



## FINAL CDEC RECOMMENDATION

### COLESEVELAM HYDROCHLORIDE

(Lodalix – Valeant Canada LP)

Indication: Hypercholesterolemia

#### Recommendation:

The Canadian Drug Expert Committee (CDEC) recommends that colesevelam not be listed at the resubmitted price.

#### Reasons for the Recommendation:

1. At the resubmitted price, colesevelam is still more costly than other bile acid sequestrants. Based on recommended daily doses, the cost of colesevelam (\$4.40 to \$7.70; 2.5 g to 4.5 g) is more than colestipol (\$0.91 to \$5.46; 5 g to 30 g) and only similar to cholestyramine at the higher dose range (\$1.32 to \$7.90; 4 g to 24 g).
2. The Committee considered the comparative clinical benefit of colesevelam to be uncertain, given that there were no randomized controlled trials (RCTs) directly comparing colesevelam with other bile acid sequestrants.

#### Background:

Colesevelam has a Health Canada indication for the reduction of cholesterol blood level in patients with hypercholesterolemia (Fredrickson type IIa) as an adjunct to diet and lifestyle changes, when the response to these measures has been inadequate, in patients:

- who are not adequately controlled with an HMG-CoA reductase inhibitor (statin) alone, or
- who are unable to tolerate a statin.

Colesevelam is a bile acid sequestrant. It is available as 625 mg tablets and the Health Canada approved dose is six tablets per day as monotherapy, or four to six tablets per day in combination therapy. Maximum recommended doses are seven tablets per day as monotherapy or six tablets per day in combination therapy.

#### Summary of CDEC Considerations:

The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of RCTs of colesevelam and a critique of the manufacturer's pharmacoeconomic evaluation. No patient groups responded to the CDR Call for Patient Input.

## Common Drug Review

No RCTs met the minimum inclusion criteria for the CDR systematic review, as there were no RCTs comparing colesevelam with other bile acid sequestrants (cholestyramine and colestipol), niacin, or ezetimibe for the indication under review. The Committee considered a summary of information relevant to colesevelam, prepared by the CDR, which included:

- placebo-controlled trials of colesevelam that did not meet the CDR systematic review protocol
- an indirect comparison of colesevelam with other bile acid sequestrants
- comparator characteristics
- a long-term (50-week) extension study
- dose-response relationship for colesevelam
- benefits and harms of colesevelam in patients with normal low-density lipoprotein cholesterol (LDL-C) at high risk for cardiovascular events.

### Summary of Findings:

#### **Benefits**

The CDR identified 10 placebo-controlled trials evaluating colesevelam in patients with hypercholesterolemia in monotherapy or in combination with a statin. None of the trials required a previous trial of statin therapy titrated to the maximum tolerated dose. Colesevelam monotherapy was consistently superior to placebo in reducing LDL-C levels by 12% to 18% in the reviewed trials. When added to a statin, colesevelam was not consistently superior to placebo (LDL-C reductions of 4% to 18%). Doses of statins used in the trials were considered low compared to the current recommendations. Gastrointestinal adverse events were more frequently reported in colesevelam groups compared with placebo groups, although the statistical significance of these differences was not reported.

The unpublished indirect comparison submitted by the manufacturer failed to detect statistically significant differences between colesevelam and cholestyramine in reduction of LDL-C; however, statistical significance was reached in favour of colesevelam compared with colestipol. The indirect comparison failed to identify between-treatment differences in gastrointestinal tolerability. CDR noted that head-to-head comparisons of bile acid sequestrants are lacking. Limitations that undermine the validity of the indirect comparison and increase the uncertainty of the results include trial heterogeneity, absence of information related to patient characteristics, and no evaluation of the quality of the methodology used in the trials.

Results of one long-term extension study indicated that sustained use of colesevelam did not lower LDL-C levels more than 15%. Approximately half of the study patients were not titrated to maximum doses of colesevelam, and the majority of patients who discontinued treatment due to adverse events did so due to gastrointestinal adverse events.

Reduction in LDL-C by colesevelam appears to be dose-dependent, but higher doses are also associated with a decreased tolerability. No studies examining the use of colesevelam in patients who were at high risk of cardiovascular events but who had normal LDL-C levels were identified by CDR.

#### **Cost and Cost-Effectiveness**

The manufacturer submitted a cost-minimization analysis comparing colesevelam with the other bile acid sequestrants (cholestyramine and colestipol) for the treatment of patients with

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## Common Drug Review

hypercholesterolemia (Fredrickson type IIa), based on the results of an indirect comparison. There is uncertainty regarding the dose equivalence of colesevelam and the comparators (cholestyramine and colestipol); therefore, CDR considered a range of dosing scenarios for these agents. Based on recommended daily doses, the cost of colesevelam (\$4.40 to \$7.70; 2.5 g to 4.5 g) is more expensive than colestipol (\$0.91 to \$5.46; 5 g to 30 g) and only similar to cholestyramine at the higher dose range (\$1.32 to \$7.90; 4 g to 24 g).

### **Patient Input Information:**

No patient groups responded to the CDR Call for Patient Input.

### **Other Discussion Points:**

- The Committee noted the manufacturer's claims of improved tolerability and reduced gastrointestinal adverse effects compared with other bile acid sequestrants; however, there is no direct evidence to support this claim.
- The Committee emphasized that the Health Canada-approved indication for colesevelam is in Fredrickson type IIa hypercholesterolemia. The Committee noted that there is considerable potential for off-label use of colesevelam in other forms of hypercholesterolemia.

### **CDEC Members:**

Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Julia Lowe, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

### **September 19, 2012 Meeting**

#### **Regrets:**

Two CDEC members did not attend.

### **November 21, 2012 Meeting**

#### **Regrets:**

None

#### **Conflicts of Interest:**

None

### **About This Document:**

CDEC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC made its recommendation. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

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The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The CDEC 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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### Common Drug Review

CDEC Meeting – September 19, 2012; CDEC Meeting – November 21, 2012

Notice of CDEC Final Recommendation – December 19, 2012

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