Common Drug Review
Pharmacoeconomic Review Report

August 2015

Drug	aflibercept (Eylea) (40 mg/mL Solution for Intravitreal Injection available as a 2 mg single-use vial)
Indication	For the treatment of neovascular (wet) age-related macular degeneration (AMD).
Listing request	As per indication.
Manufacturer	Bayer Inc.

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ABBREVIATIONS

AE	adverse event
BCVA	best corrected visual acuity
CATT	Comparisons of Age-Related Macular Degeneration Treatments Trials
CDR	CADTH Common Drug Review
CMA	cost-minimization analysis
CUA	cost-utility analysis
ETDRS	Early Treatment Diabetic Retinopathy Study
QALY	quality-adjusted life-year
VA	visual acuity
wAMD	neovascular (wet) age-related macular degeneration
WDAE	withdrawal due to adverse event

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Aflibercept (Eylea)
Study Questions	What is the incremental cost-effectiveness of aflibercept 2 mg given every other month following a loading dose of 3 monthly injections in year 1 and on an individualized regimen in subsequent years, compared with: 1. Ranibizumab 0.5 mg given monthly in year 1 for the treatment of wAMD? 2. Ranibizumab 0.5 mg given on an individualized regimen following an initial loading dose for the treatment of wAMD?
Type of Economic Evaluation	CMA and CUA
Target Population	Patients with (1) active subfoveal CNV lesions (any subtype) secondary to AMD, including juxtafoveal lesions with leakage affecting the fovea; (2) CNV comprising at least 50% of total lesion size; (3) BCVA between 73 and 53 ETDRS letters (20/40 to 20/320 Snellen equivalent)
Treatment	Aflibercept 2 mg given every other month following a loading dose of 3 monthly injections in year 1, and on an individualized regimen in subsequent years
Outcome	Proportion of patients maintaining vision (losing < 15 letters)
Comparators	1. Ranibizumab 0.5 mg given monthly in year 1, and on an individualized regimen in subsequent years 2. Ranibizumab 0.5 mg given on an individualized regimen following an initial loading dose
Perspective	Publicly funded health care system
Time Horizon	10 years for CMA, lifetime for CUA
Manufacturer's Results (Base Case)	• CMA: Aflibercept was cost saving (–$23,127) compared with ranibizumab. • CUA: Aflibercept dominated ranibizumab, saving $5,044 and resulting in 0.23 additional QALYs.
Key Limitations and CDR Estimate	• The clinical expert believed it unlikely that ranibizumab would be administered as frequently as the manufacturer's CMA base case assumed, particularly in year 1. CDR analyses showed that, while reducing the frequency of ranibizumab to match that of aflibercept reduced the absolute cost savings to –$7,298, aflibercept remained cost saving relative to ranibizumab. • Given the results of the CDR clinical review and the use of efficacy data for ranibizumab from trials that did not include aflibercept in the CUA, the focus of this report was on the CMA.

AMD = age-related macular degeneration; BCVA = best corrected visual acuity; CDR = CADTH Common Drug Review; CMA = cost-minimization analysis; CNV = choroidal neovascularization; CUA = cost-utility analysis; EDTRS = Early Treatment Diabetic Retinopathy Study; QALY = quality-adjusted life-year; VA = visual acuity; wAMD = neovascular (wet) age-related macular degeneration.

EXECUTIVE SUMMARY OF THE PHARMACOECONOMIC SUBMISSION

Background

Bayer Inc. is seeking approval for aflibercept (Eylea), a novel anti-angiogenic drug, for the treatment of neovascular (wet) age-related macular degeneration (wAMD). Aflibercept 2 mg would be given every other month following a loading dose of three monthly injections in year 1, and on an individualized regimen in subsequent years. The submitted and current market price is $1,418 per 2 mg vial.

Summary of Economic Analysis

Based on results of the VIEW 1 and VIEW 2 clinical trials, which showed that aflibercept was non-inferior to ranibizumab (Lucentis) in the proportion of patients maintaining vision, the mean change in best corrected visual acuity (BCVA), and the proportion of patients gaining ≥ 15 ETDRS letters, the manufacturer conducted a cost-minimization analysis (CMA). Expected costs with aflibercept and ranibizumab were calculated by multiplying the price per dose and the associated physician fee by the number of doses per patient expected over a 10-year analysis horizon. The dose frequency of aflibercept was based on the frequencies observed in the VIEW trials, and the dose frequency of ranibizumab was based on Canadian consensus guidelines.

In addition, the manufacturer submitted a cost-utility analysis (CUA) that explored some of the numerical differences between aflibercept and ranibizumab, which is described in the Discussion section of this report.

Results of Manufacturer's Analysis

The manufacturer's CMA base-case analysis suggested that aflibercept was cost saving (less costly and at least as effective) compared with ranibizumab, saving $23,127 over 10 years. Of note, the lifetime cost savings suggested by the CUA, after allowing for differences in effectiveness and adverse events (AEs), were substantially less (–$5,044, with an improvement of 0.23 QALYs) than the cost savings suggested by the CMA.

Interpretations and Key Limitations

- The manufacturer's CUA assumptions of superior visual acuity (VA) and reduced AEs relative to ranibizumab were not well supported. Given the results of the CDR clinical review and the use of efficacy data for ranibizumab from trials that did not include aflibercept in the CUA, the focus of this report is on the CMA.
- The main limitation of the CMA was uncertainty in the dose frequency of ranibizumab. The clinical expert felt that it was unlikely that ranibizumab would be administered as frequently as was assumed for the base-case analysis, particularly in year 1. Therefore, the base case may overestimate the expected cost of ranibizumab and the relative cost savings associated with aflibercept.

