CDEC FINAL RECOMMENDATION

AFLIBERCEPT
(Eylea — Bayer Inc.)
Indication: Diabetic Macular Edema

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that aflibercept be listed for the treatment of diabetic macular edema (DME), if the following conditions are met:

Conditions:
- Listed in a manner similar to ranibizumab
- Aflibercept should provide cost savings for drug plans relative to ranibizumab for the treatment of DME.

Reasons for the Recommendation:
1. Two double-blind randomized controlled trials (RCTs) (VIVID, N = 270; and VISTA, N = 310) demonstrated that aflibercept is superior to laser photocoagulation for improving visual acuity in patients with DME.
2. At the submitted price ($1,418.00 per vial), treatment with aflibercept appears to be less costly than treatment with ranibizumab ($1,575 per vial); however, the extent to which aflibercept is cost-saving depends on the frequency of administration.

Background:
Aflibercept is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of DME, of neovascular (wet) age-related macular degeneration, and of visual impairment due to macular edema secondary to central retinal vein occlusion. The current CADTH Common Drug Review (CDR) submission is for the treatment of DME.

Aflibercept is available as a single-use vial containing 0.278 mL solution to deliver a single dose of 2 mg/0.05 mL. For the treatment of DME, the product monograph recommends a dose of 2 mg (0.05 mL) administered by intravitreal injection once every four weeks for the first five consecutive doses, followed by one injection every eight weeks.

Summary of CDEC Considerations:
CDEC considered the following information prepared by CDR: a systematic review of double-blind RCTs and pivotal studies, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to patients with DME. CDEC also considered the findings of a multi-centre RCT undertaken by the Diabetic Retinopathy Clinical Research Network (DRCRN) and sponsored by the National Institutes of Health, designed to compare the safety and efficacy of aflibercept, bevacizumab, and ranibizumab in the treatment of DME. The results of this RCT were published after the CDR literature search had been completed; however, key safety and efficacy findings from this study were included in the final version of the CDR Clinical Review report and were discussed by CDEC.

Patient Input Information
The following is a summary of information provided by one patient group that responded to the CDR call for patient input:

- Individuals with DME suffer from a loss of vision, which has an impact on daily functioning and quality of life. Those affected can lose their ability to work, drive, and read standard print. As a result, they often need assistance from caregivers to drive them to appointments or to run errands, or to help them with household chores and meal preparation. In addition, they face an increased risk of injury.
- There are also social and emotional implications to vision loss; patients may experience depression, a sense of isolation and reduced independence, and uncertainty regarding pending loss of vision. Family dynamics often change as patients become more reliant on those around them.
- Current therapeutic options for DME include laser therapy or injection therapies (e.g., ranibizumab). Patients would benefit from having another Health Canada–approved option for the treatment of DME should one therapy cause adverse reactions or not be available.
- Patients anticipate that those taking aflibercept will require fewer injections than those taking ranibizumab, a difference many regard as important.

Clinical Trials
The CDR systematic review included two similarly designed, double-blind, double-dummy, multi-centre, active-controlled RCTs (VIVID, N = 270; and VISTA, N = 310). Participants in both trials were randomized to one of three treatment groups: aflibercept 2 mg every four weeks; aflibercept 2 mg every eight weeks after five initial injections at weeks 0, 4, 8, 12, and 16; or laser photocoagulation treatment. In accordance with the Health Canada–approved dosage regimen, the data for aflibercept 2 mg every four weeks were not a focus of the CDR review. Patients could receive additional (rescue) treatment starting at week 24, based on predefined criteria for worsening of visual acuity. The VIVID and VISTA studies were designed to continue for three years. As the primary outcome was the change in visual acuity at 52 weeks, the results presented in this review are derived from data from the first year of treatment.

