

# Drug Coverage Decision for B.C. PharmaCare

## About PharmaCare

B.C. PharmaCare is a government-funded drug plan. It helps British Columbians with the cost of eligible prescription drugs and specific medical supplies.

## Details of Drug Reviewed

<b>Drugs</b>	<b>Long-acting (once daily) drugs for treatment of overactive bladder (OAB)</b>				
	<b>darifenacin</b>	<b>fesoterodine</b>	<b>mirabegron extended-release (ER)</b>	<b>solifenacin</b>	<b>Tolterodine ER</b>
Brand Names	Enblex™	Toviaz™	Myrbetriq™	Vesicare®, generics	Detrol™ LA, generics
Dosage Forms	7.5 mg tablet 15 mg tablet	4 mg tablet 8 mg tablet	25 mg tablet 50 mg tablet	5 mg tablet 10 mg tablet	2 mg capsule 4 mg capsule
Manufacturers	Merus Labs	Pfizer Canada Inc.	Astellas Pharma Canada Inc.	Astellas Pharma Canada Inc.	Pfizer Canada Inc.
<b>Submission</b>	<b>Therapeutic Review</b>				
Use Reviewed	For the treatment of OAB				
Common Drug Review (CDR)	Darifenacin, fesoterodine, mirabegron ER and solifenacin were reviewed by CDR. Visit the CDR website for more details: <a href="http://www.cadth.ca/node/88649">www.cadth.ca/node/88649</a> . Tolterodine ER - CDR did not review.				
Drug Benefit Council (DBC)	DBC met on September 9, 2013. DBC considered various inputs including: Medical Beneficiary and Pharmaceutical Services Division (MBPSD) initiated systematic review of the clinical evidence and pharmacoeconomic report on antimuscarinic drugs for OAB ; previous Canadian Expert Drug Advisory Committee (CEDAC), Canadian Drug Expert Committee (CDEC), and DBC Recommendations and Reasons for the applicable agents; Clinical Practice Review from a Specialist, Manufacturer comments; responses to Patient Input Questionnaires from 12 patients; and a Budget Impact Analysis. No patient input was received from caregivers and no patient groups met the inclusion criteria. On November 17, 2014, mirabegron was added to the DBC's recommendation.				
<b>Drug Coverage Decision</b>	<b>Limited Coverage Benefit for generic solifenacin. Access solifenacin criteria from <a href="http://www.gov.bc.ca/pharmacarespecialauthority">www.gov.bc.ca/pharmacarespecialauthority</a></b> <b>Non-Benefit for darifenacin, fesoterodine, mirabegron ER, solifenacin (Vesicare™) and tolterodine ER (Detrol™ LA and generics)</b>				
Date	August 4, 2016				
Reason(s)	<p><b>Drug coverage decision is consistent with the DBC recommendation.</b></p> <ul style="list-style-type: none"> <li>• DBC recommended that MBPSD consider adding one of the long-acting (once daily) drugs for patients with OAB who are unable to tolerate oxybutynin immediate release (IR) due to dry mouth.</li> <li>• The long-acting drugs for OAB treatment did not demonstrate efficacy, effects on cognition and quality of life advantages over oxybutynin immediate release (IR). There was no evidence of differences in clinical efficacy between long-acting drugs.</li> <li>• The long-acting drugs for OAB treatment demonstrated an advantage over oxybutynin IR in the most common adverse event, fewer rates of dry mouth.</li> </ul>				

	<ul style="list-style-type: none"> <li>Based on economic considerations and the submitted product price, the long-acting drugs for OAB treatment were not cost-effective and/or did not offer optimal value over oxybutynin IR.</li> <li>At the time of DBC review, generic long-acting drugs for OAB treatment were not available, but generic solifenacin and tolterodine ER are now available.</li> <li>Generic solifenacin provides the best value and the least costly option compared to other long-acting drugs for treatment of OAB .</li> </ul>
Other Information	None

### The Drug Review Process in B.C.

A manufacturer submits a request to the Ministry of Health (Ministry).

An independent group called the [Drug Benefit Council](#) (DBC) gives advice to the Ministry. The DBC looks at:

- advice from a national group called the Common Drug Review
- whether the drug is safe and effective
- whether it is a good value for the people of B.C.
- the ethics of covering or not covering the drug
- input from physicians, patients, caregivers, patient groups and drug submission sponsors

The Ministry makes a decision based on many factors, including:

- advice from the DBC
- drugs used to treat similar medical conditions that B.C. PharmaCare already covers
- the overall cost of covering the drug

Visit the B.C. [Drug Review Process](#) and [PharmaCare](#) program for more information.