Results of CADTH Common Drug Review Analysis

Considering alternative dosing schedules, as ranibizumab is rarely administered monthly in clinical practice in year 1, CDR tested the impact of individualizing ranibizumab in year 1 in the CMA. This resulted in an estimated cost savings of –$15,019 over 10 years for aflibercept.

Conclusions

The manufacturer's CMA suggested that aflibercept is cost saving and at least as effective as ranibizumab. The estimated cost savings are highly dependent on the frequency of use of ranibizumab. While the manufacturer's analysis estimated the 10-year cost savings to be greater than $23,127 for aflibercept relative to ranibizumab, CDR reanalyses suggest that aflibercept could more realistically be estimated to be $7,000 to $15,000 less expensive under the assumption of equivalent efficacy.

REVIEW OF THE PHARMACOECONOMIC SUBMISSION

1. INTRODUCTION

1.1 Study Question

The manufacturer's pharmacoeconomic submission[1] noted two study questions:

1. What is the incremental cost-effectiveness of aflibercept 2 mg given every other month following a loading dose of three monthly injections in year 1 and on an individualized regimen in subsequent years, compared with ranibizumab (Lucentis) 0.5 mg given monthly in year 1 and on an individualized regimen in subsequent years, for the treatment of neovascular (wet) age-related macular degeneration (wAMD) over a lifetime horizon from the perspective of a publicly funded health care system?
2. What is the incremental cost-effectiveness of aflibercept 2 mg given every other month following a loading dose of three monthly injections in year 1 and on an individualized regimen in subsequent years, compared with ranibizumab 0.5 mg given on an individualized regimen following an initial loading dose, for the treatment of wAMD over a lifetime horizon from the perspective of a publicly funded health care system?

The difference in the study questions relates to the dosing of ranibizumab in the first year of treatment. In the first study question, the regimen for ranibizumab is monthly injections; in the second study question, the regimen for ranibizumab is an individualized regimen following a loading dose of three consecutive injections. Both study questions consider ranibizumab given on an individualized regimen in all subsequent years of treatment. Monthly injections of ranibizumab after the first year of treatment and in subsequent years were not considered because this is not the manner in which ranibizumab is employed in clinical practice.

1.2 Treatment

Aflibercept 2 mg for the treatment of wAMD.

1.3 Comparators

Ranibizumab 0.5 mg was used as the comparator on the grounds that it is the current standard of treatment for wAMD in Canada. It is recommended that ranibizumab be administered monthly, and this was the comparator regimen in the first study question. However, the submission argues that this dosing schedule is onerous and difficult for both patients and the treating physician, and that it is not routinely followed. The second study question compares aflibercept to ranibizumab administered on an individualized dosing schedule, which is less often than monthly.

The appropriateness of ranibizumab as the comparator is complicated by the possibility of the off-label use of bevacizumab (Avastin) for the treatment of wAMD. Bevacizumab is substantially less costly than either aflibercept or ranibizumab, but it is not officially approved for use in treating wAMD in Canada. Aflibercept is unlikely to be cost saving relative to bevacizumab.

1.4 Type of Economic Evaluation

Question 1 was addressed with a cost-minimization analysis (CMA) that considered the costs of drug acquisition and administration, and dose frequency. As the primary clinical evidence (VIEW 1 and VIEW

2) suggested that aflibercept was non-inferior to ranibizumab in terms of the primary outcome (the proportion of patients maintaining visual acuity [VA] at 52 weeks), this approach appears reasonable.

Question 2, which addressed the possibility of individualized ranibizumab dose frequencies, was addressed with a cost-utility analysis (CUA). This approach allowed for individualized ranibizumab dose frequencies and differential outcomes.

Both analyses were conducted from the perspective of a publicly funded health care system.

1.5 Population

The population in the economic evaluation was patients with (1) active subfoveal choroidal neovascularization (CNV) lesions (any subtype) secondary to AMD, including juxtafoveal lesions with leakage affecting the fovea; (2) CNV comprising at least 50% of total lesion size; and (3) best corrected visual acuity (BCVA) between 73 and 53 Early Treatment Diabetic Retinopathy Study chart (ETDRS) letters (20/40 to 20/320 Snellen equivalent).

2. METHODS

2.1 Model Structure

The CMA compared the total expected direct costs (drug acquisition + administration) of aflibercept and ranibizumab over a 10-year horizon, assuming that the effectiveness of both treatments was equivalent. The analysis allowed for the dose frequency, price per vial, markup, and fees associated with administration of aflibercept and ranibizumab to be adjusted, but did not allow for differential clinical outcomes.

The CUA considered the relative risks of adverse events (AEs) such as endophthalmitis, retinal hemorrhage, stroke, or myocardial infarction. Unlike the CMA, the CUA also accounted for the possibility of mortality before the end of the model horizon. Patients who experienced an AE were assumed to have discontinued treatment with aflibercept or ranibizumab, while maintaining VA.

2.2 Clinical Inputs

2.2.1 Efficacy

The CMA model was justified on the basis of the VIEW 1 and VIEW 2 clinical trials, which showed that aflibercept was non-inferior to ranibizumab in the proportion of patients maintaining VA, the mean change in BCVA, and the proportion of patients gaining ≥ 15 ETDRS letters. The dose frequency of aflibercept was derived from the combined data from the VIEW 1 and VIEW 2 trials. The dose frequency of ranibizumab was assumed to be monthly for the first 12 months, and derived from the VIEW 1 and VIEW 2 trials for the remaining horizon.

