CEDAC FINAL RECOMMENDATION and REASONS for RECOMMENDATION

SOLIFENACIN RESUBMISSION
(Vesicare® – Astellas Pharma Canada, Inc.)
Indication: Overactive Bladder

Description:
Solifenacin is a muscarinic receptor antagonist that is approved by Health Canada for the treatment of overactive bladder in adults with symptoms of urge urinary incontinence, urinary urgency and urinary frequency. The Canadian Expert Drug Advisory Committee (CEDAC) had previously recommended that solifenacin not be listed (see Notice of CEDAC Final Recommendation on January 24, 2007).

The basis of the resubmission was a confidential new price submitted by the manufacturer and new clinical trial information.

Dosage Forms:
Supplied as 5 mg and 10 mg tablets. The recommended dose is 5 mg to 10 mg administered once daily.

Recommendation:
The Canadian Expert Drug Advisory Committee recommends that solifenacin be listed for patients who cannot tolerate or have insufficient response to an adequate trial of immediate-release oxybutynin, and in a similar manner as drug plans list tolterodine.

Reasons for the Recommendation:
1. There is insufficient evidence that solifenacin provides clinically important differences in outcomes compared with oxybutynin or tolterodine.

2. Since the initial solifenacin submission reviewed by the Committee, the price has been reduced and this was an important consideration in making this recommendation. The daily cost of solifenacin [redacted] is less than tolterodine immediate-release and extended-release formulations ($1.82), but more than oxybutynin immediate release formulations ($0.40 to $0.59). The manufacturer has requested that the submitted price of solifenacin remain confidential pursuant to the Confidentiality Guidelines of the Procedure for Common Drug Review.

Summary of Committee Considerations:
In the resubmission, a lower confidential price of [redacted] per tablet, regardless of strength, was submitted. The price in the original submission was $1.64 per tablet.

Two new double-blind randomized controlled trials (RCTs) were included in this review compared with the previous solifenacin CDR review. A trial published by Choo et al., (n=354) was a 12-week study evaluating the non-inferiority of solifenacin 5 mg and 10 mg daily compared with tolterodine immediate-release (2 mg twice daily) for the primary outcome, change from baseline in mean daily micturitions. The VECTOR trial (n=132) was an 8-week study evaluating the superiority of solifenacin (5 mg daily) over oxybutynin immediate-release (5 mg three times daily) for the primary outcome, incidence and severity of dry mouth.

In the Choo trial, both solifenacin 5 mg and 10 mg daily were non-inferior to tolterodine with respect to reducing micturition frequency (range of 2.5 to 2.1 fewer micturitions per day from baseline for both drugs) and the effects on urge incontinence, urgency episodes and individual domains of quality of life scores were similar between solifenacin and tolterodine.

The VECTOR trial was small and approximately 30% of patients withdrew from the study, which reduces confidence in the efficacy results and in the magnitude of effect on the incidence of dry mouth. Dry mouth occurred significantly less frequently with solifenacin compared with oxybutynin in the VECTOR trial (35% versus 83%, respectively) and with similar frequency between solifenacin 10 mg and tolterodine in the Choo trial. Constipation occurred more frequently with solifenacin compared with tolterodine, although this difference was only statistically significant at the 10 mg dose in the Choo trial (14% versus 3%, respectively).

Elderly patients may be more prone to adverse effects of the central nervous system from anticholinergic agents used in overactive bladder. There is insufficient evidence that solifenacin has less effect on cognition than non-selective antimuscarinics such as oxybutynin.

In the original submission, the Committee considered a systematic review of three RCTs comparing solifenacin to tolterodine, ranging in duration from four to 12 weeks. Solifenacin was significantly better than tolterodine for some efficacy measures. One of the three RCTs reported that, compared with tolterodine, solifenacin resulted in fewer episodes of urge incontinence (mean reduction of 0.59 episodes per day), incontinence episodes (mean reduction of 0.49 episodes per day) and improvements in quality of life as measured by the Perception of Bladder Condition scale (mean difference of 0.18 on a total scale of 6 points). Two of the three RCTs reported a statistically significant reduction in urgency episodes for solifenacin compared with tolterodine (mean reductions ranging from 0.43 to 1.02 episodes per day). The clinical significance of these differences is uncertain. All three RCTs reported a higher incidence of constipation with solifenacin compared with tolterodine. The Committee also noted that the long serum half-life (~60 hours) and accumulation of solifenacin might increase the potential for adverse events in patients with impaired renal function.

Of Note:

1. Both published and unpublished data were reviewed and taken into consideration in making this recommendation.
2. Patients with overactive bladder may benefit from behavioural training or lifestyle modification and non-pharmacological approaches should be considered prior to initiation of any drug therapy.
3. The Committee noted the potential for increased use of these agents, given that the number of agents in the class has risen, and also had concerns about the balance between benefits and risks, especially in older populations. The Committee recommends that drug plans consider a drug class review of the effectiveness, safety and cost-effectiveness of these agents.

4. This document has been edited to remove confidential information at the manufacturer's request in conformity with the CDR Confidentiality Guidelines.

Background:

CEDAC provides formulary listing recommendations to publicly funded drug plans. Recommendations are based on an evidence-based review of the medication's effectiveness and safety and an assessment of its cost-effectiveness in comparison to other available treatment options. For example, if a new medication is more expensive than other treatments, the Committee considers whether any advantages of the new medication justify the higher price. If the recommendation is not to list a drug, the Committee has concerns regarding the balance between benefit and harm for the medication, and/or concerns about whether the medication provides good value for public drug plans.

The CEDAC Final Recommendation and Reasons for Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice. CADTH is not legally responsible for any damages arising from the use or misuse of any information contained in or implied by the contents of this document.

The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada or any provincial, territorial or federal government or the manufacturer.