Common Drug Review
Clinical Review Report

May 2017

Drug	Propiverine hydrochloride (Mictoryl/Mictoryl Pediatric)
Indication	For symptomatic treatment of urinary incontinence and/or increased urinary frequency and urgency in patients with overactive bladder
Reimbursement Request	As per indication
Dosage form(s)	30 mg and 45 mg modified-release capsules and pediatric 5 mg tablet
NOC Date	January 5, 2017
Manufacturer	Duchesnay Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included clinical experts in urology and pediatric urology who provided input on the conduct of the review and the interpretation of findings.

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ABBREVIATIONS

AE	adverse event
ANCOVA	analysis of covariance
CDR	CADTH Common Drug Review
DB	double-blind
ER	extended-release formulation
FAS	full analysis set
HRQoL	health-related quality of life
IR	immediate-release formulation
ITT	intention to treat
KHQ	King's Health Questionnaire
MCID	minimal clinically important difference
MR	modified-release formulation
N	number of patients
OAB	overactive bladder
PP	per-protocol
QoL	quality of life
RCT	randomized controlled trial
SAE	serious adverse event
TCCF	The Canadian Continence Foundation
UI	urinary incontinence
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Overactive bladder (OAB) is a chronic condition of the lower urinary tract characterized by urinary urgency, with or without urge incontinence, usually with urinary frequency and nocturia. In Canada, it is estimated that OAB affects 12% to 18% of the adult population. Propiverine hydrochloride is a detrusor relaxant drug with antimuscarinic and calcium-modulating properties for the treatment of OAB. The Health Canada–approved product monograph indication is for the symptomatic treatment of urinary incontinence (UI) and/or increased urinary frequency and urgency in patients with OAB. Propiverine is available in adult (30 mg and 45 mg extended-release formulation [ER] capsules) and pediatric (5 mg tablets, body weight–adjusted dosage up to a body weight of 35 kg, after which children and adolescents of higher body weight will receive the daily dose of 30 mg propiverine) formulations. The manufacturer requested reimbursement as per the Health Canada–approved indication.

The objective of this report is to perform a systematic review of the beneficial and harmful effects of propiverine hydrochloride (Mictoryl/Mictoryl Pediatric) for the symptomatic treatment of UI and/or increased urinary frequency and urgency in patients with OAB.

Results and Interpretation

Included Studies

The CADTH Common Drug Review (CDR) systematic review included three manufacturer-sponsored studies. All studies were randomized, multi-centre, double-blind (DB) placebo and/or active-controlled trials. Study P 659,1 (number of patients [N] = 988) compared propiverine ER (30 mg once daily) versus propiverine immediate-release formulation (IR) (15 mg twice daily) and placebo in adult OAB patients, while Study P 1169 (N = 171) compared propiverine-pediatric (weight-adjusted dose) versus placebo in OAB pediatric patients five to 10 years old and Study P 1300 (N = 324) compared propiverine ER with tolterodine in adult Chinese OAB patients. Study P 659,1 was 32 days long, while studies P 1169 and P 1300 evaluated therapy over 56 days. Studies P 659,1 and P 1300 were noninferiority trials; P 659,1 tested the noninferiority of propiverine ER versus propiverine IR with a noninferiority margin of 0.5 episodes of incontinence per day, and P 1300 tested the noninferiority of propiverine ER versus tolterodine with a noninferiority margin of one micturition episode per day. Change in daily incontinence episodes was the primary outcome in P 659,1, and it was a secondary outcome for P 1169 and P 1300. The primary outcome for P 1169 and P 1300 was change in daily micturition episodes, which was also a secondary outcome for P 659,1. Study P 659,1 included daily urge episodes and quality of life (QoL) as secondary outcomes. Other outcomes such as nocturia and pad count were deemed important by patient input and the consulted clinical experts; however, none of the included studies reported these outcomes.

In the absence of evidence for the 45 mg ER form of propiverine, the manufacturer indicated that previous pharmacokinetic studies have demonstrated that the 15 mg IR form, two times daily or three times daily, was considered to be bioequivalent to the 30 mg ER or 45 mg ER form of propiverine (once daily), respectively. Two studies evaluating the effectiveness of the IR form of propiverine (three times daily) and one study evaluating the effectiveness of the IR form of propiverine (two times daily) were submitted by the manufacturer as supporting evidence for the 45 mg and 30 mg ER form of propiverine hydrochloride, respectively, and were summarized by CDR.

The included studies were limited by their short duration (four to eight weeks), a high placebo response that is characteristic of trials in OAB, and the difficulty interpreting the clinical significance of the results. The trial populations had a relatively low frequency of micturition (nine episodes within 24 hours in Study P 1169) and low frequency of incontinence episodes (one episode within 24 hours in Study P 1300) at baseline, and included patients from Europe and China, which may limit the generalizability of the results to clinical practice in Canada. Furthermore, the available evidence did not include information about the comparative efficacy of propiverine ER in terms of nocturia or pad count; these outcomes were deemed important for patients with OAB. The incomplete reporting of results in Study P 1300 also limits the ability to interpret the clinical significance of the efficacy results.

Indication Under Review
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As per indication

Efficacy

In terms of the frequency of OAB symptoms (incontinence, micturitions, and urgency), there was no statistically significant difference between propiverine ER and propiverine IR. Propiverine ER was noninferior to propiverine IR in terms of change in daily incontinence frequency from baseline (the mean difference of propiverine IR and propiverine ER [95% confidence interval]: [redacted]). In addition, propiverine ER was noninferior to tolterodine in terms of change in daily micturition frequency from baseline (the mean difference of tolterodine and propiverine ER [95% confidence interval]: [redacted]). Propiverine ER was statistically significantly superior compared with tolterodine in terms of reducing incontinence frequency from baseline; however, the numerical difference between the two groups was not reported. When compared with placebo, propiverine ER and propiverine-pediatric were associated with a statistically significantly superior reduction in the frequency of micturition and incontinence episodes per day from baseline.

Study P 659,1 reported results of health-related quality of life (HRQoL) using the King's Health Questionnaire. The authors reported that an improvement in QoL from baseline was associated with treatment with propiverine ER, propiverine IR, and placebo. The differences between groups did not reach a statistical significance, and they showed modest clinical importance. The other two studies did not report on HRQoL.

Harms

Overall, the incidence of adverse events (AEs), serious adverse events (SAEs), and withdrawal due to adverse events (WDAEs) were similar between propiverine ER, propiverine IR, and tolterodine. The incidence of overall AEs associated with propiverine ER was double that reported for placebo; the difference was driven mainly with higher incidence of dry mouth for patients treated with propiverine. No increased risk of cardiovascular AEs was observed for propiverine ER versus propiverine IR or tolterodine.

The results from the manufacturer-submitted supporting evidence assessing the 15 mg IR of propiverine (two or three times daily) suggested that compared with placebo, treatment with propiverine IR was associated with a reduction in micturition frequency, decreased incontinence episodes, and improved

OAB symptoms. In terms of safety, in one study enrolling elderly patients with high cardiac risk, no major issues related to cardiovascular events were reported during the treatment phase in either treatment group (propiverine IR or placebo). The supporting studies provided by the manufacturer that were based on the bioequivalence of the ER and IR forms of propiverine were subject to similar limitations as the trials included in the main review (e.g., the short duration of studies, high placebo response, challenges in interpreting the clinical significance of the results) and had limited comparative efficacy and safety data reported.

Potential Place in Therapy[1]

OAB is a diagnostic classification for patients who present with frequency, urgency, and urgency incontinence. It is a common problem affecting women and men and becomes more common in the elderly. It may be idiopathic or neurogenic in origin. Children as well may manifest OAB as a component of dysfunctional voiding or from other disorders of the central nervous system, either congenital (e.g., neural tube defects, cerebral palsy) or acquired (e.g., spinal cord injury), and OAB has a major negative effect on QoL. OAB is primarily a clinical diagnosis, based on history, physical examination, and non-invasive testing such as urinalysis and culture. Specialized testing, such as urodynamics or cystoscopy, may be required in those who do not respond to the therapeutic measures described in the following (including, for example, failure to mirabegron). Thus, no specific barriers exist to identifying patients in practice that may require treatment with propiverine.

The usual therapeutic approach is initially lifestyle adjustments with timed voiding coaching, and dietary and fluid modification including avoidance of caffeinated beverages and constipation. The pharmacological options have for many years been antimuscarinic medications, which all have a similar side effect profile typical of this class of medication — dry mouth, blurred vision, constipation, and cardiac arrhythmias. In the elderly, acute confusion and deleterious impact on cognitive function limit the utility of this class of medication. There are currently six antimuscarinic drugs available for adult patients with OAB in Canada (tolterodine, trospium, darifenacin, solifenacin, oxybutynin, and fesoterodine), only one of which is indicated for pediatric patients (oxybutynin). Propiverine is an antimuscarinic that has been shown to be effective in short-term clinical trials. It has also been shown to be safe and effective in children. Comparisons with currently available antimuscarinics are limited but do show noninferiority to comparators. The medication is available as a modified-release (MR) preparation to permit once daily dosage.

The pediatric preparation of propiverine hydrochloride is a 5 mg tablet, which may present problems for younger children who often have problems swallowing tablets. Alternative treatment options for adult and pediatric patients include mirabegron (a beta-3 agonist) and intra-detrusor injections of onabotulinum toxin. However, the former (mirabegron) has a range of AEs including gastrointestinal symptoms and cardiac arrhythmias and the latter (onabotulinum toxin) requires a cystoscopy for the injection, which needs to be repeated every six to nine months and is associated with an increased risk of urinary infection and urinary retention. Because of the range of AEs, particularly with the antimuscarinics, patient discontinuation rates are very high and only 35% of patients continue on the medication after three months. Based on a retrospective analysis of Canadian drug claims data, dropout rates as high as 85% have been noted in children with long-term follow-up (up to four years).

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Based on the current available therapies and standards of care, the unmet need of adults and children with OAB is a pharmacological drug that is effective with minimal side effects. Currently available drugs have minimal effect on symptoms with significant side effects, leading to high discontinuation rates. There does not appear to be any major advantage for the use of propiverine in adults or children compared with other currently available antimuscarinic preparations or other available therapies for OAB. In particular, the utility of propiverine in children may be limited as the only available formulation is a tablet, rather than a liquid, and many children are unable to swallow tablets.

Conclusions

Three DB randomized controlled trials met the inclusion criteria for the systematic review. Two studies were conducted in adult patients, and one study was conducted in pediatric patients. Noninferiority was achieved for propiverine ER versus tolterodine in terms of change from baseline in micturition frequency. Propiverine ER showed superior results compared with tolterodine in terms of reducing incontinence frequency; furthermore, propiverine ER and propiverine-pediatric showed superiority over placebo in terms of reducing incontinence and micturition frequencies. One study showed that there was no significant effect of propiverine ER on patients' HRQoL when compared with placebo. The incidence of SAEs and WDAEs were similar between treatment groups. Dry mouth was reported at a higher rate for patients treated with propiverine ER compared with placebo. The included studies were limited by their short duration of therapy and the difficulty in interpreting the clinical significance of the results.

TABLE 1: SUMMARY OF FINDINGS

	P 659,1			P 1169		P 1300	
	Propiverine ER 30 mg q.d.	**Propiverine IR 15 mg b.i.d.**	**Placebo**	**Propiverine IR-Pediatric**	**Placebo**	**Propiverine ER 30 mg q.d.**	**Tolterodine ER 4 mg q.d.**
Number of randomized patients	391	395	202	87	84	162	162
Incontinence episodes (per 24 hours)							
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	0.8 (0.8)	1.1 (1.0)	1.3 (3.1)	0.6 (1.6)
Reduction from baseline, mean (SD)	[redacted]	[redacted]	[redacted]	0.5 (0.7)	0.2 (0.9)	0.9 (2.1)	0.3 (1.1)
Propiverine IR vs. ER	Passed noninferiority test; *P* value < 0.0001 Propi. IR-ER[a] (95% CI): [redacted]			Not applicable			
Propiverine ER vs. placebo	ER-placebo[a] (95% CI): [redacted]; *P* value [redacted]						
Propiverine IR vs. placebo	IR-placebo[a] (95% CI): [redacted] *P value* [redacted]						
Propi.-pediatric vs. placebo	Not applicable			Propi.-placebo[b] (95% CI): [redacted], *P* value = 0.0005		Not applicable	
Propiverine ER vs. tolterodine				Not applicable		Difference was SS but not reported	
Micturition episodes (per 24 hours)							
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15.2 (5.8)	14.7 (6.0)
Reduction from baseline, mean (SD)	3.631 (2.962)	3.659 (2.792)	2.968 (3.567)	[redacted]	[redacted]	4.6 (4.1)	3.8 (5.1)
Propiverine IR vs. ER	Difference[c] (95% CI): [redacted] *P* value [redacted]			Not applicable			
Propiverine ER vs. placebo	Difference[c] (95% CI): [redacted] *P* value [redacted]						
Propiverine IR vs. placebo	Difference[c] (95% CI): [redacted] *P* value [redacted]						
Propi.-pediatric vs. placebo	Not applicable			[redacted], *P* value = 0.0007		Not applicable	
Tolterodine vs. propiverine ER				Not applicable		Passed noninferiority test [d]; *P* value NR	