For question 2, the efficacy of aflibercept was derived from the VIEW trials, while the efficacy of ranibizumab was derived from a systematic review and meta-analysis of studies estimating the efficacy of individualized dosing. The CUA used to answer question 2 assumed a superior improvement in VA with aflibercept over ranibizumab, based on results from two studies that compared ranibizumab and bevacizumab (Avastin). However, neither of these studies included aflibercept, and the head-to-head trials of aflibercept versus ranibizumab (VIEW 1 and VIEW 2) did not demonstrate a superior clinical effect with aflibercept. As such, this assumption does not appear to be well justified.

2.2.2 Harms

The VIEW trials[2-6] reported similar rates of AEs with aflibercept and ranibizumab, including serious ocular adverse events (ocular SAEs), arterial thromboembolic events (ATEs), and ocular treatment-emergent adverse events (TEAEs). The CMA assumed that rates of AEs were equivalent and thus they were not explicitly modelled; the CUA model allowed for differential rates of AEs derived from the VIEW trial and the Comparisons of Age-Related Macular Degeneration Treatments Trials (CATT),[7] which were similar but slightly higher in the ranibizumab group with the exception of retinal hemorrhage, which was slightly higher with aflibercept.

2.2.3 Quality of life

Health state utility values were modelled based on a univariate equation proposed by Sharma et al.[8] that converts VA in the better-seeing eye into utility values. Quality of life (QoL) was not incorporated into the CMA model.

2.3 Costs

2.3.1 Drug costs

The cost of aflibercept was provided by the manufacturer. The cost of ranibizumab was taken from the Ontario Drug Benefit formulary. Markup was assumed to be 8%. Wastage of additional medication in each single-use vial was also assumed.

The dosing used in the CMA and CUA were based on dosing observed in the VIEW and CATT trials.

TABLE 2: TREATMENT DOSING USED IN MANUFACTURER'S ANALYSES

	Aflibercept	Ranibizumab	Data Source
CMA			
Year 1	7.5 injections	12.0 injections	VIEW trials
Years 2 to 10 (annually)	5.0 injections	5.6 injections	VIEW trials – based on individualized dosing
CUA			
Year 1	7.5 injections	6.8 injections	VIEW for aflibercept; CATT for ranibizumab
Years 2 to 10 (annually)	5.0 injections	5.7 injections	VIEW for aflibercept; CATT for ranibizumab

CATT = Comparisons of Age-Related Macular Degeneration Treatments Trials; CMA = cost-minimization analysis; CUA = cost-utility analysis.

The clinical expert believed it unlikely that ranibizumab would be administered as frequently as was assumed in the CMA and that the CATT trial also suggested a lower dose frequency. As such, the submitted CMA may overstate the cost difference between aflibercept and ranibizumab. CDR reanalyses of the CMA incorporated lower ranibizumab dose frequencies.

2.3.2 Administration costs

The cost of administering aflibercept and ranibizumab was assumed to be $105, as taken from the Ontario Schedule of Benefits (code #E147).[9]

2.3.3 Adverse event costs

AEs were not included in the CMA, but for the CUA the costs of endophthalmitis and retinal hemorrhage were derived from the Ontario Case Cost Initiative. The costs of non-fatal stroke and myocardial infarction were taken from studies by Sorenson et al.[10] and Anis et al.[11] The costs associated with different states of VA were taken from a study by Cruess et al.[12]

2.2.3 Time horizon

The time horizon of the CMA was 10 years. This was assumed to represent a lifetime horizon, as the average age of patients in the VIEW trials was 76 years. Horizons of two years and five years were tested in sensitivity analyses.

The CUA used a lifetime horizon, and continued until all patients had died or had turned 100 years of age.

2.3.4 Discounting

Costs beyond one year were discounted at 5% per year.

3. RESULTS

3.1 Manufacturer's Base Case

The results of the manufacturer's CMA base-case analysis, assuming 7.5 doses of aflibercept in the first year, 5.0 annual doses of aflibercept per year in subsequent years, and 12 doses of ranibizumab in the first year and 5.6 annual doses of ranibizumab per year in subsequent years, are shown below:

TABLE 3: SUMMARY OF MANUFACTURER'S COST-MINIMIZATION ANALYSIS BASE-CASE RESULTS

	Year 1 Drug Costs	Years 2 to 10 Drug Costs	Total Drug Costs	Administration Costs	Total Costs
Aflibercept	$11,486	$54,426	$65,912	$4,519	$70,431
Ranibizumab	$20,412	$67,706	$88,118	$5,439	$93,558
Difference	**–$8,926**	**–$13,280**	**–$22,206**	**–$920**	**–$23,127**

Source: Manufacturer's pharmacoeconomic submission, Table 15.[1]

The CMA base case suggests that aflibercept is cost saving relative to ranibizumab, saving $23,127 over 10 years at a discount of 5%. Savings in year 1 were estimated to be $8,926, and the undiscounted annual savings in subsequent years were estimated to be $1,931. The key drivers in the CMA analysis were the price per dose and dose frequency for aflibercept and ranibizumab. Dose frequency was derived from the pivotal VIEW trials, and as such may not hold in real-world practice.

