Common Drug Review
Pharmacoeconomic Review Report

July 2016

Drug	aflibercept (Eylea) 40 mg/mL solution for intravitreal injection available as a 2 mg single-use vial
Indication	Treatment of diabetic macular edema (DME)[a]
Listing request	For the treatment of DME, in a manner similar to ranibizumab
Manufacturer	Bayer Inc.

[a] Aflibercept is also indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD) and central retinal vein occlusion (CRVO), which have been reviewed separately.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in specializing in the treatment of retinal disease (ophthalmologist) who provided input on the conduct of the review and the interpretation of findings.

Parts of this material are based on information provided by the Canadian Institute for Health Information. However, the analyses, conclusions, opinions and statements expressed herein are those of the author, and not necessarily those of the Canadian Institute for Health Information.

Through the Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update – Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

AE	adverse event
BCVA	best-corrected visual acuity
CDEC	Canadian Drug Expert Committee
CDR	CADTH Common Drug Review
DME	diabetic macular edema
ETDRS	Early Treatment Diabetic Retinopathy Study
ICUR	incremental cost-utility ratio
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomized controlled trial
RR	relative risk
VA	visual acuity
VEGF	vascular endothelial growth factor

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Aflibercept (Eylea)
Study Question	"What is the incremental cost per quality-adjusted life-year (QALY) gained, from a provincial government payer perspective, for Eylea (aflibercept) compared with ranibizumab over a 20-year time horizon for the treatment of diabetic macular edema?"
Type of Economic Evaluation	Cost-utility analysis
Target Population	Patients with visual impairment due to DME based on patients enrolled in VISTA or VIVID
Treatment	Aflibercept 2 mg for intravitreal injection; two administration protocols: 1) clinical trial–based (monthly for 5 months, then bimonthly) and 2) reimbursement request (7 in year 1, 2 in year 2)
Outcome	QALYs
Comparator	Ranibizumab 0.5 mg for intravitreal injection; frequency of injection from trials included in MTC
Perspective	Provincial government payer
Time Horizon	Lifetime (20 years)
Results for Base Case	Reference (trial-based administration frequency): $586/QALY gained Reimbursement request: Aflibercept dominant
Key Limitations	• Relative efficacy: The manufacturer's model uses point estimates of relative efficacy (gain or loss of ≥ 10 or ≥ 15 ETDRS letters) from the MTC, which numerically favour aflibercept; however, these are not statistically significant, resulting in some uncertainty as to the likely clinical benefit of aflibercept. • As the cost comparison of aflibercept and ranibizumab is driven by the frequency of use, the manufacturer considered a scenario (reimbursement request scenario) assuming identical clinical outcomes to the base case but reduced frequency of administration (greater reduction for aflibercept vs. ranibizumab), which may reflect actual use. However, the validity of the assumption of maintaining similar efficacy with reduced use with both drugs is unknown. • Less frequent monitoring is assumed with aflibercept; however, it is not clear this would be the case in clinical practice.
CDR Estimate(s)	Under the assumption of similar efficacy and safety, a comparison of costs capturing injection and drug acquisition costs is appropriate. • Assuming frequency of administration of aflibercept and ranibizumab according to use in clinical trials (16.5 and 14.9 doses, respectively, over the first 3 years), aflibercept is more costly ($80 per patient over 3 years). • Assuming equal frequency of administration of both drugs (9 doses over 2 years according to CDR recommendation for ranibizumab in DME), aflibercept is less costly (cost saving of $1,384 per patient over 2 years).

CDR = CADTH Common Drug Review; DME = diabetic macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study; MTC = mixed treatment comparison; QALY = quality-adjusted life-year; vs. = versus.

EXECUTIVE SUMMARY

Background

Aflibercept (Eylea) is being reviewed for the treatment of visual impairment in patients with diabetic macular edema (DME). It is administered by intravitreal injection (2 mg) to the affected eye. Drug acquisition cost for a single injection is $1,418.