	P 659,1			P 1169		P 1300	
	Propiverine ER 30 mg q.d.	**Propiverine IR 15 mg b.i.d.**	**Placebo**	**Propiverine IR-Pediatric**	**Placebo**	**Propiverine ER 30 mg q.d.**	**Tolterodine ER 4 mg q.d.**
						[redacted]	
Urgency episodes (within 24 hours)							
Baseline, mean (SD)	6.369 (4.166)	6.192 (3.842)	6.220 (4.212)	Not reported			
Reduction from baseline, mean (SD)	2.882 (3.356)	2.578 (3.396)	1.889 (4.003)				
Propiverine IR vs. ER	Difference[c] (95% CI): [redacted] *P* value [redacted]						
Propiverine ER vs. placebo	Difference[c] (95% CI): [redacted] *P* value [redacted]						
Propiverine IR vs. placebo	Difference[c] (95% CI): [redacted] *P* value [redacted]						
Deaths, n (%)	0	0	0	0	0	0	0
Serious adverse events, n (%)	1 (0.3)	0	0	0	0	0	4 (2.5)[e]
Withdrawal due to adverse events, n (%)	11 (2.8)	15 (3.8)	1 (0.5)	2 (2.3)	1 (1.2)	5 (3.1)	12 (7.4)
• Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	0
Patients with treatment-emergent adverse events, n (%)	134 (34.3)	152 (38.5)	41 (20.3)	20 (23.0)	17 (20.2)	[redacted]	[redacted]
• Dry mouth	85 (21.7)	90 (22.8)	13 (6.4)	3 (3.4)	0	45 (27.7)	43 (26.5)
• Nausea	6 (1.5)	10 (2.5)	2 (1.0)	None reported		Cases were not summarized [e]	
• Vision blurred	18 (4.6)	15 (3.8)	1 (0.5)	1 (1.1)	0		

b.i.d. = twice daily; CI = confidence interval; CSR = Clinical Study Report; ER = extended-release formulation; IR = immediate-release formulation; n = number of patients with event; NR = not reported; *P* = probability; propi. = propiverine; q.d. = once daily; SD = standard deviation; SS = statistically significant; vs. = versus.

[a] Least square difference; in Study P 659,1, analyses of incontinence episodes were based on data of the per-protocol population (propiverine ER: n = 363; propiverine IR: n = 360; placebo: n = 187).

[b] Analyzed in intention-to-treat population (propiverine IR: n = 84; placebo: n = 80).

[c] Analyzed in intention-to-treat population (propiverine ER: n = 384; propiverine IR: n = 391; placebo: n = 199).

[d] Analyzed in per-protocol population (propiverine ER: n = 148; tolterodine: n = 139).

[e] Several cases were reported as individual reimbursements, but these cases were not summarized or counted for each group.

Source: CSRs for P 659,1,[1] P 1169,[2] and P 1300;[3] Junemann 2006,[4] Marschall 2009,[5] and Leng 2017.[6]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Overactive bladder (OAB) is a chronic condition of the lower urinary tract defined by the International Continence Society as a symptom syndrome experienced during the storage phase of the bladder. Symptoms include urinary urgency, with or without urge incontinence, usually with urinary frequency and nocturia.[7-9]

In Canada, it is estimated that OAB affects 12% to 18% of the adult population.[10] Men and women are equally affected, and the disease is more prevalent with advanced age.[9] Some individuals with OAB symptoms may also experience urinary incontinence (UI).[8] A true incidence measure of OAB is difficult since many patients are embarrassed to discuss their symptoms with their physicians or feel that OAB is a normal part of aging and must be accepted.[11,12] OAB is therefore a condition that often remains underdiagnosed.[11,13]

Patient input (APPENDIX 1) as well as published literature indicated that OAB may affect an individual's psychological and social well-being by leaving patients feeling frustrated, anxious, and embarrassed.[12] OAB has been linked to higher levels of depression, higher levels of work impairment, and greater rates of unemployment.[13] Even mild symptoms of UI have the potential to impact patient quality of life (QoL) by negatively affecting everyday participation in a variety of interpersonal, professional, and social activities.[12]

1.2 Standards of Therapy

According to Canadian and international clinical practice guidelines, OAB requires a combination of non-pharmacologic and pharmacologic treatments.[14-17] The goals of therapy are to relieve urinary symptoms, prevent complications, improve QoL, and increase functional capacity of the bladder while avoiding troubling side effects of the treatment. The general classes of drugs used in the treatment of OAB are anticholinergic drugs and combined anticholinergics and smooth muscle relaxants. Anticholinergic (antimuscarinic) drugs have long been considered the pharmacologic mainstay in the treatment of OAB. Their mechanism of action is to relax the bladder by inhibiting involuntary detrusor muscle contractions.[18] Several antimuscarinic chemical entities are approved for the treatment of OAB in Canada including oxybutynin, tolterodine, trospium, solifenacin, and darifenacin. Canadian clinical practice guidelines recommend oxybutynin as first-line treatment. Oxybutynin is the only Health Canada–approved drug for use in pediatric patients.[19]

Antimuscarinic drugs have been associated with high incidence of anticholinergic adverse events (AEs) such as dry mouth, constipation, and blurred vision that may result from antagonism of muscarinic receptors at the salivary gland, gastrointestinal tract, and central nervous system. In the elderly, there is also the risk of cognitive impairment.

1.3 Drug

Propiverine hydrochloride (propiverine) is a detrusor relaxant drug with antimuscarinic and calcium-modulating properties for the treatment of OAB. Propiverine was first approved in Germany as a 15 mg immediate-release formulation (IR); the 15 mg IR was never marketed in Canada. The modified-release formulation (MR) and extended-release formulations (ER) were developed in order to improve patients' compliance by means of a once daily dosage regimen, and to allow for improved steady-state plasma concentrations. In Canada, propiverine ER is available as 30 mg and 45 mg capsules for adult use, and as propiverine-pediatric that is available in 5 mg tablets.

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For symptomatic treatment of UI and/or increased urinary frequency and urgency in patients with OAB
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TABLE 2: KEY CHARACTERISTICS OF PROPIVERINE, TOLTERODINE, TROSPIUM, DARIFENACIN, SOLIFENACIN, OXYBUTYNIN, FESOTERODINE, AND MIRABEGRON

	Propiverine (Mictoryl, Mictoryl Pediatric)	Tolterodine (Detrol La)	Trospium Chloride (Trosec)	Darifenacin (Enablex)	Solifenacin (Act Solifenacin)	Oxybutynin	Fesoterodine (Toviaz)	Mirabegron (Myrbetriq)
Mechanism of action	Anticholinergic action results in relaxation of bladder smooth muscle, and inhibits the calcium influx and modulating the intracellular calcium in urinary bladder smooth muscle cells causing musculotropic spasmolysis	Competitive muscarinic receptor antagonist	Antispasmodic, antimuscarinic drug that antagonizes the effect of acetylcholine on muscarinic receptors in cholinergically innervated organs	Selective antagonist of the M_3 receptor (the major subtype that modulates urinary bladder muscle contraction)	Competitive muscarinic receptor antagonist with selectivity for the urinary bladder	Tertiary amine anticholinergic drug which exerts antimuscarinic as well as direct antispasmodic action on smooth muscle	Competitive muscarinic receptor antagonist	Selective beta 3-adrenoceptor agonist
Indication[a]	For symptomatic treatment of UI and/or increased urinary frequency and urgency in patients with OAB.	For the symptomatic management of patients with an OAB with symptoms of urinary frequency, urgency, or urge incontinence, or any combination of these symptoms.	For the treatment of OAB with symptoms of urge or mixed UI, urgency, and urinary frequency.	For the treatment of OAB.	For the treatment of OAB in adults with symptoms of urge UI, urinary urgency, and urinary frequency.	For the relief of symptoms associated with voiding in patients with uninhibited neurogenic and reflex neurogenic bladder (i.e., urgency, frequency, urinary leakage, urge incontinence, dysuria).	For the treatment of patients with OAB with symptoms of urinary frequency, urgency, or urge incontinence, or any combination of these symptoms.	For the treatment of OAB with symptoms of urgency, urgency incontinence, and urinary frequency.
Route of administration	p.o.							
Recommended dose	Adults: Mictoryl 30 mg and 45 mg q.d. Children with body weight up to 35 kg: Mictoryl Pediatric 5 mg. Children with body	Initial recommended max. dose is 4 mg q.d. The dose may be reduced to 2 mg q.d. based on individual response and tolerability.	20 mg b.i.d.	Recommended starting dose is 7.5 mg q.d. For those patients starting on 7.5 mg and requiring greater symptom relief, the dose may be increased to 15 mg q.d.	5 mg q.d. The dose may be increased to 10 mg q.d.	Adults: 5 mg b.i.d. or t.i.d. The max. recommended dose is 5 mg q.i.d. Children more than 5 years old: 5 mg b.i.d. The max. recommended dose is 5 mg t.i.d.	Recommended starting dose is 4 mg q.d. The dose may be increased to 8 mg q.d.	Recommended initial dose and usual therapeutic dose is 25 mg q.d. The dose may be increased to a max. recommended dose of 50 mg

	Propiverine (Mictoryl, Mictoryl Pediatric)	Tolterodine (Detrol La)	Trospium Chloride (Trosec)	Darifenacin (Enablex)	Solifenacin (Act Solifenacin)	Oxybutynin	Fesoterodine (Toviaz)	Mirabegron (Myrbetriq)
	weight > 35 kg: max. dose is 30 mg administered in two daily doses							q.d.
Serious side effects or safety issues	Side effects of anticholinergic drugs such as dry mouth, constipation, blurred vision, dizziness, and urinary retention.							Contraindicated in patients with severe uncontrolled hypertension, who are pregnant, and who are hypersensitive to this drug or its ingredient.
	Should be administered with caution in patients with autonomic neuropathy, renal impairment, mild hepatic impairment, cardiac arrhythmia; may induce acute angle-closure glaucoma. Not recommended for children younger than 5 years old.	Contraindicated in patients with urinary retention, gastric retention, uncontrolled narrow angle glaucoma, or hypersensitivity to this drug or its ingredient.	Contraindicated in patients with urinary retention, gastric retention, uncontrolled narrow angle glaucoma, or hypersensitivity to this drug or its ingredient.	Contraindicated in patients with urinary retention, gastric retention, uncontrolled narrow angle glaucoma, or hypersensitivity to this drug or its ingredient.	Contraindicated in patients with urinary retention, dependent on dialysis, with gastroparesis or narrow angle glaucoma, or hypersensitivity to this drug or its ingredient.	Contraindicated in patients with glaucoma, partial or complete obstruction of the gastrointestinal tract, paralytic ileus, intestinal atony of the elderly or debilitated patient, megacolon, toxic megacolon complicating ulcerative colitis, severe colitis, myasthenia gravis, obstructive uropathy, and when the patient has an unstable cardiovascular status in acute hemorrhage; is also contraindicated in patients who have demonstrated hypersensitivity to the product.	Contraindicated in patients with urinary retention, gastric retention, uncontrolled narrow angle glaucoma, or hypersensitivity to this drug or its ingredient.	

b.i.d. = twice daily; max. = maximum; OAB = overactive bladder; p.o. = orally; q.d. = once daily; q.i.d. = four times a day; t.i.d. = three times a day; UI = urinary incontinence.
[a] Health Canada indication.
Source: Health Canada product monographs.[19-26]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of propiverine hydrochloride (Mictoryl/Mictoryl Pediatric) for the symptomatic treatment of UI and/or increased urinary frequency and urgency in patients with OAB.

2.2 Methods

Studies selected for the systematic review included the pivotal trials submitted by the manufacturer in support of the Health Canada–approved indication in addition to trials meeting the selection criteria presented Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient population	Patients (≥ 5 years old) with urinary incontinence and/or increased urinary frequency and urgency in patients with OAB. Subgroups: • Prior treatment experience • Patient age (pediatric and adults).
Intervention	Propiverine hydrochloride at recommended doses: • Adults: 30 mg or 45 mg (MR capsules) once daily • Pediatric patients: 5 mg (coated tablets), with body-weight-adjusted dosage[a]
Comparators[b]	Tolterodine, trospium, darifenacin, solifenacin, oxybutynin, fesoterodine, onabotulinum-toxin A, mirabegron
Outcomes	**Key efficacy outcomes:** Bladder activity: • Incontinence episodes (day and night)[c] • Urge incontinence episodes (day and night)[c] • Achievement of continence • Micturition frequency[c] • Urgency episodes[c] • Nocturia episodes • Pad counts.[c] • HRQoL **Harms outcomes:** • Mortality, SAEs, AEs, WDAEs • Cardiovascular and anticholinergic AEs, cognitive function, dental caries.
Study design	Published and unpublished RCTs

AE = adverse events; HRQoL = health-related quality of life; MR = modified-release formulation; OAB = overactive bladder; RCT = randomized controlled trial; SAE = serious adverse events; WDAE = withdrawal due to adverse events.

[a] 5 mg (body weight adjusted) from the age of five years with OAB; children and adolescents of higher body weight will receive the daily dose of 30 mg propiverine.

[b] At Health Canada–approved dosages.

[c] Outcomes cited as important to patients in the patient's input submission.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates through Ovid, Embase (1974–) through Ovid, and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings) and keywords. The main search concept was Mictoryl (propiverine hydrochloride).