Outcomes
Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- Visual acuity measured with Early Treatment Diabetic Retinopathy Study (ETDRS) letters — ETDRS charts present a series of five letters of equal difficulty on each row, with standardized spacing between letters and rows. ETDRS was assessed using the following:

  - Change from baseline in best-corrected visual acuity (BCVA) as measured by ETDRS letter score at week 52
  - Proportion of patients who lost 15 letters or more in the ETDRS letter score
  - Proportion of patients who gained 15 letters or more in the ETDRS letter score.
- Proportion of eyes with a two-step improvement in the ETDRS Diabetic Retinopathy Severity Scale (DRSS) score at week 52. The DRSS consists of 13 levels of graded photographic characteristics that were defined to categorize severity of diabetic retinopathy for individual eyes, ranging from no retinopathy to severe vitreous hemorrhage.
- Change in central retinal thickness (CRT) — defined as the change from baseline in thickness of the centre subfield (the area of the retina using a 1 mm diameter around the centre of the macula) evaluated using optical coherence tomography (OCT).
- National Eye Institute (NEI) Visual Functioning Questionnaire-25 (VFQ-25) — a 25-item questionnaire that assesses 11 vision-related constructs, in addition to a single-item general health component. The possible range of the NEI VFQ-25 total score is between 0 (worst possible) and 100 (best possible).
- Serious adverse events, total adverse events, ocular adverse events, and withdrawals due to adverse events.

The primary outcome was the change in BCVA as assessed by the change in the number of ETDRS letters after 52 weeks of treatment with aflibercept 2 mg every eight weeks after five initial monthly injections compared with laser treatment.

- In both studies, aflibercept was statistically superior to laser for change from baseline in ETDRS letter score. The least squares (LS) mean differences for aflibercept versus laser were 9.1 (97.5% confidence interval [CI], 6.3 to 11.8) in VIVID and 10.4 (97.5% CI, 7.7 to 13.2) in VISTA.
- A statistically significantly greater proportion of aflibercept-treated patients gained ≥ 15 letters compared with the laser treatment group in both VIVID (27.7% versus 7.5%; $P = 0.0006$) and VISTA (29.1% versus 14.3%; $P < 0.0017$). In addition, statistically significantly fewer aflibercept-treated patients lost ≥ 15 letters compared with the laser treatment group in both VIVID (0% versus 10.6%; $P < 0.0001$) and VISTA (0.7% versus 9.1%; $P = 0.0007$). The adjusted differences of proportions for aflibercept versus laser were as follows (VIVID and VISTA, respectively):
  - Gained ≥ 15 letters: 24.2% (97.5% CI, 13.5 to 34.9) and 23.3% (97.5% CI, 13.5 to 33.1)
  - Lost ≥ 15 letters: –10.6% (97.5% CI, –16.6 to –4.6) and –8.4% (97.5% CI, –13.8 to –3.0)
- In both studies, a statistically significantly greater proportion of aflibercept-treated patients achieved a two-step or greater improvement from baseline on the ETDRS DRSS compared with the laser treatment group: 33.3% versus 9.1% in VIVID ($P < 0.0001$) and 31.1% versus 7.8% in VISTA ($P < 0.0001$). The adjusted differences of proportions for aflibercept versus laser were 19.3% (97.5% CI, 6.6 to 32.1) in VIVID and 14.9% (97.5% CI, 4.4 to 25.4) in VISTA.
- There were no statistically significant differences between aflibercept and laser with regard to changes in NEI VFQ-25 total score. The differences in LS mean change for aflibercept versus laser were:
  - VIVID: 0.80 (97.5% CI, –1.9 to 3.5); $P = 0.5034$
  - VISTA: 2.42 (97.5% CI, –0.7 to 5.6); $P = 0.0844$.

Harms (Safety and Tolerability)

- The proportion of patients who experienced at least one serious adverse event was greater in the laser treatment groups (3.9% to 4.3%) than in the aflibercept groups (1.3% to 2.2%) in VIVID and VISTA, respectively. Vitreous hemorrhage, diabetic retinopathy, and retinal revascularization were the most commonly reported serious adverse events.
- The proportions of patients who withdrew as a result of adverse events were:
  - VIVID: 3.0% in the aflibercept group and 5.9% in the laser treatment group
  - VISTA: 1.3% in the aflibercept group and 1.9% in the laser treatment group.
- Compared with patients who received aflibercept, the incidences of ocular adverse events and ocular surgeries were numerically greater in the laser group in both studies. The most commonly reported ocular adverse events were conjunctival hemorrhage, eye pain, cataract and vitreous floaters.