The submitted Markov model compares aflibercept with ranibizumab in patients with DME utilizing health states (with associated quality of life and health care costs) defined by categories of visual acuity.[1] Data from randomized controlled trials (RCTs) of aflibercept (versus laser treatment) are used to estimate changes in visual acuity (VA) in the first year; stabilization of vision then occurs for years 2 and 3, followed by deterioration over time. Relative efficacy and safety are obtained from an indirect comparison of ranibizumab versus aflibercept conducted by the manufacturer. The manufacturer assumed administration frequency of both drugs according to clinical trials included in the indirect comparison for the reference case and also assessed a listing request scenario in which similar reimbursement criteria are used for both drugs according to previous CADTH Common Drug Review (CDR) recommendations for ranibizumab (seven doses in year 1 and two doses in year 2).

CDR has previously reviewed aflibercept for wet age-related macular degeneration; the Canadian Drug Expert Committee recommended that aflibercept be listed on the condition that it provide cost savings for drug plans relative to ranibizumab.[2] CDR is currently also reviewing aflibercept for macular edema secondary to central retinal vein occlusion.

Summary of Identified Limitations and Key Results

Relative Efficacy and Safety

As no clinical trials comparing aflibercept and ranibizumab are available, the manufacturer conducted an indirect comparison. [redacted] it is appropriate to consider equal efficacy (no difference in clinical outcomes or VA-related costs by treatment) within the model.

Monitoring Costs

The model assumes a greater number of monitoring visits for ranibizumab than for aflibercept due to differences in the frequency of administration. The manufacturer states this is based on clinical opinion; however, the clinical expert consulted by CDR suggested that the frequency of monitoring (including monitoring that may occur with a visit for an injection) may not differ.

Uncertainty Surrounding Frequency and Relative Efficacy

How absolute and relative efficacy of the two treatment strategies differ by frequency of administration is unknown. The clinical expert consulted by CDR speculated that the greater frequency of administration in VIVID and VISTA aflibercept trials (compared with ranibizumab trials) was to ensure

that positive efficacy outcomes compared with laser treatment were reached. [redacted] Furthermore, there is uncertainty as to how these two drugs would be used in clinical practice. It is plausible that clinicians would adhere to trial-based dosing regimens (greater frequency for aflibercept) at least initially; the clinical expert consulted by CDR suggested that, if no discernible difference is noted in clinical practice between the two drugs, they are likely to be used in a similar manner and frequency.

Under the assumption of similar efficacy and safety, and similar monitoring costs, the primary drivers of cost using a cost-minimization framework are cost of injection ($105), drug acquisition costs ($1,418 for aflibercept and $1,575 for ranibizumab), and frequency of administration.

- Based on trial-informed frequency of injections (aflibercept: 8.5 injections in year 1, 5.1 in year 2, 2.9 in year 2; ranibizumab: 8.1 injections in year 1, 3.9 in year 2, 2.9 in year 3), incremental costs of aflibercept are $80 (–$80 for drug acquisition and +$160 for injections) compared with ranibizumab.
- When considering listing request frequency of injections (aflibercept and ranibizumab both seven in year 1 and two in year 2), incremental savings are $1,384 for aflibercept compared with ranibizumab (all due to drug acquisition costs).

Conclusions

The manufacturer's economic submission is sensitive to the comparative clinical effect estimates obtained from a mixed treatment comparison. While the results suggest some clinical differences between aflibercept and ranibizumab, no statistical difference was observed in the outcome measure used in the model (probability of gaining or losing ≥ 10 or ≥ 15 ETDRS letters). Given the limitations regarding the interpretation of the results of the manufacturer's mixed treatment comparison, discussed in the CDR Clinical Report (Appendix 6), an alternative approach to deal with the comparative clinical uncertainty is to assess the comparative costs of aflibercept and ranibizumab.