No methodological filters were applied to limit retrieval. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See APPENDIX 2 for the detailed search strategies.

The initial search was completed on November 11, 2016. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on March 15, 2017. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (https://www.cadth.ca/grey-matters):

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4.

3. RESULTS

3.1 Findings From the Literature

A total of three studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4 and described in Section 3.2.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

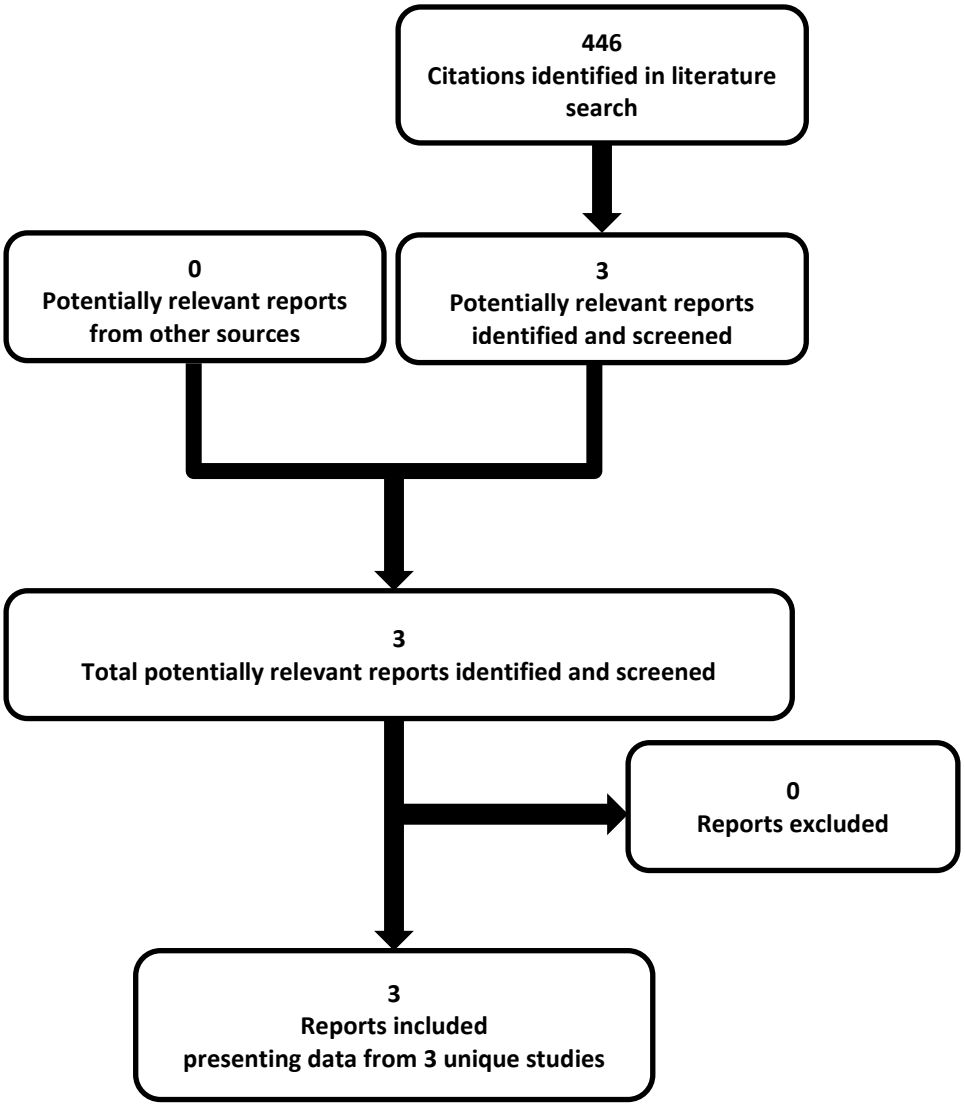

TABLE 4: DETAILS OF INCLUDED STUDIES

		P 659,1	P 1169	P 1300
DESIGNS AND POPULATIONS	**Study design**	Double-blind, double-dummy, placebo and active-controlled adaptive-design, phase III/IV RCT Noninferiority testing between active treatments for the primary outcome	Double-blind, placebo-controlled adaptive-design, phase III RCT	Double-blind, double-dummy, active-controlled RCT Noninferiority testing between active treatments for the primary outcome
	Locations	98 investigation centres in Europe	19 centres in Europe	China
	Randomized (N)	189 patients (until the interim analysis) 988 patients (total included)	60 patients (until the interim analysis) 171 patients total included	324 patients
	Inclusion criteria	Patients ≥ 18 years of age with **overactive bladder** who: • had at **least 2 incontinence** episodes within 3 days • had at **least 10 micturitions within 24 hours**.	Children aged 5 years to 10 years suffering from **overactive bladder** with: • body weight: 17 kg to 45 kg • micturition frequency of at **least 8 micturitions per day** on at least one day of the 3 days during which the bladder diary was completed • **incontinence episodes (at least one episode within** 7 days).	Patients 18 years to 75 years of age with **overactive bladder** for ≥ 3 months with: • at **least 8 micturitions within 24 hours** • urgency and/or urge incontinence • mean voided volume per single micturition less than 200 mL.
	Exclusion criteria	Symptomatic acute urinary infection		
DRUGS	**Intervention**	Propiverine IR (15 mg coated tablets p.o. b.i.d.) Propiverine ER (30 mg capsules p.o. q.d.)	Propiverine IR (5 mg coated tablets), weight-dependent: • 17 kg to 27.9 kg: 10 mg p.o. b.i.d. • 28 kg to 45 kg: 15 mg p.o. b.i.d.	Propiverine ER (30 mg capsules p.o. q.d.)
	Comparator(s)	Placebo (matching both formulations)	Placebo (matching was not specified)	Tolterodine tartrate extended-release tablet (4 mg per day) Placebo
DURATION	**Phase**			
	Run-in	7 days	21 days	14 days
	Double-blind	32 days	56 days	56 days
	Follow-up			
OUTCOMES	**Primary end point**	Incontinence episodes per day	Micturition frequency per day	Micturition frequency per day
	Other end points	Number of micturitions per day, urge episodes per day, volume of micturition, and quality of life	Incontinence episodes per week, incontinence episodes per 3 days, average voided volume, course of maximum voided volume; response rates (decrease by ≥ 1.5 micturitions per day)	Incontinence episodes per day, mean voided volume, patient's feeling of treatment benefit, time of onset of the drug action

		P 659,1	P 1169	P 1300
NOTES	**Publications**	Junemann et al. (2006)[4]	Marschall et al. (2009)[5]	Leng et al. (2017)[6]

b.i.d. = twice daily; CSR = Clinical Study Report; ER = extended-release formulation; IR = immediate-release formulation; N = number of patients; p.o. = orally; q.d. = once daily; RCT = randomized controlled trial.
Source: CSRs for P 659,1,[1] P 1169,[2] and P 1300.[3]

3.2 Included Studies

3.2.1 Description of Studies

The included studies varied from each other in terms of their primary objectives and targeted populations. The primary objective of Study P 659,1 was to compare the efficacy of propiverine hydrochloride immediate-release (propiverine IR), propiverine hydrochloride extended-release (propiverine ER), and placebo in terms of incontinence episodes within 24 hours in adult patients with OAB.[1] The objective of Study P 1169 was to compare the efficacy of propiverine hydrochloride to placebo in children with OAB and UI in terms of micturition frequency per day.[2] Study P 1300 was designed to evaluate the efficacy and safety of propiverine ER in the treatment of OAB in an adult Chinese population with urgency, urinary frequency, and/or urge UI.[3] Studies P 659,1 and P 1300 were noninferiority trials; P 659,1 tested the noninferiority of propiverine ER versus propiverine IR with a noninferiority margin of 0.5 episodes of incontinence per day, and P 1300 tested the noninferiority of propiverine ER versus tolterodine with a noninferiority margin of one micturition episode per day.

Studies P 659,1 and P 1169 were designed to include two separate consecutive cohorts.[1,2] [redacted].[1,2] Therefore, in these two studies a first cohort was conducted in order to inform the estimation of sample size for a second cohort (Cohort II). The same inclusion and exclusion criteria and interventions were used in both cohorts.

3.2.2 Populations

a) Inclusion and exclusion criteria

The included studies enrolled patients with OAB. However, there were subtle differences in the inclusion criteria between them. For example, Study P 659,1 focused mainly on adult patients with incontinence, while the emphasis of studies P 1169 and P 1300 were mainly on patients with frequent micturitions. Furthermore, Study P 1169 evaluated the efficacy of propiverine in pediatric patients, while P 659,1 and P 1300 included adult patients.

The three studies excluded patients with acute urinary infections, but there also were specific exclusion criteria for each study. For example, Study P 659,1 excluded patients who had post-void residual urine greater than or equal to 100 mL, neurogenic bladder dysfunction, or detrusor hypo– and hyperreflexia. Study P 1169 excluded patients who had bladder capacity [mL] ≥ (age + 1) × 30 [mL], post-void residual urine greater than 10 mL, dysfunctional voiding and detrusor-sphincter dyssynergy, and patients who had constipation. Both Study P 659,1 and Study P 1300 excluded patients with stress incontinence.

b) Baseline characteristics

A summary of baseline characteristics is provided in Table 5.

Studies P 659,1 and P 1300 included mainly female patients (90% and 75% respectively), while P 1169 included primarily male patients (almost 62%). The mean age in P 659,1 was 56 years, and it was 50 years in P 1300; the mean age in P 1169 was seven years.
The mean number of micturitions per day (24 hours) at baseline was the highest in Study P 1300, followed by Study P 659,1; the least number of micturitions was recorded in Study P 1169 (15, 14 and nine, respectively). The mean number of incontinence episodes per 24 hours was 3.4 episodes in Study P 659,1, 0.9 episodes in P 1169, and one episode per day in P 1300. In P 1300, the mean episodes of incontinence in the propiverine groups was 1.3, and it was 0.6 episodes in the tolterodine group.

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS

	P 659,1 [a]			P 1169 [b]		P 1300 [c]	
	Propi. ER 30 mg q.d.	**Propi. IR 15 mg b.i.d.**	**Placebo**	**Propi. IR-Pediatric**	**Placebo**	**Propi. ER 30 mg q.d.**	**Tolterodine ER, 4 mg q.d.**
N	391	395	202	84[a,b]	80[a,b]	162	162
Sex, males n (%)	43 (11.0)	42 (10.6)	19 (9.4)	49 (58.3)	55 (68.8)	41 (25.3)	39 (24.1)
Ethnicity, n (%)							
• Caucasian	391 (100)	394 (99.7)	202 (100)	Not reported			
• Chinese	–	–	–				
• Other	–	1 (0.3)	–				
Age (years), mean (SD)	[redacted]	[redacted]	[redacted]	7 (1.6)	7 (1.4)	50.9 (15.9)	49.1 (14.7)
Weight (kg), mean (SD)	Not reported			26.8 (6.7)	26.2 (5.4)	61.4 (9.9)	60.1 (10.4)
Number of micturitions; mean (SD)							
• Per day	[redacted]	[redacted]	[redacted]	8.9 (2.2)	9.1 (2.5)	15.2 (5.8)	14.7 (6.0)
• Per night	[redacted]	[redacted]	[redacted]				
Incontinence episodes, mean (SD)	3.4 (2.8)	3.3 (2.7)	3.5 (3.6)	0.8 (0.8)	1.1 (1.0)	1.3 (3.1)	0.6 (1.6)
Incontinence, n (%)							
• With urge	[redacted]	[redacted]	[redacted]	Not reported		47 (29.0)	41 (25.3)
• Without urge	[redacted]	[redacted]	[redacted]			Not reported	
• At physical strain	-	-	-				
• Without reason	[redacted]	[redacted]	[redacted]				

b.i.d. = twice daily; CSR = Clinical Study Report; ER = extended-release formulation; IR = immediate-release formulation; ITT = intention to treat; n = number of patients with event; N = number of patients; propi. = Propiverine; q.d. = once daily; SD = standard deviation.
[a] Safety population.
[b] ITT population.
[c] Full analysis set.
Source: CSRs for P 659,1,[1] P 1169,[2] P 1300,[3] Junemann et al. (2006),[4] and Marschall-Kehrel et al. (2009).[5]

3.2.3 Interventions

In Study P 659,1, patients were treated with either 30 mg propiverine ER once daily, 15 mg propiverine IR twice daily, or placebo for 32 days, each of which was taken orally. To maintain the blinding, each patient took one capsule and one tablet in the morning and one tablet in the evening. Propiverine IR is a registered drug (Mictonorm) to be used at a dose of 15 mg twice daily (i.e., 30 mg per day). The same dose was chosen for propiverine ER (i.e., 30 mg once daily), to show noninferiority compared with propiverine IR.

Patients in Study 1169 were treated orally with either propiverine hydrochloride or placebo for 56 days. Depending on their body weight, the patient was assigned either to Group A (17 kg to 27.9 kg) with a dose of 10 mg twice daily, or Group B (28 kg to 45 kg) with a dose of 15 mg twice daily.

- Group A: took two coated tablets in the morning and two coated tablets in the evening with either 10 mg twice daily propiverine hydrochloride or 10 mg twice daily placebo, randomized in a ratio of 1:1.
- Group B: took three coated tablets in the morning and three coated tablets in the evening with either 15 mg twice daily propiverine hydrochloride or 15 mg twice daily placebo, randomized in a ratio of 1:1.

