (KHQ); this is a 21-item disease-specific questionnaire that was developed and validated for patients with urinary incontinence; scores for the KHQ range from 0 to 100, where 0 indicates the best outcome or response and 100 indicates the worst outcome or response.
- Serious adverse events, total adverse events, and withdrawal due to adverse events.

The primary outcome in Study 659,1 was the change from baseline in the number of incontinence episodes per 24 hours. In Study 1169 and Study 1300 the primary outcome was the change in the micturition frequency per 24 hours.

Efficacy

All of the included trials reported reductions from baseline in OAB symptoms (incontinence, micturitions, and urgency) for propiverine 30 mg MR, propiverine-pediatric, tolterodine, and the placebo groups.

The mean differences (95% CI) for the change from baseline in the incontinence episodes per 24 hours were reported as follows:
- Propiverine MR 30 mg versus placebo: 0.77 (0.44 to 1.10) in Study 659,1, the difference was statistically significant, $P < 0.0001$.
- Propiverine MR 30 mg versus tolterodine 4 mg: statistically significant between-group difference was stated, $P = 0.0275$; however the effect estimate and 95% CI were not reported in Study 1300.
- Propiverine-pediatric (weight-dependent dose) versus placebo in children: [redacted] in Study 1169, the difference was statistically significant, $P = 0.0005$.

The mean differences (95% CI) for the change from baseline in the micturition frequency per 24 hours were reported as follows:
- Propiverine MR 30 mg versus placebo: 0.906 (0.445 to 1.368) in Study 659,1, the difference was statistically significant, $P = 0.0001$.
- Propiverine MR 30 mg versus tolterodine 4 mg: –0.42 (–1.2 to 0.35) in Study 1300, noninferiority of propiverine MR to tolterodine was met, *P* value was not reported.
- Propiverine-pediatric (weight-dependent dose) versus placebo in children: [redacted] in Study 1169, the difference was statistically significant, $P = 0.0007$.

The mean differences for the change from baseline in the urgency episodes per 24 hours in Study 659,1 were reported as follows:
- Propiverine MR 30 mg versus placebo: [redacted], the difference was statistically significant, $P =$ [redacted].

In Study 659,1, HRQoL was measured using the KHQ. While all treatments groups experienced improvement in total score from baseline to the end of treatment, propiverine MR 30 mg was not statistically significantly different from placebo.

Harms (Safety and Tolerability)
Overall, the incidence of adverse events, serious adverse events, and withdrawal due to adverse events were similar between propiverine MR and tolterodine. The incidence of overall adverse events associated with propiverine MR (34.3%) or propiverine-pediatric (23.0%) was higher than that reported for placebo (20.3% in Study 659,1and 20.2% in Study 1169). The incidence of overall adverse events was similar between propiverine MR (45.1%) and tolterodine (42%) in Study 1300.

The incidence of dry mouth was higher in the propiverine MR (21.7% to 27.7%), propiverine IR 15 mg twice daily (22.8%) and tolterodine 4 mg (26.5%) treatment groups, compared with placebo (6.4%) in the adult population. The incidence of dry mouth was lower in the pediatric population compared with the adult population, though still higher in the propiverine-pediatric group than in the placebo group: 3.4% in the propiverine-pediatric group versus no events in the placebo group.

No increased risk of cardiovascular adverse events was observed for propiverine MR versus propiverine IR or tolterodine in the adult population: palpitation and chest depression were reported in Study 659,1 and Study 1300; the rate of reporting among patients treated with propiverine ranged from 0.3% to 1.2%, while tolterodine was associated with a rate of 2.5%.

Cost and Cost-Effectiveness
The manufacturer submitted a price of $1.39 per 30 mg or 45 mg propiverine MR capsule (30 or 45 mg once daily, $1.39 per day), and of $0.37 per 5 mg IR tablet (10 mg to 30 mg per day in two doses, $0.74 to $2.22 per day).

The manufacturer submitted a cost comparison of propiverine with oxybutynin IR, tolterodine IR and ER, solifenacin, mirabegron, fesoterodine, trospium, and darifenacin for both the adult and pediatric OAB populations over a one-year time horizon, although the pediatric population analysis included only six months of time on therapy. The manufacturer assumed clinical similarity to other anticholinergics in the adult OAB population on the basis of an RCT comparing 30 mg propiverine MR once daily with 15 mg propiverine IR twice daily and placebo, and a noninferiority trial comparing 30 mg propiverine MR with 4 mg tolterodine ER. No clinical comparisons of propiverine MR with other OAB treatments were available. For the pediatric population, the manufacturer assumed clinical similarity on the basis of a propiverine IR placebo-controlled RCT and a retrospective observational cohort study of children with urinary incontinence due to OAB taking propiverine IR or oxybutynin IR tablets.

Key limitations with the manufacturer's economic submission included substantial uncertainty in the assumption of clinical similarity between propiverine and comparators, particularly in the pediatric population. Also, for the pediatric analysis, the inclusion of only 180 days of therapy over a one-year analysis time frame, the omission of oxybutynin syrup as comparator, and the underestimation of the patient weight and dose distribution likely to be seen in clinical practice were seen as limitations.

CDR reviewers accepted the manufacturer's conclusion that at an annual cost of $507 per patient, propiverine MR for adults with OAB was more expensive than oxybutynin IR ($107 per patient annually) but less expensive than trospium ($595 per patient annually). Based on CDR reanalyses for the pediatric population, propiverine-pediatric would cost a weighted-average of approximately $540 per patient annually, which was more expensive than oxybutynin IR ($71

per patient annually) and less than trospium ($595 per patient annually). The experts consulted by CDR believed the most relevant comparator for the pediatric population in Canada is oxybutynin syrup, which was not considered by the manufacturer and costs $378 less per patient annually than CDR's estimate for propiverine-pediatric. The cost of propiverine MR would need to be reduced by 79% to be considered cost-neutral to oxybutynin IR in the adult population, and by 70% to be considered cost-neutral to oxybutynin syrup in the pediatric population.

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, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

March 15, 2017 Meeting:

Regrets: None

Conflicts of Interest: None

About This Document:
CDEC provides formulary reimbursement 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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