Costs are driven largely by drug acquisition ($1,418 for aflibercept and $1,575 for ranibizumab), injection cost ($105), and frequency. Using this approach, trial-informed dosing frequency leads to similar costs: an increased cost of $80 per patient receiving aflibercept. If drugs are administered with the same frequency (both at seven doses in year 1 and two doses in year 2), patients receiving aflibercept incur lower costs ($1,384 savings for patients on aflibercept). There is uncertainty as to the impact of relative frequency on effectiveness, and what the actual relative frequency of administration of these two drugs in clinical practice will be. In addition, the conclusions are based on publicly available prices for ranibizumab.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a Markov model to compare cost and clinical outcomes of aflibercept versus ranibizumab in patients with visual impairment due to diabetic macular edema (DME).[1] A Markov model considered three time frames — an "efficacy" phase in the first year, during which treatment results in improvement in vision; a "maintenance" phase, during which visual acuity (VA) is maintained for 2 years; and a "rest of life" phase, during which VA gradually deteriorates. These phases of the model were based on efficacy studies (efficacy), extension studies (maintenance), and natural history data (rest of life). Patients in the model could reside in one of eight VA health states (defined by Early Treatment Diabetic Retinopathy Study [ETDRS] letters read) and "death." VA improvements in the first year were informed by the aflibercept group of VIVID and VISTA,[3-6] and the relative risk (RR) of gaining or losing ≥ 10 or ≥ 15 letters from the manufacturer-conducted indirect comparison was used to inform VA health status for ranibizumab. It was assumed that vision health status then stabilized in years 2 and 3, and then deteriorated in subsequent years, as per observational studies in this patient population. Adverse events (AEs) were included and were equal in both groups, based on no difference in AEs from the indirect comparison. The model considered both the study eye and the non-study eye, with different independent VA health states for each eye. Starting VA for each eye was informed by the baseline measurements of patients in the VIVID and VISTA trials. Utility-based quality of life (QoL) was assigned to each health state using a regression equation based on time trade-off analysis (Czoski-Murray),[7] and the QoL for the better-seeing eye was assessed. Patients with severe VA loss were assigned an RR of mortality based on observational data (from the general population, as well as patients with diabetes mellitus or visual impairment).

Frequency of drug administration was based on trials included in the indirect comparison (aflibercept[3-6] or ranibizumab[8] versus laser therapy) in the reference case for the first two years, and observational data from the RESTORE extension trial in year 3 (assumed to be equal in year 3 for both aflibercept and ranibizumab). To approximate the listing request "similar to ranibizumab," the frequency of administration was assumed to be seven doses in the first year and two doses in the second year for both drugs in a second analysis. Frequency of AEs was based on VIVID, VISTA, and RESTORE and was applied to both treatments (as no difference in AE rate was found in the indirect comparison). Monitoring frequency was based on expert opinion (influenced by directed frequency of administration). Cost of the drugs was from the manufacturer and the Ontario Formulary, costs of AEs were obtained from the Ontario Case Costing Initiative,[9] and costs of intravitreal injection and monitoring were obtained from the Ontario Schedule of Benefits for Physician Services.[10]

2. MANUFACTURER'S BASE CASE

The reference case (frequency of injections from clinical trials) reported additional incremental costs of aflibercept of $118 compared with ranibizumab. Drug acquisition costs were similar (lower unit cost but greater frequency with aflibercept); other cost categories are shown in Table 2. Aflibercept was associated with an additional 0.202 quality-adjusted life-years (QALYs), leading to an incremental cost-utility ratio (ICUR) of $586 per QALY gained compared with ranibizumab.

TABLE 2: INCREMENTAL COST OF AFLIBERCEPT VERSUS RANIBIZUMAB (OVER 20 YEARS)

	Aflibercept ($)	Ranibizumab ($)	Incremental ($) (Aflibercept – Ranibizumab)
Drug costs	22,316.32	22,395.89	–79.58
Administrative costs	1,652.48	1,493.06	159.42
Monitoring costs	1,359.51	1,755.63	–396.12
Adverse events	4,088.20	4,087.67	0.52
Vision-related costs	16,060.29	15,626.39	433.90
Total costs	**45,476.79**	**45,358.65**	**118.14**

Source: Based on manufacturer's submission,[1] Table 36.

The manufacturer also considered a scenario that approximated the Canadian Drug Expert Committee's previous recommendation that a maximum of nine vials of ranibizumab be reimbursed per patient for DME.[11] In this listing request analysis, the manufacturer assumed that patients using either aflibercept or ranibizumab would receive seven injections in year 1 and two in year 2. Thus, lower drug acquisition costs (savings of $1,384) were the main driver of reduced overall costs (savings of $1,346) for aflibercept compared with ranibizumab under this assumption. As the manufacturer assumed similar efficacy to the base case, this resulted in aflibercept dominating ranibizumab.

