CEDAC FINAL RECOMMENDATION and REASONS for RECOMMENDATION

DARIFENACIN RESUBMISSION
(Enablex™ – Novartis Pharmaceuticals Canada Inc.)
Indication: Overactive Bladder

Description:
Darifenacin is a muscarinic M_3 receptor antagonist approved by Health Canada for the treatment of overactive bladder. The Canadian Expert Drug Advisory Committee (CEDAC) had previously recommended that darifenacin not be listed (see Notice of CEDAC Final Recommendation on Reconsideration on October 19, 2006).

The basis of the resubmission was a confidential new price submitted by the manufacturer.

Dosage Forms:
Supplied as 7.5 mg and 15 mg extended-release tablets. The recommended dosage is 7.5 mg to 15 mg, administered once daily.

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that darifenacin 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:
The daily cost of darifenacin ($1.46) is less than tolterodine immediate-release and extended-release formulations ($1.82), but more than oxybutynin immediate release formulations ($0.40 to $0.59).

Summary of Committee Considerations:
The basis of this resubmission was a lower confidential price of $1.46 per tablet, regardless of strength. The price in the original submission was $1.58 per tablet.

There has been one new double-blind randomized controlled trial (RCT) since the original darifenacin submission. In the trial by Chapple et al, patients 65 years of age or older with overactive bladder received either darifenacin or placebo for 12 weeks (n=400). Overactive bladder is defined as urinary urgency with or without urge incontinence, usually with frequency and nocturia, in the absence of infection and other pathology. The primary outcome of this study was the median change from baseline in mean weekly urge urinary incontinence episodes. Both darifenacin and placebo arms had a reduction

in weekly urge urinary incontinence episodes, but the difference between treatment arms was not statistically significant. Relative to placebo, darifenacin was associated with statistically significant improvements in urinary frequency (micturitions/day) and quality of life measured by the overactive bladder questionnaire. Cardiac events occurred numerically more frequently in patients taking darifenacin, compared to placebo (3.4% versus 0%). There were no fractures reported in the Chapple study. However, an increased risk of fracture was identified from pooled results of the RCTs from the original CDR report, with 18 darifenacin patients compared to no placebo patients reporting a fracture. Both fracture and cardiac event rates should be monitored in future research and safety surveillance.

Elderly patients may be more prone to adverse effects of the central nervous system from anticholinergic agents used in overactive bladder. Because of its M3 receptor selectivity, darifenacin may theoretically have less effect on cognition than non-selective antimuscarinics with high central nervous system penetration, such as oxybutynin. However, there are no studies that have examined the relative effects of darifenacin on cognition in elderly patients with overactive bladder.

In the original submission, the Committee considered a systematic review of eight RCTs of one to 12 weeks in duration. Five of these trials were placebo controlled, two compared darifenacin with oxybutynin and one used tolterodine as a comparator. Of the placebo controlled RCTs, four reported a statistically significant reduction in the median number of incontinence episodes with darifenacin (range of 1.4 to 4.3 fewer episodes per week) and three reported statistically significant reductions in the median frequency of micturition with darifenacin (range of 0.7 to 0.9 fewer micturitions per day). In the RCTs comparing darifenacin with oxybutynin and tolterodine, there were no differences in efficacy between the treatment groups. Darifenacin causes typical anticholinergic side effects and the incidence of dry mouth and constipation were significantly higher in darifenacin versus placebo treated patients. In comparison with other anticholinergic agents, darifenacin was reported to cause a higher incidence of constipation compared with tolterodine and a lower incidence of dry mouth compared to oxybutynin.

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. The manufacturer has reviewed this document and has not requested the removal of any confidential information 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.

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