Due to the ranges in body weight, the dose per kg varied between 0.3 mg twice daily and 0.6 mg twice daily.

In Study P 1300, patients received either 30 mg of propiverine ER once daily or 4 mg of tolterodine once daily for 56 days, each taken orally. To maintain the blinding, each patient took one capsule and one tablet in the evening.

3.2.4 Outcomes

Change in the number of incontinence episodes per 24 hours was the primary outcome in Study P 659,1, and it was a secondary outcome in studies P 1169 and P 1300. Patients recorded the number of incontinence episodes within 24 hours in their micturition diaries for at least three consecutive days during the run-in period and for at least three consecutive days between visit three and visit four. The arithmetic means were calculated for each measurement period and were used for the statistical evaluation. There is no known minimal clinically important difference (MCID) for incontinence treatment.

The three included studies reported the number of micturitions per day. The number of micturitions for a single day was defined as the sum of all micturition numbers recorded in the bladder diary corresponding to that day. The change 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. None of the included studies provided information regarding a desired or estimated MCID to be achieved from treatment.

Study P 659,1 evaluated the impact of treatment on QoL as measured with the King's Health Questionnaire (KHQ). The validity of the questionnaire is summarized in APPENDIX 3. The standard version of KHQ is a 21-item disease-specific questionnaire that has been developed and validated for patients with UI.[27] The KHQ consists of nine domains: general health perceptions, impact on life, role limitations, physical limitations, social limitations, personal relationships, emotions, sleep/energy, and incontinence severity measures. Item scores are converted to a standardized scale. Scores for the KHQ range from zero to 100, where zero indicates the best outcome or response and 100 indicates the worst outcome or response.[27] The KHQ is a validated and widely used instrument in the study of OAB. However, the evidence of their validity showed a weak to moderate correlation between these instruments and patient-reported symptoms (correlation coefficient for bivariate analysis [*r*] = 0.16 to 0.42) in clinical trials. The recommended MCID for KHQ is five to 10 points.

None of the included studies reported on achievement of continence, nocturia, or pad counts.

3.2.5 Statistical analysis

a) Data sets analyzed

Study P 659,1 defined four data sets: safety population, intention-to-treat (ITT) population, per-protocol (PP) population and a modified PP population. Each data set was defined as following:

- **Safety data set:** All patients who received at least one dose of randomized study medication.
- **ITT data set:** All patients who received at least one dose of randomized study medication and had at least one post-baseline assessment of any efficacy variable.
- **PP data set:** All patients of the ITT population who completed the study and for whom no major protocol deviations either before or during the trial were observed and for whom the primary efficacy variable has been assessed. Patients who terminated the study prematurely due to insufficient efficacy and who had no major protocol violations were included in the analysis of the PP population. For the primary efficacy variable a change of zero was assumed for these patients if no under treatment diaries were available.
- **Modified PP data set:** PP population without the patients with a baseline volume of micturition per 24 hours of above 3.5 L (mean of values from up to three days).

Study P 1169 included four data sets that were defined as the following:

- **Safety data set:** All patients who received at least one dose of randomized study medication.
- **ITT data set:** All patients who received at least one dose of randomized study medication and provided diary data to allow the calculation of the primary efficacy variable. Patients who terminated prematurely due to insufficient efficacy and who provided no diary data at end of treatment were included in the ITT population. They were considered “non-responders” and a change of zero for the change-from-baseline variables was assumed.
- **Modified ITT data set:** All patients of the ITT population, but excluding patients of one centre that had serious deviations from the ICH-GCP) guidelines. The deviations were identified during an audit. The patients at this centre were included in the ITT population, but excluded from the modified ITT and PP populations. The modified ITT population was used in sensitivity analyses of the primary variable.
- **PP data set:** All patients of the modified ITT population who completed the trial and for whom no major protocol deviations either before or during the trial were observed. Patients who terminated the trial prematurely due to insufficient efficacy and who had no major protocol violations were included in the analysis of the PP population. If no diary data were available at end of treatment, then the same imputations as described for the ITT population were applied to these patients.

Study P 1300 defined the following data sets:

- **Safety data set:** All patients who received at least one dose of study medication and having safety records after medication were included in the safety analysis set (SAS). The SAS was used for safety analysis.
- **Full analysis set (FAS):** According to ITT, all randomized patients who received at least one dose of study medication were included in FAS. The last observation carried forward was applied for missing values.
- **PP data set:** All patients with good compliance, complying with the study protocol, neither taking forbidden medication nor violating the protocol. The PP set was used for the efficacy analysis.

In this review, ITT efficacy analyses are reported (FAS for Study P 1300), except for the analyses on the primary outcome measures of “change in the number of incontinence episodes per 24 hours” in Study P 659,1 and “change in the micturition frequency per 24 hours” in Study P 1300, which were based on a

noninferiority test, and the PP population are reported. For safety outcomes, safety data sets are reported.

b) Summary of the analysis plan

Study P 659,1

The primary efficacy variable (difference in incontinence episodes per 24 hours) was evaluated with the following a priori ordered system of hypotheses to test:

- Noninferiority of propiverine ER to propiverine IR (0.5 episode of incontinence was used as noninferiority threshold).
- Superiority of propiverine IR over placebo.
- Superiority of propiverine ER over placebo.

In this study, efficacy data were analyzed for the ITT and for the PP population. The PP population was considered as primary efficacy analysis. To this end, the data of the PP population were analyzed with an analysis of covariance (ANCOVA) with the factors treatment and country and the covariate baseline value.

In a first step, the tests were performed for Cohort II patients only by means of ANCOVA with baseline values as a covariate and with "treatment" and "country" as factors. For each of the three tests, only the two treatment groups under consideration were submitted to the ANCOVA. For the analysis of the shifted noninferiority hypothesis, the value 0.5 was subtracted from the analysis variable (difference "baseline minus end of treatment" in the number of incontinence episodes) for the propiverine IR group.

In a second step, the corresponding *P* values for each of the three hypotheses from Cohort I and Cohort II were multiplied. The resulting three products of *P* values were checked in the order of the hypotheses as specified in the aforementioned versus the pre-specified critical value $c_\alpha = 0.0038$.

The secondary efficacy variables were analyzed with an ANCOVA with the factors "treatment," "country," and the covariate baseline value. These analyses were considered exploratory. All safety analyses were conducted only on the pooled safety populations of both cohorts.

Study P 1169

The primary efficacy variable (difference in micturition episodes per 24 hours) was evaluated with an ANCOVA with the factors treatment and dose group and the covariate baseline value. The adaptive design of Bauer and Köhne was used to adjust for multiple testing due to the interim analysis. Otherwise no multiplicity issue occurs, since the primary objective involves the comparison of only two groups regarding only one single primary end point.

The following secondary efficacy variables were analyzed with an ANCOVA with the factors treatment and dose group and the covariate baseline value: change of number of incontinence episodes in the last seven days per day, change of number of incontinence episodes in the last seven days per night, change of number of incontinence episodes per 24 hours, change of average voided volume per micturition, change of volume of micturitions per 24 hours, change of liquid intake per 24 hours, change of maximum voided volume and maximum voided volume at end of treatment. Evaluation of efficacy by parents, patient and/or investigator and response rates were analyzed using Cochran-Mantel-Haenszel tests. These analyses were considered exploratory.

Study P 1300

From the provided information, the sample size of this trial was estimated using a standard deviation for the two groups of 3.0, and a change in the mean micturition frequency per 24 hours on the basis of continuous three-day records of the two groups as 3.2. The noninferiority margin was set at 1.0 with an alpha of 0.05 and power of 80%.

3.3 Patient Disposition

Patient disposition is summarized in Table 6.

Study discontinuation rate was highest in Study P 1300 (11.4%), while it ranged from 3.4% to 6.6% in studies P 659,1 and P 1169. AEs were the most prevalent reason for study discontinuation in all three studies.

TABLE 6: PATIENT DISPOSITION

	Study P 659,1			Study P 1169		Study P 1300	
	Propi. ER 30 mg q.d.	**Propi. IR 15 mg b.i.d.**	**Placebo**	**Propi. IR-Pediatric**	**Placebo**	**Propi. ER 30 mg q.d.**	**Tolterodine ER, 4 mg q.d.**
Randomized, N	391[a]	395[a]	202[a]	87[a]	84[a]	162	162
Discontinued, N (%)	23 (5.9)	26 (6.6)	11 (5.4)	3 (3.4)	4 (4.8)	14 (8.6)	23 (14.2)
• AE	11 (2.8)	15 (3.8)	1 (0.5)	2 (2.3)	1 (1.2)	5 (3.1)	12 (7.4)
• Patient absent for evaluation (i.e., poor compliance)	[redacted]	[redacted]	[redacted]	0	1 (1.2)	2 (1.2)	1 (0.6)
• Protocol violation	[redacted]	[redacted]	[redacted]	–	–	4 (2.5)	4 (2.5)
• insufficient efficacy	[redacted]	[redacted]	[redacted]	0	1 (1.2)	–	–
• Loss of follow-up	–	–	–	–	–	3 (1.9)	5 (3.1)
• Withdrew informed consent	–	–	–	–	–	0	1 (0.6)
• Other reason	[redacted]	[redacted]	[redacted]	1 (1.1)	1 (1.2)	–	–
ITT, N (%)	384 (98.2)	391 (99.0)	199 (98.5)	84 (96.6)	80 (95.2)	162 (100)	162 (100)
PP, N (%)	363 (92.8)	360 (91.1)	187 (92.6)	64 (73.6)	63 (75.0)	148 (91.4)[b]	139 (85.8)[b]
Safety, N (%)	391 (100)	395 (100)	202 (100)	87 (100)	84 (100)	162 (100)	162 (100)
Modified ITT, N (%)	–	–	–	78 (89.7)	76 (90.5)	–	–

AE = adverse event; b.i.d. = twice daily; CDR = CADTH Common Drug Review; CSR = Clinical Study Report; ER = extended-release formulation; IR = immediate-release formulation; ITT = intention-to-treat; N = number of patients; PP = per-protocol; propi. = propiverine; q.d. = once daily.
[a] For pooled Cohort I and Cohort II (Study P 659,1: 189 patients were enrolled in Cohort I; 799 patients were enrolled in Cohort II; Study P 1169: 63 patients were enrolled in Cohort I, 108 patients were enrolled in Cohort II).
[b] Calculated by CDR.
Source: CSRs for P 659,1,[1] P 1169,[2] P 1300;[3] Junemann et al. (2006),[4] and Leng et al. (2017).[6]

3.4 Critical Appraisal

3.4.1 Internal validity

In the three included studies, randomization was achieved with a centralized electronic system, and each patient had a unique randomization number and a corresponding number of study drug supplies. The authors used double-dummy methods when there were two active treatments included in the study; in this method, patients were given placebo capsules or tablets corresponding to the capsules or tablets of the active treatments used in the studies. Doing so, patients were not likely to identify the active treatment to which they were randomized. However, due to the differences in the frequency of certain AEs between the active treatments and placebo, such as dry mouth, it was possible that patients could identify their active treatment. In Study P 1300, this was not likely to happen because of the use of

two active treatments that have a similar mechanism of action (anticholinergic effect); therefore, their adverse effect profiles are not significantly different.

Study P 659,1 as well as Study P 1300 contained noninferiority evaluation of the primary outcome of each study (difference in incontinence and micturition respectively). The authors used 0.5 and 1.0 as noninferiority margins for incontinence and micturition respectively without providing a clear rational for their selection. However, the clinical experts consulted for this review estimated that these margins are clinically reasonable. The primary analyses of noninferiority were based on the PP data sets; this approach is reasonable because PP data provide more conservative estimation for the noninferiority evaluation. The authors also reported the results using the ITT data sets, and results were consistent between the difference data sets. Across all three included studies, the ITT analyses sets were not true ITT analysis sets as they were based on a modified ITT population (i.e., included patients who received at least one dose of randomized study medication).

Studies P 659,1 and P 1169 designed their studies as two consecutive cohorts. The first cohort included a relatively small sample size, and the results of the first cohorts were used to inform the sample size estimation for the second cohorts. The authors adjusted their threshold criteria (*P* value) to compensate for the multiple analyses of the primary outcomes. All secondary outcomes were declared by the authors as exploratory, and no further adjustments were performed on them.

Study P 1169 reported that one study centre had serious deviation from the ICH-GCP guidelines, and they had to exclude the results from this centre in the modified ITT analysis. The deviation of this centre was identified before the data lock, and they reported the results with and without excluding this centre. Therefore, it was not likely that the overall results of Study P 1169 would be affected with this deviation.

Study P 1300 included limited information about the statistical methods used in the analysis in the English language. The report included the original study report in Chinese language, but this content was not reviewed. The discontinuation rate in Study P 1300 was high (8.6% to 14.2%); however, the dropout rate is still below what the clinical experts consulted for the review would expect to see in clinical practice. Finally, given the imbalance in baseline incontinence frequency between the propiverine ER and tolterodine groups (1.3 versus 0.6 for propiverine ER and tolterodine respectively) the statistically significant difference between groups reported for the incontinence frequency outcome should be interpreted with caution.