Additional Studies

The DRCRN study included adults with type 1 or 2 diabetes, at least one eye with a BCVA ETDRS letter score of 78 to 24, centre-involved DME, and with no anti-VEGF treatment within the previous 12 months. Of the patients in the study, 660 were randomized (1:1:1) to receive aflibercept (2.0 mg every four weeks), bevacizumab (1.25 mg every four weeks), or ranibizumab (0.3 mg every four weeks). The primary outcome was the mean change in visual acuity at one year with adjustment for baseline visual acuity. As bevacizumab is not approved for the treatment of DME in Canada, the CDR review and CDEC deliberations focused on aflibercept and ranibizumab. Key safety and efficacy data were reported as follows:

- The mean improvement in ETDRS letters at one year was statistically significantly greater in patients treated with aflibercept compared with those treated with ranibizumab (13.3 versus 11.2 letters, respectively). The mean difference in change from baseline in ETDRS letters between the aflibercept and ranibizumab groups was 2.1 (P = 0.03).
- Central subfield retinal thickness was reduced by 169 µm ± 138 µm with aflibercept and 147 µm ± 134 µm with ranibizumab; the thickness was less than 250 µm in 66% of eyes and 58% of eyes in aflibercept and ranibizumab, respectively.
- There were no notable differences among the study groups in the rates of serious adverse events, hospitalization, death, and major cardiovascular events.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing aflibercept with ranibizumab in adults with DME, from the perspective of the public payer, over a 20-year time horizon. The model was based on three time frames for analysis and health states as defined by visual acuity. Data from RCTs of aflibercept compared with laser were used to estimate changes in visual acuity in the first year; stabilization of vision then occurred for years 2 to 3, followed by vision deterioration over time. Relative efficacy and safety were obtained from an indirect comparison of ranibizumab with aflibercept conducted by the manufacturer. Treatment frequency was based on the clinical trials included in the indirect comparison (aflibercept: 8.5 injections in year 1, 5.1 in year 2, 2.9 in year 3; ranibizumab: 8.1 in year 1, 3.9 in year 2, 2.9 in year 3), resulting in a gain of 0.202 quality-adjusted life-years and an additional cost of $118 with aflibercept over a 20-year time frame, yielding an incremental utility ratio of $586.

The manufacturer's economic submission is sensitive to the comparative clinical effect estimates obtained from the indirect comparison. While the results of the indirect comparison suggest some clinical differences between aflibercept and ranibizumab, no statistically

significant difference was observed in the outcome measure used in the model (probability of gaining or losing ≥ 10 or ≥ 15 letters). Given the uncertainty regarding the interpretation of whether clinically meaningful gains were achieved with aflibercept when compared with ranibizumab, an alternate approach is to assume similar clinical effects between the treatments and to consider the comparative costs.

Costs are driven largely by drug acquisition ($1,418 aflibercept; $1,575 ranibizumab per dose in single-use vials, based on publicly available prices for ranibizumab); injection cost ($105), and frequency of administration. When comparing drug and administration costs using dosing frequencies obtained from clinical trials, similar costs are observed for aflibercept and ranibizumab (increased cost of $80 per patient receiving aflibercept). If the two treatments are administered with the same frequency (both at seven doses in the first year and two doses in the second year), patients receiving aflibercept incur lower costs ($1,384 savings for patients on aflibercept over two years). There is uncertainty regarding the impact of relative frequency on effectiveness and what the actual relative frequency of administration of these two agents in clinical practice will be.

Other Discussion Points:
CDEC noted that there is currently variation in the listing criteria used by the CDR-participating drug plans for ranibizumab.

CDEC Members:
Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

April 8, 2015 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 CDR reviews and used in CDEC deliberations.

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

The Final 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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