2.1 Summary of Manufacturer's Sensitivity Analyses

The parameter that resulted in the greatest change in results was the relative frequency of administration of either drug, with an ICUR as high as $28,377 per QALY gained with aflibercept (same efficacy assumptions).

3. LIMITATIONS OF MANUFACTURER'S SUBMISSION

3.1 Relative Efficacy

No head-to-head trials of aflibercept versus ranibizumab exist, so the manufacturer conducted an indirect comparison. The RR of gain or loss of ≥ 10 or ≥ 15 letters was assessed. [redacted]

Additionally, in the manufacturer's listing request scenario, the frequency of injections for both drugs was assumed to be seven in year 1, two in year 2, and zero in year 3. This results in a greater reduction in aflibercept usage compared with ranibizumab; however, the manufacturer assumed the same efficacy as the base case for both drugs (i.e., the same incremental QALY of 0.202 in favour of aflibercept).

3.1.1 Relative frequency of administration

The "standard of care" frequency of injections is set, to some extent, by the study protocols of the randomized controlled trials of ranibizumab and aflibercept. A more aggressive frequency (monthly for five months, then bimonthly) was set out for aflibercept than for ranibizumab (monthly for three months, then as needed). These protocols led to differing frequency of administration for aflibercept and ranibizumab (8.5 versus 8.1 doses in year 1 and 5.1 versus 3.9 in year 2, respectively), leading to a total of 1.6 additional injections for aflibercept. It is not clear whether this increased frequency has an impact on the [redacted] (see above), or whether efficacy would be similar if frequency of injections of the two drugs were identical. The clinical expert indicates that early use is likely to be influenced by study protocols, although there is the notion that aflibercept and ranibizumab frequency may be quite similar in clinical practice; if this hold true as additional data and clinical experience matures, it is possible that both drugs will be used in a similar fashion (and similar frequency).

3.1.2 Monitoring frequency

The assumption that there is greater monitoring for ranibizumab because there are less frequent injections is based on opinion; the clinical expert consulted by CDR indicated that monitoring is likely to be similar for both drugs.

3.1.3 Other model assumptions

Many of the model parameters and inputs are associated with uncertainty. However, these factors play a minimal role, especially under the assumption of no difference in clinical efficacy. These assumptions include mortality risk with severe VA loss, increased health care costs with worsening VA, uncertainty in true QoL by VA health state, impact of better-seeing eye and worse-seeing eye on QoL, bilateral disease, etc.

3.2 CADTH Common Drug Review Analyses

3.2.1 Equal efficacy in cost-minimization analysis

[redacted] The manufacturer's model does not allow setting the RR to unity (as there is no modifiable input in the model that allows relative efficacy to be changed); however, the scenario of similar efficacy can be estimated by assuming similar QALYs and vision-related costs, and by considering only drug acquisition, administration, and monitoring.

- In the reference case (administration according to clinical trials), drug acquisition costs result in a savings of $80, administration costs an additional $159, and monitoring costs result in a savings of $396, and total incremental savings of $316 for patients receiving aflibercept (drug and administration costs for three years, monitoring costs for five years). If monitoring costs are assumed to be similar (the assumptions for differences in frequency of monitoring are not clearly established), the total incremental cost becomes ~$80 for aflibercept (over three years).
- In the listing request scenario (nine injections for both drugs), drug acquisition costs result in cost saving for aflibercept ($1,384, based on manufacturer's Table 40). Assumptions for monitoring are based on differences in frequency of administration; however, if the two drugs are administered with the same frequency, a reasonable assumption is that monitoring costs (and administration cost) would be identical.

3.2.2 Drug Utilization Data

The Canadian Institute for Health Information's National Prescription Drug Utilization Information System (NPDUIS) database[12] was accessed for ranibizumab claims by fiscal year in order to estimate frequency of administration. These data suggested that the average number of claims per participant for ranibizumab by fiscal year was 4.9 to 5.9 for included provinces (Ontario, Alberta, New Brunswick, Saskatchewan, and Prince Edward Island) in 2013. However, utilization cannot be determined by indication (DME), and it is also not clear whether patients are in their first or subsequent year of treatment. Under the assumption that utilization reflects use in DME and in years 1 and 2 years of treatment, frequency of administration is 10 to 12 over two years. For comparison, the reimbursement criteria recommended by the Canadian Drug Expert Committee for ranibizumab for DME is nine doses in two years; in clinical trials, ranibizumab and aflibercept are administered 12 and 13.6 times in two years, respectively.