**This document is intended for information only.**

It does not take the place of advice from a physician or other qualified health care provider.

# **Drug Benefit Council (DBC)**

## **Recommendation and Reasons for Recommendation**

### **FINAL**

#### **Overactive Bladder Therapeutic Review**

##### **Description:**

The purpose of the therapeutic review was to review medications for the treatment of overactive bladder (OAB) in adults.

In their review, the DBC considered the following: a systematic review of the clinical evidence, a pharmacoeconomic report; previous CEDAC, CDEC, and DBC Recommendations and Reasons for the applicable agents; Clinical Practice Review from a Specialist, Manufacturer comments; responses to Patient Input Questionnaires from 12 patients; and a Budget Impact Analysis. No patient input was received from caregivers and no patient groups met the inclusion criteria.

##### **Dosage Forms:**

- fesoterodine (Toviaz<sup>®</sup>) 4 and 8 mg tablet;
- oxybutynin IR (Ditropan<sup>®</sup>) 5 mg immediate release tablet;
- oxybutynin ER (Ditropan<sup>®</sup> XL) 5 and 10 mg extended-release tablet;
- oxybutynin CR (Uromax<sup>®</sup>) 10 and 15 mg controlled-release tablet;
- oxybutynin (Oxytrol<sup>™</sup>) 36 mg transdermal patch;
- oxybutynin (Gelnique<sup>™</sup>) 100 mg/g topical gel;
- tolterodine (Detrol<sup>™</sup>) 1 and 2 mg tablet;
- tolterodine ER (Detrol<sup>™</sup> LA) 2 and 4 mg extended-release tablet;
- solifenacin (Vesicare<sup>®</sup>) 5 and 10 mg tablet; and
- darifenacin (Enablex<sup>™</sup>) 7.5 and 15 mg extended-release tablet.
- trospium (Trosec<sup>®</sup>) 20 mg tablet

##### **Recommendations:**

1. The Drug Benefit Council (DBC) maintains their previous recommendations that oxybutynin CR, oxybutynin gel, and oxybutynin ER not be listed.
2. The DBC recommends that the Ministry of Health (Ministry) should consider adding one of the following long-acting (once daily) agents for patients with OAB who are unable to tolerate oxybutynin IR due to dry mouth. This agent should be selected based on the relative cost of the listed alternatives. Options for listing are: tolterodine

ER (Detrol LA™); trospium (Trosec™); solifenacin (Vesicare®); darifenacin (Enablex™); and fesoterodine (Toviaz®).

**UPDATE November 17, 2014:**

The DBC recommends that **mirabegron (Myrbetriq™)** be considered using the same criteria as the Ministry is using for tolterodine ER, solifenacin, darifenacin, and fesoterodine in the context of the September 2013 therapeutic review of OAB drugs.

OF NOTE: Trospium (Trosec™) is removed from the list of available options as this is not once daily therapy.

**Reasons for the Recommendation:**

**1. Summary**

- No drugs showed an efficacy advantage over oxybutynin IR. No drugs showed an advantage in effects on cognition compared to oxybutynin IR. There was no evidence of any differences in clinical efficacy in longer-acting agents.
- Tolterodine, trospium, solifenacin, darifenacin and fesoterodine showed an advantage versus oxybutynin IR in the most common adverse event, dry mouth.

**2. Clinical Efficacy**

- The review of efficacy outcomes and frequent short-term adverse events considered evidence from comparative randomized controlled trials (RCTs) and systematic reviews of RCTs. For populations not included in RCTs, such as elderly and patients with co-morbidities, and for the review of serious and less frequent adverse events, a broader range of study designs were considered.
- In order to assess net benefit the following potential beneficial and harmful effects were included: all-cause mortality; non-fatal serious adverse events (SAEs); quality of life (QOL); patient perception of improvement or cure; withdrawals due to adverse events (WDAEs); incontinence/continence endpoints; nocturia; urgency; total adverse events (AEs); common anticholinergic events (e.g. dry mouth); mean volume voided per micturition; and clinician/urodynamic measures.
- The review considered 41 comparative RCTs for all drug-drug comparisons considered in this review, 27 of which were comparisons between oxybutynin IR and other formulations of oxybutynin, tolterodine (IR or ER), darifenacin, solifenacin, or trospium (IR). With the exception of one trial comparing darifenacin with solifenacin, all other trials included either oxybutynin or tolterodine as a comparator.
- The review also included 13 placebo-controlled RCTs that exclusively enrolled the elderly; RCTs that specifically assessed cognition but were either placebo-controlled or direct comparator trials involving a formulation not included in this review; 33

non-randomized studies; and case reports, which can provide additional information on rare serious or unanticipated adverse events.

