CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

Aflibercept
(Eylea – Bayer Inc.)
New Indication: Macular edema secondary to branch retinal vein occlusion

Recommendation:
The Canadian Drug Expert Committee recommends that aflibercept be reimbursed for the treatment of branch retinal vein occlusion (BRVO) with the following clinical criteria and conditions.

Clinical criteria

1. For patients who do not respond to bevacizumab or in patients who experience thromboembolism following the initiation of bevacizumab treatment or who are at a high risk of cardiovascular adverse events.
2. Treatment should be discontinued if the patient fails to achieve clinically meaningful improvement after 24 weeks.

Conditions

1. Aflibercept should provide cost savings for drug plans relative to ranibizumab for the treatment of BRVO.

Reasons for the Recommendation:

1. The results of a CADTH Therapeutic Review of anti-VEGF drugs for treating retinal conditions suggest that there are no substantial differences among aflibercept, ranibizumab, and bevacizumab regarding the efficacy and safety of these drugs in treating retinal vein occlusion, and that switching among the anti-VEGFs occurs commonly in clinical practice.
2. The results of one randomized, double-blind, placebo-controlled trial, VIBRANT, suggest that the efficacy of aflibercept is superior to laser therapy for treating macular edema secondary to BRVO.
3. The results of an indirect comparison submitted by the manufacturer suggest that the efficacy of aflibercept is similar to that of ranibizumab and bevacizumab for treating macular edema secondary to BRVO.
4. There is no evidence of efficacy beyond 24 weeks in patients who do not respond to initial therapy.
5. Aflibercept is less expensive than ranibizumab at current prices (assuming similar injection frequencies) but is more expensive than bevacizumab.

Of Note:

1. CDEC noted that not all jurisdictions currently reimburse bevacizumab for the treatment of retinal conditions, including BRVO.
2. An inadequate response to treatment is defined as not achieving any improvement in best corrected visual acuity (BCVA) at 3 months or not achieving an improvement in BCVA at 6 months of at least 15 ETDRS letters compared to the baseline (pre-treatment) BCVA.
3. Individuals are considered to be at a high risk of cardiovascular adverse events if there is clinical evidence of atherosclerosis or they have had a previous myocardial infarction, have undergone coronary or arterial revascularization, or have a history of cerebrovascular disease (including transient ischemic attack) or peripheral arterial disease.
4. Aflibercept treatment requires administration by an ophthalmologist experienced in intravitreal injections
5. Drug plans should explore mechanisms to reduce the potentially large amount of wastage associated with single-use aflibercept vials.

Background:

Aflibercept has been approved previously by Health Canada for:

- the treatment of neovascular (wet) age-related macular degeneration (AMD)
- the treatment of diabetic macular edema (DME)
- the treatment of visual impairment due to macular edema secondary to central retinal vein occlusion (CRVO)

This submission for aflibercept was for the new Health Canada indication of treatment of visual impairment due to macular edema secondary to BRVO. Aflibercept is an anti-vascular endothelial growth factor (anti-VEGF). It is available as 40 mg/mL solution for Intravitreal Injection and the Health Canada approved dose is a 2 mg single-use vial.

Submission History:

Previous CDR reviews of aflibercept covered the indications for AMD, DME, and CRVO, each of which received a recommendation to list with clinical criteria and the condition that aflibercept provide cost savings relative to ranibizumab treatment. More recently, CADTH reviewed aflibercept in the context of a Therapeutic Review of anti-VEGF drugs for treating retinal conditions. Based on this therapeutic review, CDEC issued several recommendations in a Recommendation Report. The Recommendation Report includes the recommendation that bevacizumab is the preferred initial anti-VEGF therapy for the treatment of patients with retinal vein occlusion (RVO), although ranibizumab or aflibercept were recommended as alternative treatment options for patients who do not respond to bevacizumab or experience thromboembolism following the initiation of bevacizumab treatment or are at a high risk of cardiovascular adverse events.

Summary of CDEC Considerations:

The Committee considered the following information prepared by the Common Drug Review: a systematic review of phase III clinical trials and manufacturer-provided trials considered pivotal by Health Canada of the beneficial and harmful effects of aflibercept 40 mg/ml for the treatment of visual impairment due to macular edema secondary to branch retinal vein occlusion; a critique of the manufacturer's pharmacoeconomic evaluation; a literature review and critique of

available evidence from indirect treatment comparisons; the 2016 CADTH therapeutic review of anti-VEGF drugs used to treat retinal conditions; and previously submitted information from patient groups about outcomes and issues important to patients.