- If frequency of ranibizumab administration in patients with DME is 10 to 12 over two years, the undiscounted total cost (drug and injection) is $16,800 to $20,160. For the same total cost (drug and injection), aflibercept could be administered 11 to 13 times in two years.

TABLE 3: CADTH COMMON DRUG REVIEW REANALYSIS PRICE-REDUCTION SCENARIOS

Cost of Aflibercept Versus Ranibizumab[a]		
Price	**Cost Minimization Using Trial-Based Dosing Frequency**	**Cost Minimization Using Listing Request Dosing Frequency**
Reference	$82	–$1,398
10% reduction	–$2,185	–$2,661
20% reduction	–$4,452	–$3,923
30% reduction	–$6,719	–$5,186
40% reduction	–$8,986	–$6,449
50% reduction	–$11,253	–$7,712

[a] This analysis considers only the cost of injection ($105 per injection) and drug acquisition costs in the first three years (with a 5% discount applied in years 2 and 3).

4. ISSUES FOR CONSIDERATION

- Bevacizumab is a vascular endothelial growth factor (VEGF) inhibitor that is used in this condition by some practitioners in some jurisdictions. Its drug acquisition cost is much lower than either aflibercept or ranibizumab ($600 versus $1,418 to $1,575). However, it is not approved for use in Canada for this indication, where ranibizumab is the current standard of care.
- It is possible that suboptimal response to initial treatment with either ranibizumab or aflibercept after a period of use will lead to a switch and re-initiation of treatment using the alternative drug. Data on the effectiveness of an alternative drug in patients who have a suboptimal response to anti-VEGF therapy is not specifically presented. This may lead to greater total expenditures for these two drugs if non-constrained sequential use is permitted.
- There are other conditions in which this drug may be used. This medication is likely to be prescribed by an ophthalmologist or retina specialist only.

5. PATIENT INPUT

Patients value having a second treatment option (other than ranibizumab). Patients also place a value on less frequent injections; however, this preference runs counter to the reference case administration frequency. See the CDR Clinical Report (Appendix 1).

6. CONCLUSIONS

The manufacturer's economic submission is sensitive to the comparative clinical effect estimates obtained from a mixed treatment comparison. [redacted] Given the limitations regarding the interpretation of the results of the manufacturer's mixed treatment comparison in the CDR Clinical Report (Appendix 6), an alternative approach to deal with the comparative clinical uncertainty is to assess the comparative costs of aflibercept and ranibizumab.

Costs are driven largely by drug acquisition ($1,418 for aflibercept and $1,575 for ranibizumab), injections cost ($105), and frequency. Using this approach, trial-informed dosing frequency leads to similar costs: the increased cost of $80 per patient receiving aflibercept. If drugs are administered with the same frequency (both at seven doses in year 1 and two in year 2), patients receiving aflibercept incur lower costs ($1,384 savings for patients on aflibercept). There is uncertainty as to how relative frequency affects clinical effectiveness, and what the actual relative frequency of administration of these two drugs in clinical practice will be. In addition, the conclusions are based on publicly available prices for ranibizumab; as comparative costs are based on frequency of use, if aflibercept and ranibizumab are priced similarly per injection, then similar frequency of use will be cost-neutral to public payers.

APPENDIX 1: COST COMPARISON

The comparators presented in Table 4 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs but may be devices or procedures. Costs are manufacturer's list prices, unless otherwise specified.