The results of the CUA base case are shown in Table 4, and are consistent with the CMA results in suggesting that aflibercept is less costly and at least as effective compared with ranibizumab, although the cost savings were significantly smaller (–$5,044).

TABLE 4: SUMMARY OF MANUFACTURER'S COST-UTILITY ANALYSIS BASE-CASE RESULTS

	Cost	Cost Difference	QALYs	Difference in QALYs	ICUR
Aflibercept	$105,087		8.66		
Ranibizumab	$110,131	$5,044	8.43	–0.23	Dominated

Source: Manufacturer's pharmacoeconomic submission, Table 27.[1]

The assumption of superior improvements in VA with aflibercept, noted in Section 2.2.1, led to a gain in expected QALYs with aflibercept in the CUA model. As health state costs were lower in better VA states, this assumption also implied that expected costs would be lower with aflibercept, holding everything else unchanged. However, patients on ranibizumab were more likely to suffer an AE, which, while initially costly, was often less expensive over the long term than continuing on treatment. As patients who discontinued treatment due to AEs were assumed to maintain their VA for the remainder of the model, this likely disadvantaged aflibercept. In any case, the assumption of differential efficacy or harms outcomes did not appear to be supported in the head-to-head VIEW trials, and no formal indirect comparison of aflibercept versus individualized ranibizumab was presented.

The CUA, in contrast with the CMA, assumed a lower dose frequency with ranibizumab than with aflibercept in the first year. The impact of using this lower dose frequency in the CMA was tested in a CDR reanalysis.

3.2 Summary of the Manufacturer's Sensitivity Analyses

3.2.1 One-way sensitivity analyses

The manufacturer ran a number of sensitivity analyses for the CMA (Table 5). Under all scenarios, aflibercept remained cost saving relative to ranibizumab.

TABLE 5: RESULTS OF MANUFACTURER'S CMA SENSITIVITY ANALYSES

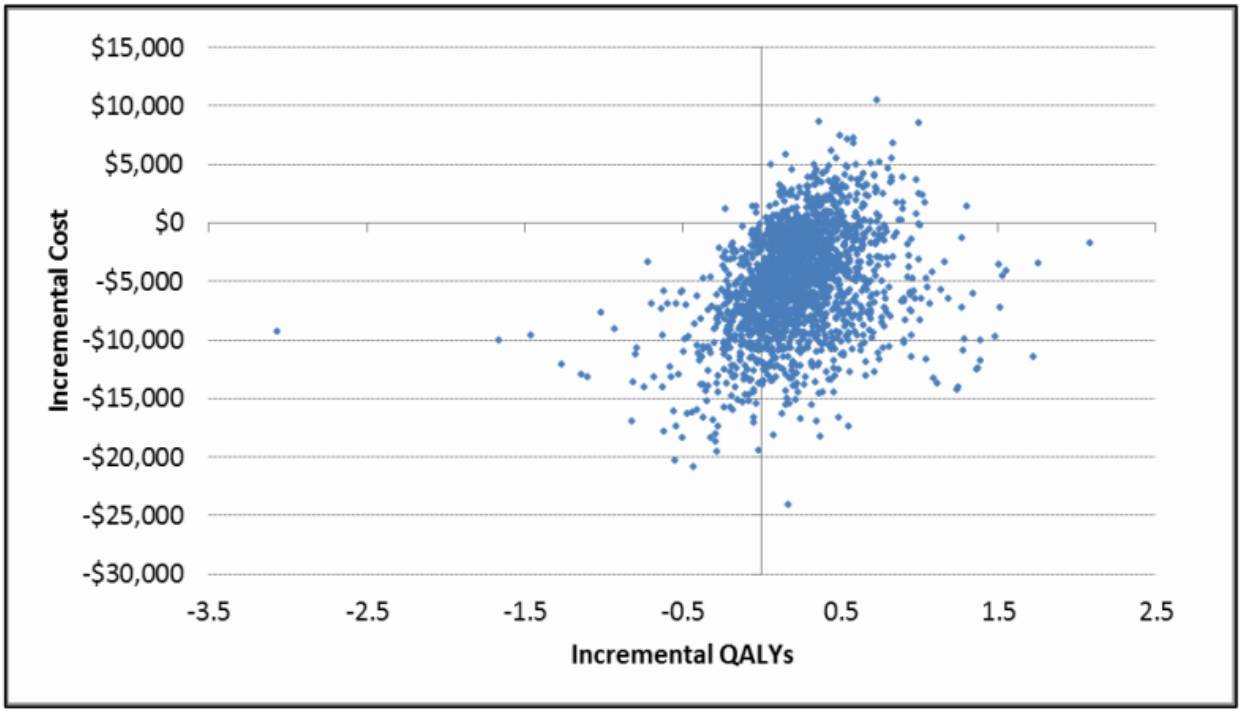
Manufacturer's CMA Scenario	Relative Cost of Aflibercept
Frequency of ranibizumab (9/year in year 1; 6/year in years 2 to 10)	–$22,843
Frequency of aflibercept (12/year in year 1; 5/year in years 2 to 10)	–$15,763
2-year time horizon	–$11,238
5-year time horizon	–$16,247
0% discount rate	–$26,781

CMA = cost-minimization analysis.
Source: Manufacturer's pharmacoeconomic submission, Table 16 and Table 17.[1]

3.2.2 Probabilistic sensitivity analysis

No probabilistic sensitivity analyses were conducted for the CMA model. A scatterplot of CUA simulations from the manufacturer's submission is shown below (Figure 1):

FIGURE 1: PROBABILISTIC SENSITIVITY ANALYSES — INCREMENTAL COST-EFFECTIVENESS SCATTERPLOT



QALY = quality-adjusted life-year.
Source: Manufacturer's pharmacoeconomic submission, Figure 7.[1]

The manufacturer suggests that aflibercept is associated with improved outcomes and lower costs relative to ranibizumab in 80% of the probabilistic simulations. The manufacturer's CUA cost-effectiveness acceptability frontier suggests that aflibercept would be preferred to ranibizumab at all willingness-to-pay thresholds up to at least $150,000 per QALY.

