# CEDAC FINAL RECOMMENDATION

## DESVENLAFAXINE
## (Pristiq™ – Wyeth Canada)
## Indication: Major Depressive Disorder

**Recommendation:**
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that desvenlafaxine not be listed.

**Reasons for the Recommendation:**
1. There were no randomized controlled trials comparing desvenlafaxine at Health Canada approved doses with its parent compound, venlafaxine and desvenlafaxine is more expensive than generic venlafaxine at recommended daily doses.

**Of Note:**
1. The Committee noted the importance of having relevant and robust randomized controlled trials that permit comparisons between an active metabolite and its parent compound.

**Background**
Desvenlafaxine is approved by Health Canada for the treatment of major depressive disorder. It is a serotonin-norepinephrine reuptake inhibitor and is the active metabolite of the antidepressant venlafaxine. It is available as 50 mg and 100 mg extended-release tablets, and the Health Canada approved dose is 50 mg daily, to a maximum of 100 mg daily.

**Summary of CEDAC Considerations:**
The Committee considered the following information prepared by the Common Drug Review: a systematic review of double-blind randomized controlled trials of desvenlafaxine and a critique of the manufacturer's pharmacoeconomic evaluation.

***Clinical Trials***
The systematic review included four double-blind randomized placebo-controlled trials evaluating desvenlafaxine at Health Canada-recommended doses (50 mg and/or 100 mg daily) in adults with major depressive disorder. Three of the trials evaluated desvenlafaxine 50 mg, and four of the trials evaluated desvenlafaxine 100 mg. One of the trials also included a duloxetine reference group, but the study was not designed for statistical comparisons between the desvenlafaxine and duloxetine groups and the manufacturer did not present these comparisons.

All four trials were of short duration, eight weeks, with sample sizes from 474 to 638. Study withdrawals were high; approximately 20% in three of the four trials. There were no differences in withdrawals between desvenlafaxine (50 mg or 100 mg) and placebo in any of the studies. Trials included patients with mild to moderate depression who were otherwise healthy limiting external validity.

### *Outcomes*

The primary outcome in the four trials was change from baseline in the 17-item Hamilton Rating Scale for Depression (HAM-$D_{17}$). The CDR systematic review also considered the following outcomes: quality of life, functional outcomes, remission, response and change from baseline in the Montgomery Asberg Depression Rating Scale (MADRS).

### *Efficacy or Effectiveness*

- Improvements in HAM-$D_{17}$ scores from baseline were statistically significant for desvenlafaxine 50 mg compared with placebo in two of three trials and for desvenlafaxine 100 mg compared with placebo in three of four trials. A difference of three points in HAM-$D_{17}$ scores is considered clinically significant. Treatment differences compared with placebo ranged from 1.1 (95% CI: -0.6 to 2.7) to 3.0 (95% CI: 1.4 to 4.7) for desvenlafaxine 50 mg or 100 mg.
- Remission was defined as a HAM-$D_{17}$ total score of ≤ 7 out of a total possible score of 52, where higher scores on the HAM-$D_{17}$ indicate more severe depression. A statistically significant difference was observed in only one of three trials comparing desvenlafaxine 50 mg with placebo and in two of four trials comparing desvenlafaxine 100 mg with placebo.
- Responders were defined as patients having a 50% improvement in HAM-$D_{17}$ score, compared with baseline. A statistically significant difference in the proportion of responders was observed in one of three trials comparing desvenlafaxine 50 mg with placebo and in two of four trials comparing desvenlafaxine 100 mg with placebo.
- Statistically significant improvements in quality of life, functional outcomes and improvements in MADRS scores for desvenlafaxine compared with placebo were not consistently observed across desvenlafaxine doses and across the four trials.

### *Harms (Safety and Tolerability)*

- Nausea was the most frequently observed adverse event among patients receiving desvenlafaxine compared with placebo. A dose-dependent increase in harm was observed for adverse events such as sexual dysfunction, insomnia, somnolence, and dry mouth.
- There was one suicide in a patient receiving desvenlafaxine 100 mg and five reports of suicidal ideation or behaviour in patients receiving desvenlafaxine and no reports in placebo-treated patients. Serious adverse events were few and similar between treatment groups.

### *Cost and Cost-Effectiveness*

The manufacturer submitted a cost-minimization analysis comparing the price of desvenlafaxine to venlafaxine and selective serotonin reuptake inhibitors (SSRIs). This analysis was based on the manufacturer's claims of similar efficacy and safety between desvenlafaxine and venlafaxine, and similar efficacy between desvenlafaxine and SSRIs. There is no randomized controlled trial evidence to support these claims.

At recommended doses, the daily cost of desvenlafaxine ($2.57) is greater than generic venlafaxine ($0.84 to $2.52) and within the range of costs of SSRIs ($0.63 to $3.21).

**Other Discussion Points:**

- Desvenlafaxine differs from venlafaxine as it is metabolized independently of the cytochrome P450 2D6 enzyme, however, desvenlafaxine is a minor cytochrome P450 3A4 enzyme inhibitor. No meaningful data were provided assessing the clinical relevance of these pharmacokinetic properties.
- Venlafaxine is the parent drug of desvenlafaxine and is considered the most relevant comparator. No trials were found that compared desvenlafaxine at the Health Canada-approved doses with venlafaxine, or with other commonly prescribed comparators such as SSRIs.

**CEDAC Members Participating**

July 15th, 2009: Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, Dr. Yvonne Shevchuk, and Dr. Kelly Zarnke.

September 16th, 2009: Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Mr. John Deven, Dr. Michael Evans, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, and Dr. Kelly Zarnke.

**Regrets**

July 15th, 2009: Dr. Michael Evans.

September 16th, 2009: Dr. Yvonne Shevchuk.

**Conflicts of Interest**

CEDAC members reported no conflicts of interest related to this submission.

**About This Document:**

CEDAC provides formulary listing recommendations to publicly funded drug plans.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CEDAC made its recommendation. An overview of these reviews, as well as a plain language version of this document is posted on the CADTH website when available.

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

The CEDAC Final 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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