CDEC FINAL RECOMMENDATION

AFLIBERCEPT
(Eylea — Bayer Inc.)
Indication: Macular Edema Secondary to Central Retinal Vein Occlusion

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that aflibercept be listed for the treatment of macular edema secondary to central retinal vein occlusion (CRVO), if the following clinical criterion and condition are met:

Clinical criterion:
- Not previously treated with a vascular endothelial growth factor (VEGF) inhibitor.

Condition:
- Aflibercept should provide cost savings for drug plans relative to ranibizumab for the treatment of CRVO.

Reasons for the Recommendation:
1. Two double-blind, sham-controlled, randomized controlled studies (RCTs) (COPERNICUS, N = 188; and GALILEO, N = 171) suggest that 24 weeks of treatment with 2 mg aflibercept every four weeks is superior to sham injection for improving visual acuity in patients with CRVO.
2. At the submitted price ($1,418.00 per vial), 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 VEGF inhibitor indicated for the treatment of diabetic macular edema (DME), of neovascular (wet) age-related macular degeneration, and of visual impairment due to macular edema secondary to CRVO. The current CADTH Common Drug Review (CDR) submission is for treatment of macular edema secondary to CRVO.

Aflibercept is available as a single-use vial containing a 0.278 mL solution to deliver a single dose of 2 mg/0.05 mL. For the treatment of CRVO, the product monograph recommends a dose of 2 mg (0.05 mL) administered by intravitreal injection once every month, with the interval

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between two doses not being shorter than one month. The product monograph states the treatment interval may be extended up to three months based on visual and anatomic outcomes and that prescribers are advised to periodically assess the need for continued therapy.

Summary of CDEC Considerations:
CDEC considered the following information prepared by CDR: a systematic review of RCTs and pivotal studies, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to individuals with CRVO.

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 loss associated with CRVO has an impact on the daily functioning and quality of life of those who are affected by this condition. Patients with CRVO may lose their ability to work, drive, and read standard print. As a result, they often need assistance from caregivers to drive them to appointments, 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 CRVO include laser therapy or injection therapies (e.g., ranibizumab). Patients would benefit from having another Health Canada–approved option for the treatment of CRVO should one therapy cause adverse reactions or not be available .
- Patients anticipate that those taking aflibercept will require fewer injections than those taking ranibizumab. Many would regard this difference as important.

Clinical Trials
The CDR systematic review included two studies, GALILEO (N = 171) and COPERNICUS (N = 188). Both studies were randomized, multi-centre, double-masked, sham-controlled studies designed to assess the superiority of aflibercept over sham injection for the treatment of macular edema secondary to CRVO. GALILEO was a 76-week, two-group RCT conducted in 10 countries in Europe and the Asia-Pacific region. COPERNICUS was a 100-week, two-group RCT conducted in five countries including Canada. The duration of the masked, controlled treatment period in both studies was 24 weeks. In both studies, patients were treatment-naive adults with macular edema secondary to CRVO and best-corrected visual acuity (BCVA) scores measured with an Early Treatment Diabetic Retinopathy Study (ETDRS) letter score of 20/40 (73 letters) to 20/320 (24 letters) in the study eye. In both studies, patients were randomized to receive either 2 mg intravitreal (IVT) aflibercept or a sham injection every four weeks. The primary efficacy outcome was the proportion of patients who gained at least 15 BCVA letters at 24 weeks compared with baseline.

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

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- 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:
  - Proportion of patients who gained 15 letters or more in the ETDRS letter score
  - Change from baseline in BCVA as measured by ETDRS letter score at week 24
  - Proportion of patients who lost 15 letters or more in the ETDRS letter score.
- 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, and withdrawal due to adverse events.

In both GALILEO and COPERNICUS, the primary efficacy outcome was the proportion of patients who gained at least 15 ETDRS letters at week 24 (discontinued patients prior to week 24 were judged as failures) compared with baseline.

