CDEC FINAL RECOMMENDATION

AFLIBERCEPT
(Eylea — Bayer Inc.)
Indication: Wet Age-related Macular Degeneration

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that aflibercept be listed for the treatment of neovascular (wet) age-related macular degeneration (AMD), if the following condition is met:

Condition:
- Drug plan cost for the treatment of wet AMD with aflibercept should provide cost-savings relative to the treatment of wet AMD with ranibizumab.

Reasons for the Recommendation:
1. Two double-blind randomized controlled trials (RCTs) (VIEW 1 and VIEW 2) demonstrated that aflibercept is non-inferior and clinically equivalent to ranibizumab for maintaining vision in treatment-naive patients with wet AMD.
2. At the submitted price, treatment of wet AMD with aflibercept appears to be less costly than treatment with ranibizumab.

Background:
Aflibercept is a recombinant fusion protein consisting of portions of human VEGF receptor 1 and 2 extracellular domains fused to the Fc portion of human IgG1 and formulated as an iso-osmotic solution for IVT administration. Aflibercept is indicated for the treatment of patients with wet AMD. Aflibercept is available as a single-use vial containing 278 µL solution to deliver a single dose of 2 mg/0.05 mL. The recommended dose is 2 mg (0.05 mL) administered by intravitreal injection every month for the first three months, followed by 2 mg (0.05 mL) through intravitreal injection every two months.

Summary of CDEC Considerations
CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs of aflibercept in wet AMD, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to individuals living with wet AMD.

Patient Input Information

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

- Visual impairment severely affects the quality of life of individuals with wet AMD. Patients may lose their ability to complete daily activities and become reliant on the assistance of caregivers to attend medical appointments, prepare meals, go shopping, and participate in social activities. Depression can also set in due to the reduction or loss of independence, the actual or potential loss of employment, the loss of driving privileges, and the fear of a life with little or no vision. Patients also become more susceptible to falls.
- Caregivers have to deal with all the emotional effects of vision loss in someone who had been previously independent. They may be required to take time off work to transport patients and to perform or help with a variety of household tasks.
- Individuals with wet AMD would prefer a treatment that required less frequent injections than are required for treatment with ranibizumab.
- Individuals with wet AMD would also like to have access to another approved treatment since ranibizumab does not work as well as desired for all patients.

Clinical Trials

The CDR systematic review included two similarly designed double-blind, multi-centre, active-controlled, RCTs (VIEW 1 [N = 1,217] and VIEW 2 [N = 1,240]). Both studies assessed whether aflibercept was non-inferior to ranibizumab for preventing moderate vision loss (≥ 15 Early Treatment Diabetic Retinopathy Study [ETDRS] letters) in treatment-naive patients with wet AMD. VIEW 1 and VIEW 2 included a 52-week, fixed-dose phase and a subsequent 44-week flexible-dose phase. Both VIEW 1 and VIEW 2 randomized patients to one of the following four treatment groups: 0.5 mg aflibercept every four weeks; 2 mg aflibercept every four weeks; 2 mg aflibercept every eight weeks after three injections at weeks 0, 4, and 8 (to maintain masking, sham injections were given at the interim four-week visits after week 8); or 0.5 mg ranibizumab every four weeks. The CDR review focused on the recommended dosage regimen of aflibercept (2 mg every eight weeks) and ranibizumab (0.5 mg four weeks).

Outcomes

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

- The proportion of patients with maintained vision — defined as a visual acuity loss of fewer than 15 ETDRS letters compared with baseline at week 52.
- Visual acuity measured with 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 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.
- Visual acuity measured with the Snellen Eye Chart — a commonly employed test of visual acuity used in clinical practice.
- 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, and withdrawals due to adverse events.

The primary outcome analysis was non-inferiority of aflibercept to ranibizumab in the proportion of patients maintaining vision (i.e., loss of < 15 letters) at week 52 (per-protocol analysis set [PPS]) in both studies. The non-inferiority margin was set as < 10% of the 95% confidence interval (CI) of the difference between ranibizumab and aflibercept in the proportion of patients who maintained vision at week 52 compared with baseline. The clinical equivalence margin was < 5% of the same 95% CI.