3.3 CADTH Common Drug Review Analyses

The CDR ran a number of alternative scenarios using the CMA model.

As a result of limitations with the CUA model (described elsewhere in the report), CDR reanalyses focused on the CMA. CDR expects that, in clinical practice, the dose frequency of ranibizumab will be individualized in the first year, similar to the CUA assumptions, with an estimated mean dosing schedule of 6.8 injections in the first year and 5.7 in subsequent years; this regimen is reflected in the most-likely scenario. Assuming aflibercept is dosed an average of 7.5 times in the first year and five times in subsequent years, this would result in cost savings of $15,019 per patient over 10 years.

How aflibercept will actually be dosed in clinical practice is uncertain; however, if physicians individualize aflibercept immediately following the loading doses, it is unlikely to be used more frequently than ranibizumab and would remain cost saving.

TABLE 6: RESULTS OF CADTH COMMON DRUG REVIEW ALTERNATIVE SCENARIOS

CDR Scenario	Relative Cost (Cost Savings) of Aflibercept
Aflibercept administered at same frequency as ranibizumab	($8,784)
Ranibizumab administered at same frequency as aflibercept	($7,298)
Ranibizumab administered at CUA frequency	($15,019)
Aflibercept at same price per vial as ranibizumab	($15,829)
Ranibizumab at same price per vial as aflibercept	($14,343)
Bevacizumab as comparator (assuming $600/dose; 9 doses per year)	$15,484

CDR = CADTH Common Drug Review; CUA = cost-utility analysis.

TABLE 7: EFFECT OF CHANGES IN THE PRICE OF RANIBIZUMAB ON THE COST SAVINGS ASSOCIATED WITH AFLIBERCEPT IN TWO RANIBIZUMAB DOSING SCENARIOS

Relative Price of Ranibizumab	Price Per Vial of Ranibizumab	Relative Cost (Cost Savings) of Aflibercept When Ranibizumab Dosed Monthly in Year 1	Relative Cost (Cost Savings) With Aflibercept When Ranibizumab Dosed as in CUA
100% (base case)	$1,575	($23,127)	($15,019)
90%	$1,417	($14,315)	($6,971)
81% (threshold, rounded)	$1,281	($6,384)	$0
80%	$1,260	($5,503)	$1,077
74% (threshold, rounded)	$1,161	$0	$5,906
70%	$1,102	$3,309	$9,125
60%	$945	$12,121	$17,174
50%	$788	$20,932	$25,222
40%	$630	$29,744	$33,270
30%	$472	$38,556	$41,318
20%	$315	$47,368	$49,366
10%	$158	$56,180	$57,415

CUA = cost-utility analysis.

CDR analysis of the CMA model suggests that the cost-savings threshold price of ranibizumab is $1,161 if both drugs are dosed at the frequencies presented in the manufacturer's CMA (Table 7). If ranibizumab is priced above this threshold, aflibercept appears to be the cost-saving alternative. At prices below this threshold, ranibizumab appears to be the cost-saving alternative. However, when ranibizumab is dosed at the CUA frequency, which CDR reviewers consider more likely in clinical practice, then the cost-saving threshold price of ranibizumab would be $1,281.

4. DISCUSSION

The manufacturer submitted a CMA model in which it assumed that the clinical outcomes and AEs associated with aflibercept and ranibizumab were equivalent. The manufacturer also submitted a CUA model that allowed for the outcomes and the rate of AEs to differ. The CMA model suggested that aflibercept would be less costly due to less frequent administration and a lower drug acquisition price. However, there is considerable uncertainty in the relative frequency of dosing likely to be seen in clinical practice between aflibercept and ranibizumab. CDR reanalysis of the CMA model suggested that aflibercept would remain the cost-saving alternative if it is administered at the same frequency as ranibizumab (holding prices constant), if it had the same price as ranibizumab (holding frequencies constant), or if ranibizumab were individually dosed immediately following the three monthly loading injections (as in the CUA). CDR threshold analyses suggested that aflibercept would be cost saving relative to ranibizumab even if the price of the latter were reduced by up to 25% when ranibizumab was used monthly in the first year, or by up to 18% when ranibizumab was individualized immediately following the loading doses.

The CUA base case also suggested that aflibercept would be slightly less costly and slightly more effective than ranibizumab after allowing for differential outcomes and AE rates over a lifetime horizon. However, as noted in Section 3.1, the estimated cost savings associated with aflibercept in the CUA were substantially smaller than the savings indicated by the CMA. This is most likely due to ranibizumab being dosed less frequently than aflibercept in the first year while all patients remain in the model, as well as to the potentially longer time spent on treatment in the aflibercept group due to the assumption of reduced AEs relative to ranibizumab. However, there is some uncertainty associated with the assumptions for relative efficacy and harms inputs of the CUA; thus, assumption of clinical equivalence while exploring multiple treatment frequencies in the CMA was preferred.