Efficacy

- A statistically significantly greater proportion of aflibercept-treated patients achieved an improvement of at least 15 BCVA letters compared with sham-injected patients at 24 weeks. The adjusted difference between the aflibercept and sham groups was 38.3% (95% confidence interval [CI], 24.4% to 52.1%) and 44.8% (95% CI, 33.0% to 56.0%) for GALILEO and COPERNICUS, respectively.
- Aflibercept treatment was associated with a statistically significantly greater improvement in baseline visual acuity compared with sham injection. At 24 weeks, the least squares mean difference (LSMD) for change from baseline BCVA between the aflibercept and sham injection groups was 14.7 letters (95% CI, 10.8 to 18.7 letters) in GALILEO and 21.7 letters (95% CI, 17.4 to 26.0 letters) in COPERNICUS.
- Aflibercept was associated with a statistically significant improvement in NEI VFQ-25 total score compared with the sham treatment. The LSMDs between the aflibercept and sham groups were 4.2 (95% CI, 1.7 to 6.8) in GALILEO and 6.26 (95% CI, 2.61 to 9.91) in COPERNICUS.
- In both GALILEO and COPERNICUS, aflibercept-treated patients had a statistically significantly greater decrease in CRT compared with the sham-injected group at 24 weeks. The LSMDs between the aflibercept and sham groups were –239 µm (95% CI, –286 µm to –192 µm) and –311 µm (95% CI, –389 µm to –234 µm) in GALILEO and COPERNICUS, respectively.

Harms (Safety and Tolerability)

- There were fewer serious adverse events in the aflibercept treatment groups (8.7% and 9.6% for GALILEO and COPERNICUS, respectively) compared with the sham injection groups (14.7% and 21.6%, respectively) through 24 weeks.
- The proportion of patients who withdrew as result of adverse events was lower in the aflibercept treatment groups (1.9% and 1.8%) compared with sham-injected patients (8.8% and 6.8%).

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- Arterial thromboembolic events were infrequent (fewer than seven overall through 52 weeks across both studies). In COPERNICUS, fewer aflibercept-treated patients experienced a ≥ 10 mm Hg increase in intraocular pressure (2.6%) compared with the sham injection group (9.5%), but there was no difference between treatments in GALILEO (2.9% for both aflibercept- and sham-treated patients).

Cost and Cost-Effectiveness

The manufacturer submitted a cost minimization analysis with an assumption of similar clinical efficacy and harms, based on the results of an unpublished network meta-analysis that compared aflibercept, ranibizumab, and dexamethasone implants in adults with CRVO. Two main analyses were provided: a clinical trial analysis and a reimbursement request analysis. The analyses were conducted from a payer perspective where drug acquisition, injection, and monitoring costs were included. The clinical trial analysis assumed weighted average frequency of administration from the COPERNICUS and GALILEO trials for aflibercept and from the CRUISE trial for ranibizumab: 8.4 injections in year 1 and 3.0 in year 2 for aflibercept, versus 8.8 injections in year 1 and 3.5 in year 2 for ranibizumab. For the reimbursement request analysis, the manufacturer used the CDEC recommendation for ranibizumab that reimbursement be limited to a maximum of 24 months and 12 vials for patients with CRVO to assume that both agents would be administered nine times in year 1 and three times in year 2. The manufacturer reported in its clinical trial analysis that the use of aflibercept resulted in a savings of $3,174 per patient when compared with ranibizumab over two years (total cost per patient for aflibercept of $18,302, versus $21,476 for ranibizumab), while in the reimbursement request analysis, the manufacturer reported a savings of $1,796 per patient receiving aflibercept compared with ranibizumab over two years ($19,216 for aflibercept, versus $21,012 for ranibizumab).

At the submitted price of $1,418 per vial, the cost per dose of aflibercept (2 mg) is less than ranibizumab ($1,575 per 0.5 mg dose), based on single-use vials. Aflibercept is cost-saving compared with ranibizumab at recommended dosing. The extent to which aflibercept will be cost-saving for the treatment of CRVO will depend on the frequency of administration in clinical practice relative to ranibizumab.

Other Discussion Points:

CDEC noted the following:

- Bevacizumab is not approved in Canada for the treatment of macular edema secondary to CRVO, but is reimbursed by some CDR-participating drug plans for the treatment of CRVO.
- There is currently variation in the listing criteria used by the CDR-participating drug plans for ranibizumab.

Research Gaps:

CDEC noted that there are no studies directly comparing aflibercept against ranibizumab for the treatment of macular edema secondary to CRVO.

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

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

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