Patient Input Information

No patient input was received by CADTH for this submission. Since no patient input specific to this submission was received, CADTH clinical reviewers summarized patient input received previously from patient groups for the CDR reviews of aflibercept for diabetic macular edema and aflibercept for macular edema secondary to central retinal vein occlusion.

Clinical Trials

The CDR systematic review included one phase III randomized controlled trial of adults with visual impairment due to macular edema secondary to branch retinal vein occlusion.
The study included 183 patients randomized to either 2 mg aflibercept once every 4 weeks or laser treatment. The primary outcome was the proportion of patients who gained 15 or more letters in BCVA (ETDRS) at 24 weeks, with a subsequent follow-up of 28 weeks, to a total study period of 52 weeks. Limitations of the study included lack of power to assess relevant safety outcomes, lack of generalizability to patients who received previous treatment for BRVO or have concomitant retinal disease, and lack of direct evidence to compare against other anti-VEGF therapies used currently for macular edema.

Outcomes

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

- Number of patients with best corrected visual acuity (BCVA) gain ≥ 15 letters ETDRS
- Mean difference in BCVA change from baseline,
- Quality of life
- Serious adverse events, total adverse events, and withdrawals due to adverse events

Efficacy

The VIBRANT study demonstrated that a statistically significantly greater proportion of patients treated with aflibercept gained ≥15 ETDRS letters from baseline to week 24 than those treated with laser (52.7% vs 26.7%, p=0.0003). Patients treated with aflibercept also gained an average of 17.0 ETDRS letters (±11.88) at week 24 from baseline compared to 6.9 letters for those treated with laser (p<0.0001). Aflibercept was not associated with a statistically significant improvement in health-related quality of life measure (NEI VFQ-25) compared to the laser group.

Harms

In the VIBRANT trial, there were similar serious adverse events with aflibercept compared with laser treatment. Potentially serious concerns of anti-VEGF treatment include the theoretical increased risk of cardiovascular events as well as the serious complication of endophthalmitis. While aflibercept-treated patients did not appear to experience increased rates of adverse events for either of these categories of harm in the VIBRANT study, the study was underpowered to capture and detect any true differences between the two interventions for such relatively infrequent harms.

Evidence from indirect treatment comparisons
The critique included one manufacturer-submitted indirect treatment comparison (ITC) and one published indirect treatment comparison identified in the literature search. The available indirect evidence from two ITCs suggested that aflibercept is not associated with any significant differences in efficacy or safety outcomes when compared to the other anti-VEGFs, bevacizumab and ranibizumab, although this conclusion was highly uncertain.

Cost and Cost-Effectiveness
At the submitted price (which reflects the current Ontario Drug Benefit list price), aflibercept ($1,418 per dose) is less expensive than ranibizumab ($1,575 per dose), although both drugs are more expensive than bevacizumab (estimated at $40 per dose).

The manufacturer submitted a cost minimization analysis comparing aflibercept to ranibizumab over a two-year time horizon, from the perspective of a public healthcare payer. Only drug acquisition costs, injection administration costs, and monitoring costs were included in the calculation. The choice of analysis was based on the results of an unpublished network meta-analysis that compared aflibercept, ranibizumab, bevacizumab, dexamethasone, triamcinolone, and laser in patients with macular edema secondary to BRVO. Two main analyses were conducted. The 'clinical trial analysis' used the mean number of injections in year one from the one-year VIBRANT trial for aflibercept (9.0 injections) and the one-year BRAVO trial for ranibizumab (8.4 injections); and, the mean number of injections for both drugs in year two was obtained from the ranibizumab HORIZON extension study (2.1 injections). The 'equivalent injection frequency analysis' assumed a total of 12 injections over two years for both drugs, 9 in year one and three in year two. Both analyses assumed a total of 15 monitoring visits for aflibercept and 24 for ranibizumab, based on the manufacturer's interpretation of how the treat-and-extend and as-needed therapy regimens recommended in the product monographs would be monitored.

The manufacturer reported that use of aflibercept would result in a saving of $1,243 to $2,376 per patient when compared to ranibizumab over two years, depending on the frequency of injections. Assuming efficacy, safety, and injection frequency are equivalent, reanalyses by CDR estimated that the use of aflibercept is likely to result in savings of between $1,600 and $2,000 (considering 10 and 12 injections, respectively) per patient over the first two years of therapy compared to ranibizumab, but would cost $13,000 to $16,000 more than bevacizumab.

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, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

May 18, 2016:

Regrets: None

Conflicts of Interest: None

July 20, 2016:

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. CADTH addressed the request in accordance with the *CDR Confidentiality Guidelines.*

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