TABLE 4: COST-COMPARISON TABLE FOR DRUGS USED FOR DIABETIC MACULAR EDEMA

Drug/Comparator	Strength	Dosage Form	Unit Price ($)	Recommended Treatment Dose	Annual Cost ($)
Aflibercept (Eylea)	40 mg/mL (0.278 mL vial)	Intravitreal injection	1,418.00[a]	2 mg monthly (every 4 weeks) for five doses, then every 2 months (8 weeks)	11,344 (8 injections) 8,508 (6 injections)
Ranibizumab (Lucentis)	10 mg/mL (0.23 mL vial)	Intravitreal injection	1,575.00	0.5 mg monthly Treatment is continued until VA is achieved (stable VA for 3 consecutive months)	18,900 (12 injections) 11,025 (7 injections)[b] 6,300 (4 injections)[b]
Laser photocoagulation therapy	NA	NA	182.75[c]	As needed when re-treatment criteria met, but no more frequently than every 12 weeks[d]	731 (4 treatments) 548 (3 treatments) 183 (1 treatment)
Other treatments used that are not currently indicated					
Bevacizumab (Avastin)	100 mg/4 mL 400 mg/16 mL	Injection	600.00[e] 2,400.00[e]	1.25 or 2.5 mg monthly or every 6 weeks[f]	Up to $7,200[g]
Dexamethasone intravitreal implant (Ozurdex)	0.7 mg	Implant device	1,295.00[h]	0.7 mg not more than every 6 months[i]	1,295 (1 treatment) 2,590 (2 treatments)
Pegaptanib sodium (Macugen)	0.3 mg/90 µL	Pre-filled syringe	1,013.91	0.3 mg every 6 weeks[j]	8,111 (8 injections)
Triamcinolone (Kenalog, generic)	40 mg/1 mL 50 mg/5 mL 200 mg/5 mL	Injection	8.20 17.80 16.71	4 mg every 3 months[k]	33
Triamcinolone (Triesence)	40 mg/1 mL	Intravitreal injection	43.40[l]	4 mg every 3 months[k]	174

NA = not applicable.
[a] Manufacturer's submission, also the Ontario Drug Benefit list price.
[b] Based on rounded average use in RESTORE: 7 doses in year 1 and 4 doses in year 2.
[c] Ontario Schedule of Benefits for Physician Services (May 1, 2014), code E154.
[d] VIVID trial dosing.
[e] Per-protocol set, January 2014.
[f] Based on http://www.cadth.ca/media/pdf/RD0028_RR_avastin_L3_e.pdf.
[g] Maximum cost, which assumes monthly injections and that vials are not split between patients.
[h] Quebec formulary price (December 2014).
[i] Monograph dosing for macular edema following central retinal vein occlusion, monograph recommends limit of two doses per patient.
[j] Monograph dosing for wet age-related macular degeneration (wAMD).
[k] Standard Care versus Corticosteroid for Retinal Vein Occlusion (SCORE) study dosing.
[l] McKesson Canada wholesale price (December 2014).
Source: Ontario Drug Benefit (December 2014) unless otherwise stated.

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 5: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS AFLIBERCEPT RELATIVE TO RANIBIZUMAB?

Aflibercept Versus Ranibizumab	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)				X		
Drug treatment costs alone		X				
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	$586 per QALY					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year.
Source: Based on manufacturer's results.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 6: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?	X		
Comments *Reviewer to provide comments if checking "no"*	None		
Was the material included (content) sufficient?	X		
Comments *Reviewer to provide comments if checking "poor"*	None		
Was the submission well organized and was information easy to locate?	X		
Comments *Reviewer to provide comments if checking "poor"*	None		

TABLE 7: AUTHOR INFORMATION

Authors	Affiliations		
Monika Mogilnicka	Bayer, Inc.		
	Yes	**No**	**Uncertain**
Authors signed a letter indicating agreement with entire document		X	
Authors had independent control over the methods and right to publish analysis			X

APPENDIX 4: SUMMARY OF OTHER HEALTH TECHNOLOGY ASSESSMENT REVIEWS OF DRUG

Aflibercept for diabetic macular edema (DME) has recently been reviewed by the Pharmaceutical Benefits Advisory Committee (PBAC; Australia) as well as the Federal Joint Committee (G-BA) using information examined by the Institute for Quality and Efficiency in Health Care (IQWiG, Germany). Neither organization had published detailed English-language information regarding the submissions as of January 2015.

The PBAC[13] recommended the listing of aflibercept on a cost-minimization basis with ranibizumab. On the basis of direct evidence presented in the submission, patients treated with aflibercept had a gain of approximately 10.1 letters in best-corrected visual acuity (BCVA) when compared with patients treated with laser photocoagulation over a 12-month duration of follow-up. On the basis of an indirect comparison of aflibercept with ranibizumab (equi-effective dose determined to be aflibercept 2 mg and ranibizumab 0.5 mg), the PBAC noted that the frequency of adverse events appears to be similar and that the gain in BCVA is approximately 4.81 letters for aflibercept over 12 months. However, this difference could be an artifact of the different trial populations and does not represent a clinically significant improvement in vision-related quality of life. The PBAC also considered aflibercept to be non-inferior to bevacizumab in terms of effectiveness and safety (equi-effective dose determined to be aflibercept 2 mg and bevacizumab 1.5 mg).