None of the included studies provided information about what could be considered MCID for the evaluated outcomes. The interpretation of these data was limited to the statistical significance and what was considered clinically significant by the consulted clinical experts.

3.4.2 External validity

Several issues were noticed that could affect the external validity of the included studies. Studies P 659,1 and P 1300 included mainly Caucasian or Chinese adults; consequently, their results might not be representative to all Canadian patients from other ethnicities who have OAB. Furthermore, the clinical experts raised concerns about the low baseline frequency of micturition in Study P 1169 and the incontinence episodes in Study P 1300. The clinical experts confirmed that there is no clear threshold of micturition per day to consider that a certain patient has OAB, and the clinician has to take into consideration the impact of micturition frequency on function and daily activities as well. However, the

clinical experts considered nine micturition episodes per day to be slightly lower than what they would expect to see in clinical trials.

The use of a 30 mg ER dose of propiverine was mainly based on the approved daily dosage of propiverine IR (15 mg twice daily) used in Europe, and the manufacturer indicated that a bioequivalence evaluation supported the choice of the treatment dosage. There was no evidence available to assess the comparative efficacy of propiverine ER 45 mg that was also approved for use in Canada. Furthermore, no randomized controlled trial (RCT) evidence was provided to assess the efficacy and safety of propiverine-pediatric compared with active treatments such as oxybutynin. One study assessing the efficacy, tolerability, and safety of propiverine versus oxybutynin in the pediatric population was submitted by the manufacturer as supporting evidence; however such evidence was limited to an observational study design and was not included in the CDR review.[28]

None of the included studies reported results of incontinence or micturition during the night, achievement of continence, nocturia, or pad counts. These outcomes were considered important by the consulted clinical experts and/or by the patients' group who provided input to this review (APPENDIX 1). In the regulatory decision summary of propiverine by Health Canada, it is stated that "long-term studies on OAB adult patients confirmed that there was no loss of efficacy up to 2 years of propiverine treatment."[29] However, it is unclear what evidence this statement was based on. The consulted clinical experts estimated that the length of the included studies was not sufficient to reflect the long-term efficacy and safety of the evaluated treatments. The clinical experts emphasized that OAB patients have a tendency to lose interest with the treatment due to the long-term AEs of the anticholinergic drugs; they reported that treatment withdrawal could reach 40% to 60%. Such withdrawal rates could not be captured in the included studies due to their relatively short durations.

3.5 Efficacy

Only those efficacy outcomes identified in the review protocol are reported in the following (Section 2.2, Table 3).

3.5.1 Incontinence episodes (day/night)

A summary of incontinence results is reported in Table 7.

Study P 659,1 demonstrated that propiverine ER was noninferior to propiverine IR; the least square difference between the two formulations in terms of change from baseline in incontinence within 24 hours was [redacted] episodes. Furthermore, the study showed the superiority of propiverine ER and IR over placebo; the least square differences (95% confidence interval) were [redacted] and [redacted] for the two formulations respectively. These results were consistence for the ITT and PP analyses data sets.

Studies P 1169 and P 1300 demonstrated that propiverine was superior to placebo and tolterodine in reducing incontinence episodes within 24 hours, respectively; P 1169 reported that the least square difference between propiverine-pediatric and placebo was [redacted], but P 1300 did not report the difference between propiverine ER and tolterodine.

Despite the statistical significance of the reported comparisons, the clinical experts consulted for this review indicated that the reported differences between groups did not reach a clinically significant difference. The clinical experts recognized, however, that the change is similar to the effect seen for other antimuscarinics.

TABLE 7: SUMMARY OF INCONTINENCE FREQUENCY

	Study P 659,1 [b]			Study P 1169 [c]		Study P 1130 [d]	
Incontinence Episodes Within 24 Hours, Mean (SD)[a]	**Propi. ER 30 mg q.d.**	**Propi. IR 15 mg b.i.d.**	**Placebo**	**Propi. IR-Pediatric**	**Placebo**	**Propi. ER 30 mg q.d.**	**Toltero. ER 4 mg q.d.**
N	363	360	187	[redacted]	[redacted]	162	162
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.3 (3.1)	0.6 (1.6)
End of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.3 (1.6)	0.3 (1.1)
Reduction from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.9 (2.1)	0.3 (1.1)
Differences[e] (95% CI)							
Propiverine IR vs. ER	*P* value [redacted];[f]; Propi. IR – ER (95% CI): [redacted]			Not applicable			
Propiverine ER vs. placebo	*P* value [redacted] ER – placebo (95% CI): [redacted]						
Propiverine IR vs. placebo	*P* value = [redacted]; IR – placebo (95% CI): [redacted]						
Propi-pediatric vs. placebo	Not applicable			*P* value = 0.0005 Propi. – placebo (95% CI): [redacted]		Not applicable	
Propiverine ER vs. tolterodine				Not applicable		*P* value = 0.0275 Propi. ER – tolterodine (95% CI) Not reported	

b.i.d. = twice daily; CI = confidence intervals; ER = extended-release formulation; FAS = full analysis set; IR = immediate-release formulation; ITT = intention-to-treat; n = number of patients with event; N = number of patients; *P* = probability; PP = per-protocol; Propi. = Propiverine; q.d. = once daily; SD = standard deviation; Toltero. = Tolterodine; vs. = versus.

[a] The types of incontinence were not specified in Study P 659,1 and Study P 1169. Based on additional information provided by the manufacturer,[30] it was indicated that "urge incontinence" was evaluated exclusively in Study P 1300.

[b] PP population data (propiverine ER: n = 363; propiverine IR: n = 360; placebo: n = 187).

[c] ITT population data (propiverine IR: n = 84; placebo: n = 80).

[d] FAS (propiverine ER: n = 162; tolterodine: n = 162).

[e] Least square differences.

[f] One-sided *P* value for shifted noninferiority hypothesis.

Source: CSRs for P 659,1,[1] P 1169,[2] P 1300;[3] Junemann et al. (2006),[4] and Leng et al. (2017)[6].

3.5.2 Urge incontinence episodes (day/night)

The types of incontinence episodes were not explicitly stated for P 659,1 or P 1300. Based on additional information provided by the manufacturer,[30] it was indicated that "urge incontinence" was measured exclusively in P 1300. Study results with respect to the change in urge incontinence episodes from baseline between treatment groups are presented in Section 3.5.1. Study P 659,1 did not specify whether "urge incontinence episodes" were measured exclusively. Urge incontinence episodes were not assessed in Study P 1169.

3.5.3 Achievement of continence

No results reported.

3.5.4 Micturition frequency

Results of micturition frequency are provided in Table 8.

Study P 659,1 showed that propiverine ER was not statistically different from propiverine IR for change in micturition frequency within 24 hours from baseline ([redacted]). However, both propiverine formulations (ER and IR) were statistically significantly different from placebo; the least square differences from placebo were [redacted](95% confidence interval [redacted]) and [redacted](95% confidence interval [redacted]) for the ER and IR formulations respectively.

Studies P 1169 and P 1130 reported that propiverine was statistically significantly different from placebo and tolterodine. The least square difference between propiverine-pediatric was [redacted]. Study P 1300 reported a mean difference of [redacted] between the two groups (tolterodine and propiverine ER). The upper limit of 95% confidence interval did not exceed the noninferiority margin (1.0) stated in the protocol.

The clinical experts consulted for this review estimated that the reported differences between groups did not reach a clinically significant difference.

TABLE 8: SUMMARY OF MICTURITION FREQUENCY (ITT POPULATION UNLESS OTHERWISE STATED)

	Study P 659,1			Study P 1169		Study P 1300 [a]	
Micturition Frequency Within 24 Hours, Mean (SD)	**Propi. ER 30 mg q.d.**	**Propi. IR 15 mg b.i.d.**	**Placebo**	**Propi. IR-Pediatric**	**Placebo**	**Propi. ER 30 mg q.d.**	**Toltero. ER 4 mg q.d.**
N	384	391	199	[redacted]	[redacted]	148	139
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15.2 (5.8)	14.7 (6.0)
End of treatment	9.043 (3.071)	9.120 (3.250)	10.275 (3.832)	[redacted]	[redacted]	10.6 (4.5)	10.9 (4.8)
Change from baseline	3.631 (2.962)	3.659 (2.792)	2.968 (3.567)	[redacted]	[redacted]	4.6 (4.1)	3.8 (5.1)
Differences[b] (95% CI)							
Propiverine IR – ER	*P* value [redacted]			Not applicable			
Propiverine ER – placebo	*P* value[c] [redacted]						
Propiverine IR – placebo	*P* value[c] [redacted]						
Propi.-pediatric – placebo	Not applicable			*P* value[d] = 0.0007; [redacted]		Not applicable	
Tolterodine – Propiverine ER				Not applicable		[redacted], *P* value NR	

b.i.d. = twice daily; CI = confidence interval; CSR = Clinical Study Report; ER = extended-release formulation; IR = immediate-release formulation; ITT = intention-to-treat; n = number of patients with event; N = number of patients; NR = not reported; *P* = probability; propi. = propiverine; q.d. = once daily; SD = standard deviation; toltero. = tolterodine.

[a] Per-protocol population (propiverine ER: n = 148; tolterodine: n = 139).

[b] Least square differences.

[c] Two-sided *P* values for classical null-hypothesis.

[d] One-sided *P* value of treatment for the ITT population was used in the confirmatory analysis (one-sided level: 0.025).

Source: CSRs for P 659,1,[1] P 1169,[2] P 1300;[3] Junemann et al. (2006),[4] and Leng et al. (2017).[6]

3.5.5 Urgency episodes

Results of urgency frequency are provided in Table 9.

Study 659,1 reported that propiverine ER was not statistically different from propiverine IR; the least square difference between the two treatments was 0.37 episodes of urgency. The least square difference between propiverine ER and placebo was [redacted] (95% confidence interval [redacted]); this difference was statistically significant. The clinical experts estimated that the difference between propiverine ER and placebo was clinically modest. However, propiverine IR was not statistically significantly different from placebo in terms of difference in change from baseline in urgency frequency.

Neither P 1169 nor P 1130 reported the effect of treatment on urinary urgency.

TABLE 9: SUMMARY OF URGENCY FREQUENCY (INTENTION-TO-TREAT POPULATION)

	Study P 659,1		
Urgency Frequency Within 24 Hours, Mean (SD)	**Propi. ER 30 mg q.d.**	**Propi. IR 15 mg b.i.d.**	**Placebo**
N	384	391	199
Baseline	6.369 (4.166)	6.192 (3.842)	6.220 (4.212)
End of treatment	3.805 (3.269)	4.112 (3.638)	4.503 (4.034)
Change from baseline	2.882 (3.356)	2.578 (3.396)	1.889 (4.003)
Differences (95% CI)			
Propiverine IR – ER	*P* value[a] = [redacted]; [redacted]		
Propiverine ER – placebo	*P* value[a] = [redacted]; [redacted]		
Propiverine IR – placebo	*P* value[a] = [redacted]; [redacted]		

b.i.d. = twice daily; CI = confidence interval; CSR = Clinical Study Report; ER = extended-release formulation; IR = immediate-release formulation; N = number of patients; *P* = probability; propi. = propiverine; q.d. = once daily; SD = standard deviation.
[a] Two-sided *P* values for classical null-hypothesis.
Source: CSR for P 659,1.[1]

3.5.6 Nocturia episodes

No results reported.

3.5.7 Pad counts

No results reported.

3.5.8 Health-related quality of life

Study 659,1 reported results for the KHQ, and Table 10 provides a summary of these results. In terms of total score, propiverine ER was not statistically significantly different from propiverine IR or placebo.

TABLE 10: SUMMARY OF KING'S HEALTH QUESTIONNAIRE (INTENTION-TO-TREAT POPULATION)

	Study P 659,1		
Mean (SD)	Propi. ER 30 mg q.d.	Propi. IR 15 mg b.i.d.	Placebo
General health perception			
N	363	369	189
Baseline	46.5 (21.3)	46.5 (21.3)	45.9 (20.5)
End of treatment	35.1 (19.2)	35.5 (18.5)	39.6 (21.3)

	Study P 659,1		
Mean (SD)	Propi. ER 30 mg q.d.	Propi. IR 15 mg b.i.d.	Placebo
Change from baseline	10.9 (20.3)	11.3 (21.8)	6.9 (19.3)
Incontinence impact			
N	[redacted]	[redacted]	[redacted]
Baseline	[redacted]	[redacted]	[redacted]
End of treatment	[redacted]	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]	[redacted]
Role limitation			
N	[redacted]	[redacted]	[redacted]
Baseline	[redacted]	[redacted]	[redacted]
End of treatment	[redacted]	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]	[redacted]
Physical limitation			
N	[redacted]	[redacted]	[redacted]
Baseline	[redacted]	[redacted]	[redacted]
End of treatment	[redacted]	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]	[redacted]
Social limitation			
N	[redacted]	[redacted]	[redacted]
Baseline	[redacted]	[redacted]	[redacted]
End of treatment	[redacted]	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]	[redacted]
Total score			
N	[redacted]	[redacted]	[redacted]
Baseline	[redacted]	[redacted]	[redacted]
End of treatment	[redacted]	[redacted]	[redacted]
Change from baseline	19.288 (20.049)	19.028 (20.261)	13.895 (17.066)
Differences (95% CI)			
Propiverine IR vs. ER	*P* value[a] [redacted]		
Propiverine ER vs. placebo	*P* value[a] [redacted]		
Propiverine IR vs. placebo	*P* value[a] [redacted]		

b.i.d. = twice daily; CI = confidence interval; CSR = Clinical Study Report; ER = extended-release formulation; IR = immediate-release formulation; N = number of patients; *P* = probability; propi. = propiverine; q.d. = once daily; SD = standard deviation; vs. = versus.
[a] Two-sided *P* values for classical null-hypothesis.
Source: CSR for P 659,1.[1]

3.6 Harms

A summary of harm outcomes is provided in Table 11.