Efficacy

- Aflibercept was non-inferior and clinically equivalent to ranibizumab for maintaining vision over 52 weeks. Between-group difference of changes from baseline were –0.7% (95% CI, –4.5 to 3.1%; *P* = 0.73) and –1.13 (95% CI, –4.81 to 2.55; *P* = 0.55) in VIEW 1 and VIEW 2 respectively, which was below the pre-specified non-inferiority margin of 10% and the clinical equivalence margin of 5%.
- There was no statistically significant difference in the change from baseline to week 52 in ETDRS letter score in the study eye. The least square mean difference between the aflibercept and ranibizumab groups was 0.26 (95% CI, –1.97 to 2.49) in VIEW 1 and –0.90 (95% CI, –3.06 to 1.26) in VIEW 2.
- There was no statistically significant difference between the aflibercept and ranibizumab groups for the proportion of patients who gained ≥ 15 EDTRS letters at 52 weeks:
  - VIEW 1: 31% in both the aflibercept and ranibizumab groups; difference of proportions –0.40% (95% CI, –7.7% to 7.0%).
  - VIEW 2: 31% with aflibercept and 34% with ranibizumab; difference of proportions –2.65% (95% CI, –10.2% to 4.9%).
- There was no statistically significant difference between the aflibercept and ranibizumab groups for the proportion of patients who [redacted]:
  [redacted]
- The NEI VFQ-25 total score improved by approximately five points in both the ranibizumab and aflibercept groups in both studies and there were no statistically significant differences between the two groups.
- The proportion of legal blindness decreased in both groups of VIEW 1 and VIEW 2. [redacted]

Harms (Safety and Tolerability)

- The proportion of patients with at least one serious adverse event was reported as follows:
  - VIEW 1: 18.5% with aflibercept and 22.4% with ranibizumab.
  - VIEW 2: 15.6% with aflibercept and 12.0% with ranibizumab.
- The proportion of patients with at least one adverse event was reported as follows:
  - VIEW 1: 95% with either aflibercept or ranibizumab.
  - VIEW 2: 90% with aflibercept and 86% with ranibizumab.
- The proportion of patients who withdrew from the trial due to adverse events was:
  - VIEW 1: 1.3% in both the aflibercept and ranibizumab groups.
  - VIEW 2: 2.9% with aflibercept and 0.7% with ranibizumab.
- The most commonly reported adverse events were conjunctival hemorrhage, vitreous floaters, eye pain, vitreous detachment, reduced visual acuity, retinal pigment epitheliopathy, macular degeneration, and increased intraocular pressure.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis that assumed similar efficacy and harms, based on the results of head-to-head trials in patients with wet AMD, when aflibercept was administered every eight weeks in the first year after three monthly loading doses and as needed thereafter compared with ranibizumab administered monthly for the first year and as needed thereafter. The manufacturer assumed that health care costs were the same for both drugs with the exception of the number of injection administrations. The manufacturer also submitted a cost-utility analysis comparing aflibercept and ranibizumab (with individualized dosing), but given concerns regarding some of the assumptions in the model and the results of the head-to-head study, the cost-minimization analysis was deemed appropriate. The manufacturer concluded that treatment with aflibercept would result in cost-savings of $23,127 per patient over 10 years compared with ranibizumab. Based on ranibizumab dosing frequencies more likely to be used in clinical practice (6.8 to 7.5 doses in the first year and 5.0 to 5.8 doses per year thereafter) and uncertainty in the frequency with which aflibercept will be used (7.5 to 12 doses in first year and 5.0 to 5.8 doses per year thereafter), CDR estimated the potential cost-savings with aflibercept to be in the range of $7,000 to $15,000 per patient relative to ranibizumab when patients were treated for 10 years.

At the submitted price of $1,418 per vial, the per-dose cost of aflibercept (2 mg per dose) is less than ranibizumab ($1,575 per 0.5 mg dose), based on single-use vials. At recommended dosing, aflibercept (2 mg every two months after monthly doses for three months — 7 doses; $9,926) would remain less costly in the first year compared with ranibizumab (0.5 mg monthly; $18,900). The cost-savings for aflibercept would depend on any individualized dosing of aflibercept and ranibizumab.

Other Discussion Points:

CDEC noted the following:

- A clinical expert consulted during the CDR review suggested that, in clinical practice, there is the potential that aflibercept may be administered more frequently than recommended in the product monograph.
- Treatment with aflibercept requires fewer injections than treatment with ranibizumab.
- Bevacizumab is less costly than ranibizumab; however, this drug is not approved for the treatment of wet AMD. CDEC noted that some CDR-participating drug plans currently reimburse for bevacizumab in wet AMD.

Research Gaps:

CDEC noted that there is insufficient evidence regarding the following:

- Limited evidence regarding the safety and efficacy of aflibercept beyond 52 weeks of treatment.
- There is no RCT evidence regarding the use of aflibercept in treatment-experienced patients or patients requiring treatment in both eyes.

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.

September 17, 2014 Meeting

Regrets:
None

Conflicts of Interest:
None

About This Document:
CDEC provides formulary listing recommendations or advice to CDR participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The CDEC recommendation or record of advice 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.