Aflibercept has been approved for funding for the treatment of wAMD by Scotland[13] if a patient access scheme were available, by England if patients would otherwise be treated with ranibizumab,[14] and by Quebec[15] and Australia[16] with strict criteria under exceptional status (see Appendix 2: Other Health Technology assessment Findings). There are also suggestions that France may fund bevacizumab (Avastin) for the treatment of wAMD.

If bevacizumab were used as a comparator to aflibercept, aflibercept would not be a cost-saving alternative. Bevacizumab is not currently approved for use in wAMD in Canada, but is reimbursed in several jurisdictions (e.g., British Columbia, New Brunswick, Nova Scotia, and Yukon). Of note, as aflibercept, ranibizumab, and bevacizumab are all currently available in package sizes exceeding the doses used in wAMD, it would be of benefit for the manufacturers and drug plans to explore opportunities to reduce the amount of wastage associated with these vials.

TABLE 8: KEY LIMITATIONS OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Parameter/Assumption	Issue	Impact
CMA analysis horizon	10-year horizon may overstate actual treatment duration	May overestimate the potential absolute cost savings associated with aflibercept, but the manufacturer's sensitivity analysis shows that it is still likely to be cost saving at a 2-year horizon
Frequency of ranibizumab administration	Ranibizumab unlikely to be administered at the frequency assumed in CMA base case for year 1	May overstate potential cost savings associated with aflibercept, but CDR analysis suggests aflibercept is likely to be cost saving even when ranibizumab is administered at the same frequency as aflibercept
Assumption of superior VA improvements with aflibercept in CUA	CUA assumed a superior improvement in VA with aflibercept by using data from the CATT trial for ranibizumab. However, this was not demonstrated in head-to-head trials of aflibercept versus ranibizumab (VIEW 1 and VIEW 2)	May overstate expected QALYs and understated expected costs relative to ranibizumab in CUA

CATT = Comparisons of Age-Related Macular Degeneration Treatments Trials; CDR = CADTH Common Drug Review; CMA = cost-minimization analysis; QALY = quality-adjusted life-year; VA = visual acuity.

Patient input

Input received from a patient group expressed concern over the financial burdens related to decreasing VA, including requiring assistance for daily tasks and transportation. Patients also associated decreased vision with an increase in injuries such as falls, which may have impacts on the health care system not apparent from a pharmaceutical payer's perspective, or on other measures of costs due to visual health states. Additionally, due to the nature of anti-vascular endothelial growth factor (VEGF) eye injections, many patients have to travel to gain access to treatments, a financial burden that prevents some patients from receiving optimal care. With its reduced dosing schedule, aflibercept is seen as an option to alleviate some treatment and travel expenses without compromising outcomes.

5. CONCLUSIONS

At the submitted price of $1,418 per vial, aflibercept is less costly than ranibizumab. The extent of cost savings is highly dependent on the dose frequency used. The manufacturer's CMA estimated a 10-year cost savings of $23,127 with aflibercept. Based on the dose frequencies more likely to be used in clinical practice, CDR analyses estimated the potential cost savings to be in the range of $7,000 to $15,000 if patients were treated for 10 years.

APPENDIX 1: COST COMPARISON TABLE OF ANTI-VEGF THERAPIES FOR WAMD

Clinical experts have deemed the comparators presented in Table 9 to be appropriate. 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 9: COST COMPARISON TABLE FOR ANTI-VEGF THERAPIES FOR NEOVASCULAR (WET) AGE-RELATED MACULAR DEGENERATION

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Annual Cost Per Eye ($)
Aflibercept (Eylea)	**40 mg/mL**	**0.05 mL vial**	**1,418.00[a]**	**Year 1: 2 mg monthly for 3 months, then 2 mg every 2 months** **Year 2: Individualized regime**	**9,926 (7 injections)** **5,672 to 8,508 (4 to 6 injections)**
Ranibizumab (Lucentis)	10 mg/mL	0.23 mL vial	1,575.00[b]	0.5 mg monthly Based on listing recommendation[c]: Year 1 Years 2 and 3	18,900 (12 injections) 14,175 (9 injections) 9,450 (6 injections)
Pegaptanib sodium (Macugen)	0.3 mg	90 mcL pre-filled syringe	1,013.91[d]	0.3 mg every 6 weeks	8,839

CDR = CADTH Common Drug Review; VEGF = vascular endothelial growth factor; wAMD = neovascular (wet) age-related macular degeneration.
Note: Excess medication in vials or syringes is assumed to be wasted for all comparators.
[a] Manufacturer's confidential submitted price.
[b] Ontario Formulary (June 2014).
[c] Recommended reimbursement maximum as detailed in CDR recommendation for Lucentis for wAMD (March 27, 2008).
[d] Quebec Formulary (June 2014).

It is worth noting that bevacizumab is not currently approved for use for neovascular (wet) age-related macular degeneration (wAMD) in Canada, but its costs are reimbursed in several jurisdictions (e.g., British Columbia, New Brunswick, Nova Scotia, and Yukon). Based on the Proactive Pharma Solutions (PPS) Buyer's Guide (January 2014), bevacizumab is priced at $600 per 100 mg vial or $2,400 per 400 mg vial. At a dose of 1.25 mg every one to two months (e-Therapeutics+ AMD entry, June 2014), the annual cost per eye would be $3,600 to $7,200, or less if multiple doses can be batched from a single vial.