The IQWiG concluded[14] that aflibercept showed no relevant differences when compared with ranibizumab in patients with DME in whom the fovea centralis is affected; thus, aflibercept did not prove to represent an added benefit. The G-BA specified that, for patients with DME in whom the fovea centralis is not affected, laser photocoagulation is the appropriate comparator. As the manufacturer did not provide data for these patients, the G-BA again concluded that there was no proof of added benefit.

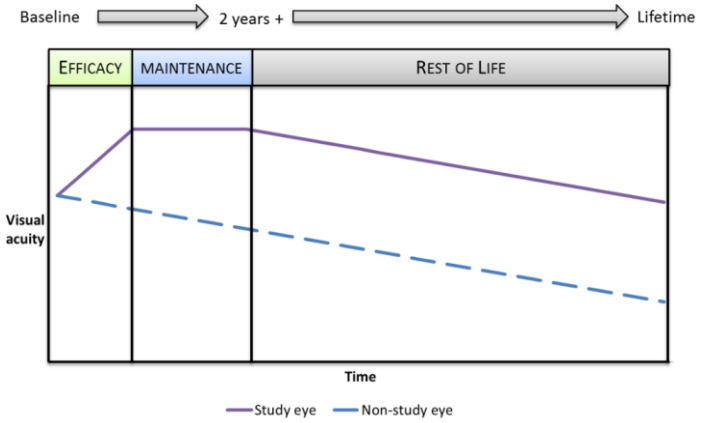
APPENDIX 5: REVIEWER WORKSHEETS

Manufacturer's Model Structure

A Markov model with three time frames representing the efficacy phase (during which visual acuity [VA] in treated patients improves) in year 1, the maintenance phase (during which VA in treated patients stabilizes) in year 2 and 3, and the "rest of life" (during which VA gradually deteriorates over time) was used (Figure 1). Over each four-week cycle, patients could transition through health states that were defined by Early Treatment Diabetic Retinopathy Study (ETDRS) letters read (Table 8), and "death." The model considered both the study eye (SE) and the non-study eye (NSE). In the efficacy phase, VA in the SE could improve, worsen, or stay the same; VA in the NSE could either worsen or stay the same. In the maintenance phase, SE VA was assumed to stay the same; NSE VA could stay the same or deteriorate. In the "rest of life" time period, both the SE and NSE could either stay in the same VA health state or deteriorate over time.

The model independently captured VA in both the SE and the NSE.

FIGURE 1: TIME PERIODS IN MANUFACTURER'S MODEL



Source: Based on manufacturer's Pharmacoeconomic Submission,[1] Figure 4.

TABLE 8: HEALTH STATES (DEFINED BY ETDRS LETTERS READ) IN MANUFACTURER'S SUBMISSION

Vision Health State	ETDRS Read
VA1	86 to 100
VA2	76 to 85
VA3	66 to 75
VA4	56 to 65
VA5	46 to 55
VA6	36 to 45
VA7	26 to 35 (blindness)
VA8	0 to 25 (blindness)

ETDRS = Early Treatment Diabetic Retinopathy Study; VA = visual acuity.
Source: Based on manufacturer's Pharmacoeconomic Submission,[1] Table 8.