3.6.1 Adverse events

Rate of AEs varied from 20% in the placebo groups of P 659,1 and P 1169 to 45% in propiverine ER group in P 1300. The most common treatment-emergent AE was dry mouth; it was frequently reported in propiverine ER (22% to 28%), propiverine IR (23%), and tolterodine (27%). Propiverine-pediatric was associated with 3.4% of dry mouth cases compared with 0% in the placebo group.

In Study P 659,1, blurred vision was reported more frequently with patients treated with propiverine ER (4.6%) than propiverine IR or placebo (3.8% and 0.5% respectively). Influenza was also more frequently reported in propiverine-pediatric than placebo in Study P 1169 (4.6% versus 1.2% respectively).

3.6.2 Serious adverse events

Serious adverse events (SAEs) were limited to one case of femoral neck fracture in the propiverine ER group in Study P 659,1. Study P 1300 reported one case each of dysphagia, bladder tumour, common cold complicated by pneumonia, and pregnancy — all of which were reported in the tolterodine group.

3.6.3 Withdrawals due to adverse events

Withdrawals due to adverse events (WDAEs) ranged from 2.3% to 3.1% in the propiverine treatment groups across studies. Study P 1300 reported 7.4% of WDAEs in the tolterodine group compared with 3.1% for propiverine ER group.

3.6.4 Mortality

There were no deaths reported in the included studies.

3.6.5 Notable harms

None of the included studies reported AEs related to cognitive functioning, mood, or dental caries. AEs related to the anticholinergic effects of treatments were most commonly dry mouth and blurred vision (both described above).

Palpitation and chest depression were reported in P 659,1 and P 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%.

TABLE 11: HARMS (SAFETY POPULATION)

	Study P 659,1			Study P 1169		Study P 1300	
	Propiverine ER 30 mg q.d.	**Propiverine IR 15 mg b.i.d.**	**Placebo**	**Propiverine IR-Pediatric**	**Placebo**	**Propiverine ER 30 mg q.d.**	**Tolterodine ER 4 mg q.d.**
N	391	395	202	87	84	162	162
Death, n (%)	0	0	0	0	0	0	0
Serious adverse events, n (%)	1 (0.3)[a]	0	0	0	0	0	4 (2.5)[b]
Withdrawal due to adverse events, n (%)	11 (2.8)	14 (3.5)	1 (0.5)	2 (2.3)	1 (1.2)	5 (3.1%)	12 (7.4%)
• Gastrointestinal disorders	[redacted]	[redacted]	0	[redacted]	[redacted]	0	0
Patients with treatment-emergent adverse events,[c] n (%)	134 (34.3)	152 (38.5)	41 (20.3)	20 (23.0)	17 (20.2)	73 (45.1)	68 (42.0)
• Dry mouth	85 (21.7)	90 (22.8)	13 (6.4)	3 (3.4)	0	45 (27.7)	43 (26.5)
• Constipation	13 (3.3)	15 (3.8)	2 (1.0)	2 (2.3)	0	5 (3.1)	2 (1.2)
• Nausea	6 (1.5)	10 (2.5)	2 (1.0)	None reported		Cases were not summarized[d]	
• Vision blurred	18 (4.6)	15 (3.8)	1 (0.5)	[redacted]	[redacted]		
• Dry eye	None reported					4 (2.5)	1 (0.6)
• Influenza	[redacted]	[redacted]	[redacted]	4 (4.6)	1 (1.2)	None reported	
• Urinary tract infection	[redacted]	[redacted]	[redacted]	2 (2.3)	1 (1.2)	Cases were not summarized[d]	
• Palpitation/chest depression	[redacted]	[redacted]	[redacted]	None reported		2 (1.2)	4 (2.5)

b.i.d. = twice daily; CSR = Clinical Study Report; ER = extended-release formulation; IR = immediate-release formulation; n = number of patients with event; N = number of patients; q.d. = once daily.
[a] Femoral neck fracture.
[b] These were dysphagia, bladder tumour, common cold complicated by pneumonia, and pregnancy.
[c] Frequency of less than 2%.
[d] Several cases were reported as individual reimbursements, but these cases were not summarized and counted for each group.
Source: CSRs for P 659,1,[1] P 1169,[2] and P 1300.[3]

4. DISCUSSION

4.1 Summary of Available Evidence

Three manufacturer-sponsored studies were included in this review. All studies were randomized, multi-centre, double-blind (DB) placebo and/or active-controlled trials. Study P 659,1 (number of patients [N] = 988) compared propiverine ER versus propiverine IR and placebo in adult OAB patients, while Study P 1169 (N = 171) compared propiverine-pediatric versus placebo in OAB pediatric patients five years to 10 years old and Study P 1300 (N = 324) compared propiverine ER versus tolterodine in adult Chinese patients with OAB. The duration of Study P 659,1 was 32 days, while studies P 1169 and P 1300 evaluated therapy over 56 days. Change in daily incontinence episodes was the primary outcome in Study P 659,1, and was a secondary outcome for P 1169 and P 1300. The primary outcome for P 1169 and P 1300 was the change in daily micturition episodes, which was also a secondary outcome for P 659,1. Other secondary outcomes for Study P 659,1 included daily urge episodes and QoL. Other OAB symptoms that were deemed important by the patient groups providing input for this review and the consulted clinical experts included outcomes such as nocturia and pad count; however, none of the included studies reported these outcomes.

In the absence of evidence for the 45 mg ER form of propiverine, the manufacturer indicated that previous pharmacokinetic studies have demonstrated that the 15 mg IR form, two times daily or three times daily, was considered to be bioequivalent to the 30 mg ER or 45 mg ER form of propiverine (once daily), respectively.[31] Two studies evaluating the effectiveness of the IR form of propiverine (three times daily) compared with placebo and oxybutynin/placebo,[32,33] and one study evaluating the effectiveness of the IR form of propiverine (two times daily) compared with tolterodine,[34] were submitted by the manufacturer as supporting evidence for the 45 mg and 30 mg MR form of propiverine hydrochloride, respectively, and are summarized in APPENDIX 4: SUMMARY OF MANUFACTURER-SUBMITTED SUPPORTING STUDIES (PROPIVERINE IMMEDIATE-RELEASE FORMULATION)

The included studies were limited by their short duration (four weeks to eight weeks). The trial populations had a relatively low frequency of micturition (nine episodes within 24 hours in Study P 1169) and low frequency of incontinence episodes (one episode within 24 hours in Study P 1300) at baseline, and included patients from Europe and China, which may limit the generalizability of the results to clinical practice in Canada.

4.2 Interpretation of Results

4.2.1 Efficacy

The inclusion criteria for the three included studies were consistent with the relevant Health Canada–approved indication for propiverine (i.e., patients with OAB symptoms of UI and/or increased urinary frequency and urgency). The included studies reported reductions in the frequency of OAB symptoms (incontinence, micturition frequency, urgency) from baseline to the end of treatment (four weeks or eight weeks) for the placebo, propiverine IR, propiverine ER, and tolterodine groups. Interpretation of within– and between-group differences is limited due to the absence of a known threshold of change that can be considered clinically significant. The interpretation of the results is further complicated by the placebo effect commonly identified in OAB studies.[35]

The mean change from baseline in OAB symptom outcomes for propiverine ER versus propiverine IR was not statistically significantly different. Tolterodine is widely used in Canada for the control of OAB symptoms, and Study P 1300 showed that propiverine ER was not statistically different from tolterodine

in terms of reducing micturition frequency. Study P 1300 reported that propiverine ER was superior to tolterodine in reducing incontinence frequency from baseline; however, this result should be interpreted with caution because of the imbalanced baseline incontinence frequency between the two groups at baseline (1.3 versus 0.6 for propiverine ER and tolterodine respectively). Such imbalance, although not statistically significant, might have a role in the overall difference in change from baseline. When compared with placebo, propiverine ER and propiverine-pediatric showed statistically superior reduction in the reported OAB symptom outcomes.

Patient input indicated that getting up in the night and wearing incontinence pads are significant sequelae of having OAB that may impact patient's QoL. Unfortunately, the included studies did not report on these outcomes. Study P 659,1 evaluated health-related quality of life (HRQoL) using the KHQ. The results showed an improvement in QoL from baseline was associated with propiverine ER, propiverine IR, and placebo. The differences between groups did not reach a statistical significance, and they showed modest clinical importance.

4.2.2 Harms

Overall, the incidences of AEs, SAEs, and WDAEs were similar between propiverine ER, propiverine IR, and tolterodine. The incidence of overall AEs associated with propiverine ER was double that reported for placebo; the difference was driven mainly with higher incidence of dry mouth with propiverine. WDAEs were relatively low in the three studies (1% to 7%); the clinical experts consulted for this review estimated a withdrawal rate of 40% to 60% when these drugs are used on longer-term basis. This highlights the limitation of the included studies due to their short duration.

Of the notable harms specified in the protocol, studies P 659,1 and P 1300 reported that propiverine was associated with a slightly lower incidence of palpitation and chest depression than tolterodine. None of the included studies reported AEs related to cognitive functioning, mood, or dental caries. AEs related to the anticholinergic effects of treatments were presented mainly in the form of dry mouth and blurred vision.

The results from the manufacturer-submitted supporting evidence assessing the 15 mg IR formulation of propiverine (two or three times daily) suggested that compared with placebo, treatment with propiverine IR was associated with a reduction in micturition frequency, decreased incontinence episodes, and improved OAB symptoms. In terms of safety, in one study enrolling elderly patients with high cardiac risk, no major issues related to cardiovascular events were reported during the treatment phase in either treatment group (propiverine IR or placebo). The supporting studies provided by the manufacturer that were based on the bioequivalence of the ER and IR forms of propiverine were subject to similar limitations as the trials included in the main review (e.g., the short duration of studies, high placebo response, challenges in interpreting the clinical significance of the results) and the limited comparative efficacy and safety data reported.

4.3 Potential Place in Therapy[2]

OAB is a diagnostic classification for patients who present with frequency, urgency, and urgency incontinence. It is a common problem affecting women and men and becomes more common in the elderly. It may be idiopathic or neurogenic in origin. Children as well may manifest OAB as a component of dysfunctional voiding or from other disorders of the central nervous system, either congenital (e.g.,

[2] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

neural tube defects, cerebral palsy) or acquired (e.g., spinal cord injury), and OAB has a major negative effect on QoL. OAB is primarily a clinical diagnosis, based on history, physical examination, and non-invasive testing such as urinalysis and culture. Specialized testing, such as urodynamics or cystoscopy, may be required in those who do not respond to the therapeutic measures described in the following (including, for example, failure to mirabegron). Thus, no specific barriers exist to identifying patients in practice that may require treatment with propiverine.

The usual therapeutic approach is initially lifestyle adjustments with timed voiding coaching, and dietary and fluid modification including avoidance of caffeinated beverages and constipation. The pharmacological options have for many years been antimuscarinic medications,[36] which all have a similar side effect profile typical of this class of medication — dry mouth, blurred vision, constipation, and cardiac arrhythmias. In the elderly, acute confusion and deleterious impact on cognitive function limit the utility of this class of medication. There are currently six antimuscarinic drugs available for adult patients with OAB in Canada (tolterodine, trospium, darifenacin, solifenacin, oxybutynin, and fesoterodine), only one of which is indicated for pediatric patients (oxybutynin). Propiverine is an antimuscarinic which has been shown to be effective in short-term clinical trials. It has also been shown to be safe and effective in children. Comparisons with currently available antimuscarinics are limited but do show noninferiority to comparators. The medication is available as an MR preparation to permit once daily dosage.

The pediatric preparation is a 5 mg tablet, which may present problems for younger children who often have problems swallowing tablets. Alternative treatment options for adult and pediatric patients include mirabegron (a beta-3 agonist) and intra-detrusor injections of onabotulinum toxin. However, the former (mirabegron) has a range of AEs including gastrointestinal symptoms and cardiac arrhythmias and the latter (onabotulinum toxin) requires a cystoscopy for the injection, which needs to be repeated every six months to nine months and is associated with an increased risk of urinary infection and urinary retention. Because of the range of AEs, particularly with the antimuscarinics, patient discontinuation rates are very high and only 35% of patients continue on the medication after three months. Based on a retrospective analysis of Canadian drug claims data, dropout rates as high as 85% have been noted in children with long-term follow-up (up to four years).[37]

Based on the current available therapies and standards of care, the unmet need of adults and children with OAB is a pharmacological drug that is effective with minimal side effects. Currently available drugs have minimal effect on symptoms with significant side effects, leading to high discontinuation rates. There does not appear to be any major advantage for the use of propiverine in adults or children compared with other currently available antimuscarinic preparations or other available therapies for OAB. In particular, the utility of propiverine in children may be limited as the only available formulation is a tablet, rather than a liquid, and many children are unable to swallow tablets.