APPENDIX 2: OTHER HEALTH TECHNOLOGY ASSESSMENT FINDINGS

Four health technology assessment (HTA) bodies have published recommendations regarding aflibercept for this indication: the National Institute for Health and Care Excellence (NICE), the Scottish Medicines Consortium (SMC), the Quebec *Institut national d'excellence en santé et en services sociaux* (INESSS), and the Australian Pharmaceutical Benefits Advisory Committee (PBAC). A summary of these recommendations is provided below.

TABLE 10: OTHER HEALTH TECHNOLOGY ASSESSMENT FINDINGS

	NICE (July 2013)[14]	SMC (Mar 2013)[13]	INESSS (Apr 2014)[15]	PBAC (Mar 2012)[16]
Drug	**Aflibercept (Eylea)**			
Price	List price: £816 per vial (C$1,492)[a] Confidential PAS not included	Year 1: £6,528; year 2: £3,264 (C$11,937; C$5,968) Confidential PAS not included	C$1,418 per vial Annual costs redacted	NR
Treatment	Aflibercept 2 mg every 8 weeks	Aflibercept 2 mg every 8 weeks year 1 after 3 loading doses, as needed year 2	Aflibercept 2 mg every 8 weeks after 3 monthly doses year 1, then individualized	Aflibercept 2 mg, 7 times per year
Comparator	RAN 0.5 mg as needed	RAN 0.5 mg monthly to maximum vision achieved, then as needed	RAN 0.5 mg monthly during year 1, then individualized	RAN 0.5 mg, 8.8 times per year
Population modelled	Patients with wAMD	Patients with wAMD not previously treated with anti-VEGF	Patients with wAMD	Patients with wAMD
Time horizon	Lifetime/ 25 years	25 years	10 years	NR
Discount rate	3.5%	NR	NR	NR
Type of model	Cost-utility analysis	Cost-utility analysis	Cost-minimization analysis; cost-utility analysis deemed unnecessary and inappropriately done	Cost-minimization analysis
Key outcomes	ICERs, QALYs	ICERs, QALYs	Treatment costs	Treatment costs
Results	• Base case: Dominant • PSA: CEAC 100% at WTP threshold of £20,000/QALY • ERG reanalysis (better-seeing eye; 0% to 50% discount to RAN): ICER from aflibercept dominant to £9,0002/QALY	• Base case with PAS: Dominant, less costly and 0.0107 QALY gained. • SA indicated dominance is robust, but showed greatest sensitivity to relative monitoring visits and OCT scans. • Removing non-significant differences from model and keeping PAS maintains	• Manufacturer: Cost savings due to less frequent injections and lower cost per dose. • INESSS: In clinical practice, the frequency of injections is likely similar for both medications, thus aflibercept is cost saving based on price per treatment.	• Appears to be cost saving

	NICE (July 2013)[14]	SMC (Mar 2013)[13]	INESSS (Apr 2014)[15]	PBAC (Mar 2012)[16]
	• Other ERG analyses: ICERs ranged from £1,690,000 saved/QALY lost to RAN dominant.	cost savings.		
Sources of uncertainty	Heterogeneity across studies in NMA, best/worst/both eye modelling, treatment-stopping modelling.	NMA outcomes, monitoring, and OCT scan frequency for RAN, assumptions of equivalent discontinuations, and AEs.	Relative frequency of treatment, equivalent efficacy, and harms assumptions	Relative frequency of treatment, lack of data on patients failing RAN. Second year extension of VIEW not available.
Recommendations	• NICE appears to have received a different model than CDR, complicated by PAS for both comparators. NICE recommended aflibercept as a cost-effective use of resources where RAN would otherwise be used. • SMC recommended aflibercept be accepted for use within NHS Scotland if PAS available. • INESSS appears to have received analyses similar to CDR. INESSS recommended aflibercept be accepted as an exceptional status drug with strict clinical criteria. • PBAC recommended listing aflibercept as an authority-required benefit and recommended restriction to treatment-naive patients; the Pharmaceutical Benefits Scheme has since lifted the treatment history restriction.[17]			

£ = British pounds; C$ = Canadian dollars; AE = adverse event; CDR = CADTH Common Drug Review; CEAC = cost-effectiveness acceptability curve; ERG = Evidence Review Group; HTA = Health Technology Assessment; ICER = incremental cost-effectiveness ratio; INESSS = Quebec Institut national d'excellence en santé et en services sociaux; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; NR = not reported; OCT = optical coherence tomography; PAS = Patient Access Scheme; PBAC = Australian Pharmaceutical Benefits Advisory Committee; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year; RAN = ranibizumab; SA = sensitivity analyses; SMC = Scottish Medicines Consortium; VA = visual acuity; wAMD = neovascular (wet) age-related macular degeneration; WTP = willingness-to-pay; VEGF = vascular endothelial growth factor.

[a] £1.00 ≈ C$1.8286 (Bank of Canada, July 9, 2014).

APPENDIX 3: SUMMARY OF KEY OUTCOMES

TABLE 11: 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	Cost saving based on CMA					

CE = cost-effectiveness; CMA = cost-minimization analysis; NA = not applicable.

Table 11 is based on both the manufacturer's results and CADTH Common Drug Review reanalysis.

APPENDIX 4: ADDITIONAL INFORMATION

TABLE 12: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?			X
Comments	The CMA was clear transparent, but the CUA was difficult to interpret and manipulate. The use of different ranibizumab dose frequencies between the CMA and CUA was poorly explained and justified.		
Was the material included (content) sufficient?	X		
Comments	None		
Was the submission well organized and was information easy to locate?	X		
Comments	None		

CMA = cost-minimization analysis; CUA = cost-utility analysis.