Data Sources

TABLE 9: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy	VIVID and VISTA were used to inform the probability of transitioning through VA health states in the first year for aflibercept. The RR of gaining or losing 10 or 15 letters or more at 52 weeks in the manufacturer-conducted MTC was used to inform ranibizumab. No change in VA health state occurred in years 2 and 3.	Appropriate; however, model used point estimate [redacted]
Natural history	Observational data from the ETDRS study group[15] were used to estimate decline in VA in the "rest of life" phase, assuming a linear decline.	Appropriate
Utilities	Utility for each health state from time trade-off analysis (Czoski-Murray)[7] using regression equation. Disutilities for AEs were obtained from literature sources.	True utility-based quality of life by VA health status not clear
Resource use — drug administration	Frequency of aflibercept and ranibizumab administration based on clinical trials for years 1 to 3; analysis assuming identical reimbursement criteria (9 vials in total) is assessed	Unclear whether trial-mandated administration (and differences) reflect real world utilization
Resource use — monitoring	Monthly visits in year 1 for ranibizumab (product monograph), but only during administration (from expert opinions) for aflibercept; similar assumptions lead to less frequent monitoring visits in year 2 and 3 for aflibercept	Evidence to support differences in resource use of monitoring very weak; CDR clinical expert indicated that patients likely to be monitored in a similar fashion
AEs	The MTC did not demonstrate statistically significant differences in AE events, so equal risk of AE was applied to both groups, based on weighted average from VIVID, VISTA and RESTORE. AEs included cataract, endophthalmitis, retinal detachment, vitreous hemorrhage, increased intraocular pressure, and arterial thromboembolic event.	There may be lack of power to demonstrate true differences in AEs.
Mortality	Mortality risk of the general population was used, and the RR of mortality due to severe unilateral or bilateral visual impairment was estimated.	Appropriate
Costs		Appropriate
Drug	Aflibercept cost from Bayer; ranibizumab cost from Ontario Formulary	
Administration	Ontario Schedule of Benefits for vitreous injection	
AEs	From Ontario Case Costing Initiative where possible	
Health state	From Canadian costing study of DME patients (Gondor);[16] drug and indirect costs removed; cost of visual impairment by severity estimated	

AE = adverse event; CDR = CADTH Common Drug Review; DME = diabetic macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study; MTC = mixed treatment comparison; RR = relative risk; VA = visual acuity.

Manufacturer's Key Assumptions

TABLE 10: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
Point estimate of RR from manufacturer's MTC can be used to estimate relative effectiveness.	[redacted]
[redacted]	Reasonable assumption; however, as these events are rare, there may be a lack of power to identify true differences.
Frequency of administration of both treatments can be informed by trials.	The frequency of administration is mandated by study design, and it is not clear that this will reflect true drug utilization.

MTC = mixed treatment comparison; RR = relative risk.

Manufacturer's Results

The manufacturer's base case reports an incremental cost of aflibercept of $118 and additional quality-adjusted life-years (QALYs) of 2.02 compared with ranibizumab, resulting in an incremental cost-utility ratio of $586 per QALY gained from aflibercept. The incremental costs by category are shown in Table 2.

The manufacturer is requesting reimbursement of aflibercept in the same manner as ranibizumab, stated as a total of nine injections (seven in the first year and two in the second year). In an analysis in which only this parameter is modified, the drug acquisition costs are lower for aflibercept versus ranibizumab (–$1,384), and the total costs are also lower (–$1,345), resulting in ranibizumab being dominated by aflibercept.

In the manufacturer-conducted sensitivity analysis, the frequency of administration of both aflibercept and ranibizumab had the greatest impact on results.

CADTH Common Drug Review Reanalysis

Comparison of Costs Based on Assumption of Equal Efficacy

[redacted] The manufacturer's model does not appear to have an option to set the risk ratio to unity; however, the scenario of similar efficacy can be estimated by assuming similar QALYs and vision-related costs, and considering only drug acquisition, administration, and monitoring.

- In the manufacturer's reference case (administration as per clinical trials), comparing aflibercept with ranibizumab, the incremental drug acquisition cost is –$80, administration is $159, and monitoring –$396, for a total incremental cost saving of $316 per patient for aflibercept (based on three years of drug and administration costs and five years of monitoring costs). If monitoring costs are assumed to be similar (the assumptions concerning differences in frequency of monitoring are not clearly established), the total incremental cost is ~$80 for aflibercept for three years of therapy.

In the reimbursement request scenario (seven injections for both drugs in year 1 and two in year 2), drug acquisition cost is $1,384 less for aflibercept per patient (based on two years of drug and administration costs and five years of monitoring costs). Assumptions concerning monitoring are based on differences in frequency of administration; however, if the two drugs are administered with the same frequency, a reasonable assumption is that monitoring costs (and administration costs) would be identical, in which case aflibercept would cost $1,398 less over two years.

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