5. CONCLUSIONS

Three DB RCTs met the inclusion criteria for the systematic review. Two studies were conducted in adult patients, and one study was conducted in pediatric patients. Noninferiority was achieved for propiverine ER versus tolterodine in terms of change from baseline in micturition frequency. Propiverine ER showed superior results compared with tolterodine in terms of reducing incontinence frequency; furthermore, propiverine ER and propiverine-pediatric showed superiority over placebo in terms of reducing incontinence and micturition frequencies. One study showed that there was no significant effect of propiverine ER on patients' HRQoL when compared with placebo. The incidence of SAEs and WDAEs were similar between treatment groups. Dry mouth was reported at a higher rate for patients treated with propiverine ER compared with placebo. The included studies were limited by their short duration of therapy and the difficulty in interpreting the clinical significance of the results.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

The Canadian Continence Foundation (TCCF) is a national non-profit organization serving the interests of people experiencing incontinence.[38] TCCF is led by people with incontinence and health professionals from all health disciplines. Public donations, health care professionals, and private industry support its work. Its mission is to enhance quality of life (QoL) for people with incontinence by helping them or their caregivers to confidently access cures and treatment options. TCCF implements and encourages public and professional education, support, advocacy, and research to advance incontinence treatment and management.

TCCF is supported by individual and corporate donations and has received both restricted and unrestricted educational grants from Astellas, Pfizer, 3M, Tena, Laborie, and My Liberty Life. TCCF declared no conflict of interest with the preparation of this submission.

2. Condition-related Information

Information in this submission was obtained through an online survey conducted between June and August 2016 in both English and French. Twenty-one responses were received. This survey was an update of two earlier surveys that were conducted between March 2013 and May 2014 and were completed by 169 respondents. Additional information was gathered through one-on-one telephone interviews with three patients (September to October 2016) as well as informal discussions with six other patients (June to August 2016).

Urinary incontinence (UI) is involuntary loss of urine. Overactive bladder (OAB) is one of the causes of UI and troublesome lower urinary tract symptoms, and affects approximately 15% of the Canadian adult population. Symptoms of OAB include urgency, usually with frequency and nocturia, with or without urgency incontinence. Urgency incontinence and OAB is associated with significant social isolation, stigma, marked impairment in QoL, reduced workplace productivity, and increased absence from work. A 2008 Ontario Health Technology Advisory Committee report indicated that UI is one of four major predictors for long-term care admissions, along with falls and fall-related injuries, dementia, and social isolation; in addition, UI plays a significant role in the other three conditions. However, very few people talk to their doctor about their symptoms. A Canadian urinary bladder survey conservatively estimated that, among patients more than 40 years of age who had symptoms of UI, only 26% discussed their condition with a doctor.

All survey 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 in 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 QoL. One respondent had to quit her job because of her poor relationships with her co-workers — they felt she was “lazy” and “not efficient or productive” when she had to constantly go to the bathroom due to her symptoms. During the patient interviews and discussions, UI or OAB was found to have a negative impact on family relationships, particularly on spousal interaction and sexual activity. OAB also has a significant impact on caregivers. In addition, managing OAB has financial

consequences. More than one-third of respondents said that buying UI supplies such as pads or underwear was costly.

3. Current Therapy-Related Information

All surveyed patients have received some form of pharmacotherapy for OAB. The most frequently mentioned medications included Myrbetriq, Detrol, Vesicare, and oxybutynin. Approximately two-thirds of respondents tried at least one medication in the past year, 35.7% tried two, and 35.7% tried three. Even though most of the medications were in the same drug class, more than one-third of respondents felt there was some difference between medications. Some patients stated that medical therapy for incontinence or OAB "is not a one-size-fits all proposition" and "what may work for one patient, won't necessarily work for another patient." Of those patients who have tried more than three medications, 28.6% reported that "cycling" through treatments was extremely disruptive. In most cases, patients indicated that these treatments were ineffective in symptom control. The side effects related to the treatment led to concerns over tolerability and affected patient's willingness to continue with the prescribed medications. Dry mouth (38.1%) and dizziness (14.3%) were the most common side effects related to the current treatments reported by survey respondents. Behavioural modification and/or physiotherapy were also used in patients with OAB, often in combination with medications.

Survey respondents indicated the following unmet needs:

- medications that work (52.4%)
- medications with no side effects (42.9%)
- educational materials and resources (38.1%)
- public awareness (to decrease the stigma around the disease) (38.1%)
- access to publicly reimbursed medications (33%)
- access to holistic treatment options and peer support (33%).

4. Expectations About the Drug Being Reviewed

Propiverine is not available in Canada. Its extended-release formulation (ER) is a more recent development, and the once daily administration is expected to have benefits for patients in terms of their ability to adhere to medication. Information on propiverine was gathered through a literature search on PubMed for relevant clinical trials, the author's personal experience, and the summary of product characteristics provided by the manufacturer.

The efficacy, safety, and tolerability of propiverine have been evaluated in clinical trials enrolling adults and children with OAB/UI. Propiverine was found to be effective in controlling disease-related symptoms in studies up to 12 weeks, with a similar or lower frequency of adverse events compared with tolterodine or oxybutynin. The efficacy of propiverine ER has been assessed in combination with alpha blockers in men in trials up to one year in duration. This formulation was shown to be effective in controlling OAB symptoms. In addition, propiverine ER was considered cost-effective in the UK health care system.

TCCF suggests that, from a clinical perspective, propiverine is a useful addition to the armamentarium of medications available for incontinence where patient adherence is a challenge.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	November 11, 2016
Alerts:	Weekly search updates until March 15, 2017
Study Types:	No search filters were applied
Limits:	No date or language limits were used Human filter was applied

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj	Requires words are adjacent to each other (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.rn	CAS registry number
.nm	Name of substance word
ppez	Ovid database code; Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R**)** 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1.	(mictoryl* or detrunorm* or mictonorm* or propiverin* or 468GE2241L or bup-4 or bup4 or 4556-98-8 or CCRIS-3443 or NSC-172140).ti,ab,ot,kf,hw,rn,nm.
2.	(60569-19-9 or 54556-98-8).rn,nm.
3.	1 or 2
4.	3 use ppez
5.	(mictoryl* or detrunorm* or mictonorm* or propiverin* or 468GE2241L or bup-4 or bup4 or 4556-98-8 or CCRIS-3443 or NSC-172140).ti,ab,kw.
6.	*propiverine/
7.	5 or 6
8.	7 use oemezd
9.	4 OR 8

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	November 2016
Keywords:	Mictoryl (propiverine hydrochloride) and overactive bladder
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

APPENDIX 3: VALIDITY OF OUTCOME MEASURES

Aim

The King's Health Questionnaire (KHQ) is a disease-specific quality of life (QoL) measure that is commonly used in clinical trials of patients with overactive bladder (OAB). The aim of this section is to summarize the validity of the KHQ in patients with OAB.

Findings

Instrument	Type	Evidence of Validity	MCID	References
King's Health Questionnaire	0 to 100 point scale	Yes	5 to 10 points	Kelleher et al. (1997)[27] Margolis el al. (2011)[39] Reese et al. (2003)[40] Van Kerrebroeck et al.(2009)[41] Luz et al. (2017)[42]

MCID = minimal clinically important difference.

The standard version of the KHQ is a 21-item disease-specific QoL questionnaire that has been developed and validated in patients with UI.[27] The KHQ consists of nine domains: two single-item domains (general health perceptions and incontinence impact), and seven multi-item domains (role limitations, physical limitations, social limitations, personal relationships, emotions, sleep/energy, and severity/coping). In addition, a multi-item symptom severity scale is included in KHQ. Individual item scores are converted to a standardized scale. Domain scores of the KHQ range from zero to 100, where zero indicates the best outcome or response and 100 indicates the worst outcome or response. The symptom severity scale is scored from zero (best) to 30 (worst).[27,41]

The KHQ was validated in a study of 24 patients with OAB[39] conducted in the US. Reese et al.[40] evaluated the psychometric properties of the KHQ in 1,284 patients with OAB, and concluded that the KHQ had adequate reliability and validity as an OAB-specific measure of health-related quality of life.[40] There were statistically significant correlations between seven domains of KHQ (incontinence impact, role limitations, physical limitations, social limitations, sleep/energy, severity/coping, and symptom severity) and patient-reported OAB symptoms such as urge incontinence episodes (median percentage change) that were observed in patients after 12 weeks of treatment with tolterodine (correlation coefficient for bivariate analysis [r] = 0.16 to 0.32, P value ≤ 0.0011).[41] A minimal clinically important difference (MCID) of five points has been reported for each domain of the KHQ in patients with OAB in earlier literature.[43,44] In the most recent study, a change of 10 points was recommended in patients who had undergone UI surgery to define subjective outcomes.[42]

Conclusion

The KHQ is a validated and widely used instrument in the study of OAB. However, the evidence of its validity showed a weak to moderate correlation between these instruments and patient-reported symptoms (r = 0.16 to 0.42) in clinical trials. The recommended MCID for KHQ is five to 10 points.

APPENDIX 4: SUMMARY OF MANUFACTURER-SUBMITTED SUPPORTING STUDIES (PROPIVERINE IMMEDIATE-RELEASE FORMULATION)

Objective

Propiverine hydrochloride 30 mg and 45 mg modified-release formulation (MR) capsules are indicated for symptomatic treatment of urinary incontinence (UI) and/or increased urinary frequency and urgency in adult patients with overactive bladder (OAB). The pivotal studies submitted by the manufacturer included evidence for propiverine extended-release formulation (ER) 30 mg in the target population;[1,3] however, there was no evidence to support the 45 mg ER formulation in these trials. The manufacturer indicated that the evidence for the 45 mg ER formulation is supported by trials that use the 15 mg immediate-release formulation (IR) (first approved in Germany)[45] three times per day on the basis of bioequivalence between propiverine IR and ER. The IR 15 mg dosage form was not submitted to Health Canada and was never marketed in Canada;[45] however, the bioequivalence of the IR and MR formulations was demonstrated in a double-blind (DB), crossover randomized controlled trial (RCT) that compared the pharmacokinetic profile of propiverine 45 mg MR and propiverine IR 15 mg three times per day in healthy volunteers.[31] The purpose of this appendix is to summarize the results of three DB RCTs that evaluated the clinical efficacy of propiverine IR 15 mg twice daily or three times a day compared with tolterodine, oxybutynin, or placebo in adult patients with OAB.[32-34] These studies were submitted by the manufacturer as supportive evidence for the 30 mg and 45 mg MR forms of propiverine hydrochloride.

Study Characteristics

Two DB RCTs[32,33] evaluated the efficacy and safety of propiverine IR 15 mg three times a day compared with placebo or oxybutynin and one DB RCT evaluated the efficacy and safety of propiverine IR 15 mg twice daily compared with tolterodine.[34] A summary of study characteristics can be found in Table 12.

Studies of Propiverine Immediate-Release Formulation 15 mg Three Times a Day

The study by Dorschner et al.[32] enrolled elderly patients (greater than 60 years) who had symptoms of urgency, urge incontinence, or mixed urge-stress incontinence. The patients were identified as a "cardiac-risk population" based on the Lown classification. Patients were randomized to four weeks of propiverine IR 15 mg three times a day or placebo. The primary efficacy end point was change in micturition frequency at day 28, and the safety outcomes focused primarily on cardiac end points (for example, ECG at rest, 24-hour ambulatory ECG, and laboratory parameters). A total of 107 patients were initially recruited; nine were excluded from the efficacy analysis due to non-compliance, premature withdrawal, and violating urological exclusion criteria. At baseline, patient demographic characteristics were similar between treatment groups. The mean age was 68.4 years (standard deviation 6.5) in the propiverine group and 66.5 years (standard deviation 6.0) in the placebo group. There were more females than males in both groups (81.6% in the propiverine group and 75.5% in the group). The prevalence of concomitant cardiovascular disorders was similar between the treatment groups.

In the study by Madersbacher et al.,[33] the efficacy and tolerability of propiverine were compared with oxybutynin and placebo in patients with urgency and urge incontinence. Eligible patients were randomized to four weeks treatment with propiverine IR 15 mg three times a day, oxybutynin 5 mg twice daily or placebo, at a ratio of 2:2:1. There were 366 patients enrolled in the study. Patient baseline characteristics were similar between the three treatment groups. The mean age ranged between 47.6

years (standard deviation 12.0) in the placebo group to 49.6 years (standard deviation 13.0) in the propiverine group and 50.3 years (standard deviation 13.5) in the oxybutynin group. The majority of the patients across all treatment groups were female (92.9% to 93.7%), and had been experiencing urge incontinence for between 2.0 years (placebo) and 2.4 years (active treatment groups). Approximately 25% to 33% of the patients received previous treatment for urge incontinence.

Study of Propiverine Immediate-Release Formulation 15 mg Twice Daily

In the study by Junemann et al.,[34] the efficacy and tolerability of propiverine were compared with tolterodine in patients with OAB. Eligible patients were randomized to four weeks of treatment with propiverine IR 15 mg twice daily, or tolterodine 2 mg twice daily. Two hundred and one patients were considered in the intention-to-treat (ITT) population, of whom 78.6% were female and the mean age of patients was 56.3 years (standard deviation 14.91). The per-protocol (PP) population consisted of 155 patients (20 patients did not have a primary end point measured, while 26 violated inclusion or exclusion criteria). Noninferiority of propiverine versus tolterodine was assessed based on the primary end point of maximum cystometric bladder capacity (noninferiority margin 30 mL); all other outcomes were considered exploratory.