- **Tolterodine versus oxybutynin:** available RCTs do not provide evidence of an efficacy advantage for tolterodine versus oxybutynin. The adverse event profiles for tolterodine IR and oxybutynin IR were similar, although fewer patients on tolterodine IR experienced WDAEs, AEs, or dry mouth compared to oxybutynin IR. No published RCTs comparing tolterodine with oxybutynin assessed cognition.
- **Trospium versus oxybutynin:** available RCTs do not provide evidence of an efficacy advantage for trospium versus oxybutynin. Trospium was associated with lower rates of WDAEs and total AEs; however, the level of evidence was low and insufficient to assess specific AEs such as dry mouth. No published RCTs comparing trospium with oxybutynin assessed cognition.
- **Darifenacin versus oxybutynin:** available RCTs do not provide evidence of an efficacy advantage for darifenacin versus oxybutynin. The rates of SAEs, WDAEs, and total AEs were similar. Darifenacin was associated with less dry mouth than oxybutynin and showed a trend for increased incidence of constipation. No published RCTs comparing darifenacin with oxybutynin assessed cognition.
- **Solifenacin versus oxybutynin:** available RCTs do not provide evidence of an efficacy advantage for solifenacin versus oxybutynin. The rate of WDAEs, total AEs, and dry mouth were lower based on one small, comparative trial of short duration. None of the available studies were adequately powered to assess or actively assessed cognition.
- **Fesoterodine versus oxybutynin:** there were no RCTs comparing fesoterodine with oxybutynin IR. A meta-analysis comparing fesoterodine to tolterodine ER found more patients experienced SAEs, WDAEs, and any AEs (including dry mouth, constipation, and dyspepsia) on fesoterodine. On OAB-specific QOL scales, fesoterodine improved some measures (symptom bother, reduction in micturition episodes, nocturia) compared to tolterodine, but not others (urinary incontinence). More patients reported improvement or cure with fesoterodine, based on 3-day bladder diaries. No information is available on cognition.
- **Different formulations of oxybutynin:** available RCTs show fewer patients on oxybutynin ER experienced dry mouth compared to oxybutynin IR. However, quality of life scores improved less on oxybutynin ER.
- One RCT comparing transdermal and oral oxybutynin IR failed to show equivalence for the patients who were responders, meaning there is insufficient evidence to conclude a therapeutic advantage of transdermal over oral oxybutynin. There were no direct comparator trials for oxybutynin gel.

### 3. Safety

- Placebo-controlled trials on the elderly were included for supplemental information on harms of anticholinergic agents, including cognition. One 4-week trial on patients with OAB compared oxybutynin ER to placebo in cognitively impaired, elderly females who were residents of nursing home facilities. No patient experienced

delirium during the study, and no differences between oxybutynin ER and placebo were detected.

#### **4. Economic Considerations**

- The DBC found no evidence to support the use of longer acting anticholinergic agents for OAB in patients who did not tolerate or who had insufficient response to oxybutynin IR, and no evidence to discern any differences in clinical efficacy of longer-acting agents.
- As no drugs showed clinically meaningful advantage compared to oxybutynin IR, and there was less dry mouth with some of the alternative medications, a least costly option should be selected for coverage from the available alternative agents (tolterodine ER (Detrol LA™); trospium (Trosec™); solifenacin (Vesicare®); darifenacin (Enablex™); and fesoterodine (Toviaz®)).

#### **5. Of Note**

- DBC noted that there are insufficient data to support the use of any of the long-acting drugs in patients with OAB who have an insufficient response to oxybutynin IR, or in patients not tolerating oxybutynin IR due to AEs other than dry mouth.
- The DBC previously recommended not to list oxybutynin ER, oxybutynin CR, oxybutynin gel, darifenacin, and solifenacin.
- Patients, caregivers, and patient groups state that OAB affects symptoms like frequency, urgency, nocturia, affects sleep, and causes social embarrassment. Patients expect improvements in urinary symptoms, sleep, and improved QOL from their medications.