TABLE 13: AUTHOR INFORMATION

Authors	Affiliations
Mark Jeddi Steve Kymes	Bayer Inc. Medwin Group

	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[a]

[a] Bayer had input into Methods, but Medwin indicated full control over Methods.

REFERENCES

1. Pharmacoeconomic evaluation. In: CDR submission: Eylea® (aflibercept, solution for intravitreal injection) 2 mg. Company: Bayer Inc. [**CONFIDENTIAL** manufacturer's submission]. Toronto: Bayer Inc; 2013 Nov 13.
2. Clinical Study Report: VGFT-OD-0605 (Year 1) : A randomized, double masked, active controlled phase 3 study of the efficacy, safety, and tolerability of repeated doses of intravitreal VEGF Trap in subjects with neovascular age-related macular degeneration VEGF Trap-Eye: investigation of efficacy and safety in wet AMD (VIEW 1) [**CONFIDENTIAL** internal manufacturer's report]. Tarrytown (NY): Regeneron Pharmaceuticals, Inc.; 2011 Jan 25.
3. Clinical Study Report: A36355 (Year 1): A randomized, double masked, active controlled, phase 3 study of the efficacy, safety, and tolerability of repeated doses of intravitreal VEGF Trap-Eye in subjects with neovascular age-related macular degeneration (AMD) (VIEW 2) [**CONFIDENTIAL** internal manufacturer's report]. Leverkusen (DE): Bayer HealthCare AG; 2012 Nov 13.
4. Clinical Study Report: A62515 (Year 2): A randomized, double masked, active controlled, phase 3 study of the efficacy, safety, and tolerability of repeated doses of intravitreal VEGF Trap-Eye in subjects with neovascular age-related macular degeneration (AMD) (VIEW 2) [**CONFIDENTIAL** internal manufacturer's report]. Berlin (DE): Bayer HealthCare AG; 2012 Dec 18.
5. Heier JS, Brown DM, Chong V, Korobelnik JF, Kaiser PK, Nguyen QD, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology. 2012 Dec;119(12):2537-48. Erratum in: Ophthalmology. 2013 Jan;120(1):209-10.
6. Heier JS, Brown DM, Chong V, Korobelnik JF, Kaiser PK, Nguyen QD, et al. Erratum: Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology. 2013 Jan;120(1):209-10.
7. CATT Research Group, Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med [Internet]. 2011 May 19 [cited 2014 Jul 11];364(20):1897-908. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3157322
8. Sharma S, Brown GC, Brown MM, Shah GK, Snow K, Brown H, et al. Converting visual acuity to utilities. Can J Ophthalmol. 2000 Aug;35(5):267-72.
9. Ontario Ministry of Health and Long-Term Care [Internet]. Toronto: OMHLTC. Schedule of benefits for physician services under the Health Insurance Act; 2014 May 1 [cited 2014 May 1]. Available from: http://www.health.gov.on.ca/english/providers/program/ohip/sob/physserv/physserv_mn.html
10. Sorensen SV, Kansal AR, Connolly S, Peng S, Linnehan J, Bradley-Kennedy C, et al. Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation: a Canadian payer perspective. Thromb Haemost. 2011 May;105(5):908-19.
11. Anis AH, Sun H, Singh S, Woolcott J, Nosyk B, Brisson M. A cost-utility analysis of losartan versus atenolol in the treatment of hypertension with left ventricular hypertrophy. PharmacoEconomics. 2006;24(4):387-400.

12. Cruess AF, Zlateva G, Xu X, Soubrane G, Pauleikhoff D, Lotery A, et al. Economic burden of bilateral neovascular age-related macular degeneration: multi-country observational study. PharmacoEconomics. 2008;26(1):57-73.

13. Aflibercept 40mg/mL solution for intravitreal injection (Eylea®) [Internet]. Glasgow (UK): Scottish Medicines Consortium; 2013 Aug 3. [cited 2014 Jul 10]. Available from: https://www.scottishmedicines.org.uk/files/advice/aflibercept_Eylea_FINAL_March_2013_Amended_030413_for_website.pdf

14. National Institute for Health and Care Excellence. Aflibercept solution for injection for treating wet age-related macular degeneration [Internet]. London: The Institute; 2013 Jul. [cited 2014 May 21]. (NICE technology appraisal guidance 294). Available from: http://www.nice.org.uk/guidance/ta294

15. Eylea^{MC} - dégénérescence maculaire liée à l'âge (DMLA) [Internet]. Québec (QC): Institute national d'excellence en santé et en services sociaux; 2014 Apr. [cited 2014 Jul 11]. Available from: http://www.inesss.qc.ca/en/activites/drug-products/drug-products-undergoing-evaluation-and-evaluated/extract-notice-to-the-minister/eylea.html

16. Pharmaceutical Benefits Scheme (PBS). Aflibercept, solution for intravitreal injection, 40mg per mL, Eylea® - March 2012 [Internet]. [Canberra]: Department of Health, Australian Government; 2012 Mar. [cited 2014 Jul 16]. Available from: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2012-03/aflibercept

17. Pharmaceutical Benefits Scheme (PBS). Important new medicines listed on the PBS [Internet]. [Canberra]: Department of Health, Australian Government; 2012 Oct 24. [cited 2014 Aug 11]. Available from: http://www.pbs.gov.au/info/news/2012/10/important-new-medicines-listed-on-pbs