TABLE 12: STUDY CHARACTERISTICS

		Dorschner Et Al. (2000)[32]	Madersbacher Et Al. (1999)[33]	Junemann Et Al. (2005)[34]
DESIGNS & POPULATIONS	**Study design**	DB RCT, multi-centre, placebo-controlled, parallel group	DB RCT, multi-centre, placebo and active-controlled, parallel group	DB RCT, multi-centre, active-controlled, parallel group
	Locations	Multiple sites in Europe	32 sites in Europe	31 centres in Europe
	Enrolled (N)	107 (98 included in efficacy analysis)	366 (310 included in efficacy analysis; 366 included in safety analysis)	201 (201 in ITT population, 155 in PP population)
	Inclusion criteria	• Elderly patients (≥ 60 years of age) with urgency, urge incontinence, or mixed urge-stress incontinence • Micturition frequency > 7 episodes per day • Urinary incontinence > 0 episodes per day • Micturition volume < 300 mL per micturition	• Adult patients (≥ 18 years of age) with urgency and urge incontinence • Maximum cystometric bladder capacity of ≤ 300 mL	• Adult patients (≥ 18 years of age) with OAB (at least one unstable detrusor contraction at a minimum of 10 cm H_2O combined with ≥ 8 micturitions per 24 hours) • Sensoric urge incontinence (at least one incontinence episode with ≥ 8 micturitions per 24 hours)
	Exclusion criteria	• Acute urinary tract infection • Mechanical or functional bladder emptying disorders • Micturition volume of > 300 mL in uroflow • Renal insufficiency • Serious, life-threatening cardiovascular diseases • Myocardial infarction < previous 3 months, unstable coronary heart disease, implanted cardiac pacemaker, and other severe cardiac conditions	• Detrusor hyperreflexia • Post-operative bladder incontinence • Infravesical obstruction • Post-void residual urine of > 15% of the maximal cystometric bladder capacity • Acute urinary tract infections • Glaucoma • Clinically relevant cardiac/renal/hepatic dysfunctions • Frequency/nocturia due to	• Stress urinary incontinence • Multiple sclerosis • Maximum cystometric bladder capacity of > 300 mL • Post-void residual ≥ 50 mL • Acute urinary tract infection • Intermittent catheterization • Operations of the lower urinary tract within previous 4 weeks • Anomalies of the lower genitourinary tract

		Dorschner Et Al. (2000)[32]	Madersbacher Et Al. (1999)[33]	Junemann Et Al. (2005)[34]
			heart or renal insufficiency or overt cerebral sclerosis	
Drugs	**Intervention**	• Propiverine IR 15 mg t.i.d. for 4 weeks	• Propiverine IR 15 mg t.i.d. for 4 weeks	• Propiverine IR 15 mg b.i.d. for 4 weeks
	Comparator(s)	• Placebo for 4 weeks	• Oxybutynin 5 mg b.i.d. for 4 weeks • Placebo for 4 weeks	• Tolterodine 2 mg b.i.d. for 4 weeks
Duration	**Phase**			
	Run-in period	2 weeks, placebo run-in	1 week run-in	1 week run-in
	Core phase	4 weeks		
	Follow-up	Last visit was on day 28		
Outcomes	**Primary end point**	• Micturition diary (micturition frequency/volume/incontinence episodes)	• Urodynamic analysis (e.g., cystometric bladder capacity)	• Urodynamic evaluations (e.g., max. cystometric bladder capacity)
	Other end points	• Uroflow • Residual urine by ultrasound • Patient's and physician's assessment of the improvement of clinical symptoms • HRQoL • Safety: ECG, 24-h ambulatory ECG, lab works, AEs	• AEs and tolerability • Frequency of micturition • Degree of incontinence • Symptom improvement	• Volume at first urge • Post-void residual • Frequency volume chart • Frequency of micturition • Voided volume • Incontinence and urgency episodes • King's Health Questionnaire score • Safety: AEs, laboratory variables, vital parameters

AE = adverse event; b.i.d. = two times per day; DB = double-blind; ECG = electrocardiography; h = hour; HRQoL = health-related quality of life; IR = immediate-release formulation; ITT = intention-to-treat; OAB = overactive bladder; PP = per-protocol; RCT = randomized controlled trial; t.i.d. = three times a day.

Findings

In the study by Dorschner et al.,[32] four weeks of treatment with propiverine was associated with statistically significant reduction of the micturition frequency (approximately two episodes per 24-hour period) compared with placebo. The change from baseline is considered clinically relevant according to the clinical expert consulted for this review; however, the numerical difference compared with placebo was not reported. Patients in the propiverine group had a statistically significant reduction in incontinence episodes (approximately 0.5 episodes per 24 hour period); however, the difference was not considered to be clinically relevant. In addition, a higher proportion of patients treated with propiverine and their physicians indicated experiencing improvements in symptoms compared with those treated with placebo. In terms of harm outcomes, propiverine had a similar safety profile compared with placebo, as measured by resting and ambulatory ECG, occurrence of cardiac events, and laboratory tests.

In the study by Madersbacher et al., propiverine was superior to placebo in reducing frequency of micturition and urgency episodes, and had a similar effect in improving clinical symptoms as oxybutynin. Patients in both propiverine and oxybutynin groups reported more adverse events (AEs) and withdrawals due to adverse events (WDAEs) compared with those in the placebo group.

In Junemann et al.,[34] propiverine was noninferior to tolterodine based on a noninferiority margin of 30 mL for change in cystometric capacity from baseline (propiverine mean change 55.8 mL [standard deviation 116.2] versus tolterodine mean change 70.1 mL [standard deviation 101.3]). There were no statistically significant differences in efficacy outcomes between propivirine and tolterodine; however, these were all considered exploratory in nature. The number of AEs and WDAEs were similar between the two groups; there were no differences in laboratory paramters reported, and more patients in the tolterodine group experienced cardiac disorders.

TABLE 13: RESULTS OF CLINICAL EFFICACY AND SAFETY

	Dorschner et al.[32]		Madersbacher et al.[33]			Junemann et al. (2005)[34]	
	Propi. IR 15 mg t.i.d. (N = 49)[a]	**Placebo (N = 49)[a]**	**Propi. IR 15 mg t.i.d. (N = 126)[a]**	**Oxy. 5 mg b.i.d. (N = 121)[a]**	**Placebo (N = 63)[a]**	**Propi. IR 15 mg b.i.d. (N = 75) Safety Analysis Set (N = 100)**	**Toltero. 2 mg b.i.d. (N = 80) Safety Analysis Set (N = 101)**
Efficacy							
Micturition frequency per 24 hours, mean (SD)							
Baseline	8.7 (4.2)	7.1 (3.0)	10.4	12.6	11.5	NR	NR
End of treatment	6.5 (3.2)	6.5 (3.5)	8.5	10.2	10.5	NR	NR
Reduction from baseline	–22%	NR	–1.9[b]	–2.4[b]	–1.0[b]	–3.07 (2.29)[c]	–2.95 (2.88)[c]
P value for between-group comparison	*P* ≤ 0.01		NR			*P* = 0.80	
Incontinence episodes per 24 hours, mean							
Baseline	0.9	0.4	NR			NR	
End of treatment	0.3	0.2					
Reduction from baseline	0.6 (–55%)	0.1 (–37%)					
P value for between-group comparison	*P* = 0.048						
% of severe incontinence (with Gaudenz score 13 to 26)							
Baseline	NR		53	56	56	NR	
End of treatment			14	21	22		
Urgency episodes per 24 hours, mean							
Baseline	NR		9.5	12.4	11.3	NR	NR
End of treatment			6.4	9.4	10.1	NR	NR
Reduction from baseline			–2.9[b]	–3.0[b]	–1.2[b]	–3.34 (3.07)[c]	–2.80 (3.73)[c]
P value for between-group comparison			NR			*P* = 0.37	
Assessment of improvement of clinical symptoms — by patients							
Improvement of overall symptoms: • Improved • No change	NR		 83% 15%	 79% 19%	 68% 32%	NR	

	Dorschner et al.[32]		Madersbacher et al.[33]			Junemann et al. (2005)[34]	
	Propi. IR 15 mg t.i.d. (N = 49)[a]	**Placebo (N = 49)[a]**	**Propi. IR 15 mg t.i.d. (N = 126)[a]**	**Oxy. 5 mg b.i.d. (N = 121)[a]**	**Placebo (N = 63)[a]**	**Propi. IR 15 mg b.i.d. (N = 75) Safety Analysis Set (N = 100)**	**Toltero. 2 mg b.i.d. (N = 80) Safety Analysis Set (N = 101)**
Improvement of urgency: • Symptom-free • Improved • Unchanged	 30.6% 59.2% 10.2%	 14.3% 38.8% 46.9%	NR			NR	
Improvement of incontinence: • Symptom-free • Improved • Insufficient	 48.8% 39.5% 11.6%	 31.1% 22.2% 46.7%	NR			NR	
Assessment of improvement of clinical symptoms — by physicians							
Improvement of urgency: • Symptom-free • Improved • Unchanged	 30.6% 57.1% 12.2%	 10.2% 38.8% 51.0%	NR			NR	
Improvement of incontinence: • Symptom-free • Improved • Unchanged	 41.9% 46.6% 11.6%	 28.9% 20.0% 51.1%	NR			NR	
Safety							
AEs							
n (%)	2 (4.1)	8 (16.3)	96 (64)[b]	105 (72)[b]	31 (42)[b]	42 (42)	43 (43)
SAEs							
NR							
WDAEs							
n (%)	NR		20 (13)	16 (11)	7 (9.7)	6 (NR)	6 (NR)
Notable harm							
Change in standard ECG, n (%)	No significant differences resulted in heart rate, P-Q interval, QRS interval, Q-T interval or Q-Tc interval between 2 groups at any visits.		1 (0.7)	3 (2.1)	2 (2.8)	NR	
24-hour ambulatory ECG	No significant changes between treatment groups.		NR			NR	

	Dorschner et al.[32]		Madersbacher et al.[33]			Junemann et al. (2005)[34]	
	Propi. IR 15 mg t.i.d. (N = 49)[a]	**Placebo (N = 49)[a]**	**Propi. IR 15 mg t.i.d. (N = 126)[a]**	**Oxy. 5 mg b.i.d. (N = 121)[a]**	**Placebo (N = 63)[a]**	**Propi. IR 15 mg b.i.d. (N = 75) Safety Analysis Set (N = 100)**	**Toltero. 2 mg b.i.d. (N = 80) Safety Analysis Set (N = 101)**
Cardiac events	Neither a sustained ventricular tachycardia, paroxysmal supraventricular tachycardia, intermittent atrial fibrillation nor a torsade de pointes tachycardia were observed in the patients.		NR			One AE identified as a cardiac disorder was reported in the propiverine group; six were reported in the tolterodine group.	
Abnormal lab parameters, n (%)	No significant changes in lab parameters or electrolyte concentrations were observed between treatment groups.		14 (9.4)	19 (13)	2 (2.8)	No differences between treatment groups reported.	

AE = adverse event; b.i.d. = twice daily; CDR = CADTH Common Drug Review; ECG = electrocardiography; IR = immediate-release formulation; n = number of patients with event; N = number of patients; NR = not reported; oxy. = oxybutynin; *P* = probability; propi. = propiverine; SAE = serious adverse event; SD = standard deviation; t.i.d. = three times a day; toltero. = tolterodine; WDAE = withdrawal due to adverse event.

[a] Efficacy population.

[b] Calculated by CDR.

[c] Per-protocol population.

Summary

Three DB RCTs evaluated the clinical efficacy and safety of propiverine IR 15 mg three times daily or propiverine IR 15 mg two times daily for adult patients with OAB and increased urinary frequency, urgency, and/or urge incontinence. The results demonstrated that compared with placebo, treatment with propiverine IR was associated with a reduction in micturition frequency, decreased incontinence episodes, and improved OAB symptoms. Compared with oxybutynin, propiverine IR 15 mg three times a day had a similar effect, and compared with tolterodine, propiverine IR 15 mg twice daily was noninferior based on change in cystometric capacity from baseline. In the study enrolling elderly patients with high cardiac risk,[32] no major issues related to cardiovascular events were reported during the treatment phase in either treatment group. In the study comparing propiverine with oxybutynin and placebo, patients receiving active treatments experienced more AEs and discontinuations due to AEs compared with patients in the placebo group.

All studies were based on a treatment duration of four weeks. According to the clinical experts consulted by CADTH for this review, patient dropout is high over time, so a period of four weeks may not adequately capture the tolerability of the drugs studied in these trials. The details of the methods of randomization and blinding were limited in Dorschner et al. and Junemann et al., and it is unclear whether the studies were adequately powered to detect differences between the groups. All end points except the primary end point in Junemann et al. were considered exploratory in nature. Finally, all three studies were conducted in Europe and were published between 1999 and 2005, and therefore the patient characteristics, practice patterns, and the formulation of the drugs could be considerably different from the present-day Canadian patient population. The generalizability of the study results to a Canadian population is limited.

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