Common Drug Review
Pharmacoeconomic Review Report

June 2016

Drug	aflibercept (Eylea) (40 mg/mL solution for intravitreal injection available as a 2 mg single-use vial)
Indication	Treatment of visual impairment due to macular edema secondary to central retinal vein occlusion (CRVO)[a]
Listing request	List for the treatment of visual impairment due to macular edema secondary to central retinal vein occlusion (CRVO), similar to ranibizumab
Manufacturer	Bayer Inc.

[a] Aflibercept is also indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD) and diabetic macular edema (DME), which have been reviewed separately.

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.

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.

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The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions.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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TABLE OF CONTENTS

ABBREVIATIONS II

SUMMARY 1

APPENDIX 1: PRICE-REDUCTION ANALYSIS 4
APPENDIX 2: REVIEWER WORKSHEETS 5

REFERENCES 10

Tables

Table 1: Cost-Comparison Table for Central Retinal Vein Occlusion Medications 3
Table 2: Estimated Additional Cost (Savings) per Vial for Aflibercept Versus Ranibizumab at Various Price Reductions 4
Table 3: Summary of Manufacturer's Submission 5
Table 4: Manufacturer's Drug, Administration, and Monitoring Costs 6
Table 5: Manufacturer's Administration and Monitoring Frequencies 6
Table 6: Results of Manufacturer's Clinical Trial and Reimbursement-Request Analyses 7
Table 7: CDR Sensitivity Analyses Regarding Relative Frequency and Costs of Treatments 8
Table 8: Key Limitations 9

ABBREVIATIONS

CDEC	Canadian Drug Expert Committee
CDR	CADTH Common Drug Review
CRVO	central retinal vein occlusion
NMA	network meta-analysis

SUMMARY

Background

Aflibercept (Eylea) is indicated for the treatment of visual impairment due to macular edema secondary to central retinal vein occlusion (CRVO).[1] It is administered by intravitreal injection at a dose of 2 mg and is available at a cost of $1,418 per single-use vial. The manufacturer is requesting a listing similar to that of ranibizumab for CRVO.

The CADTH Common Drug Review (CDR) has previously reviewed aflibercept for wet age-related macular degeneration; the Canadian Drug Expert Committee (CDEC) 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 diabetic macular edema.

Summary of the Economic Analysis Submitted by the Manufacturer

The manufacturer submitted a cost-minimization analysis[3] comparing aflibercept to ranibizumab 0.5 mg in patients with CRVO consistent with those enrolled in the COPERNICUS[4] and GALILEO[5] aflibercept versus sham trials over a two-year time horizon from the perspective of a public health care payer. Clinical similarity was assumed based on the results of an unpublished network meta-analysis that included aflibercept, ranibizumab, and dexamethasone trials.[6]

The manufacturer submitted two main analyses: the "clinical trial analysis" and the "reimbursement-request analysis," both of which included drug acquisition costs (Ontario Drug Benefit Formulary and manufacturer-submitted price), and injection and monitoring costs (Ontario Schedule of Benefits for Physician Services). A 5% discount was applied in year 2 for both analyses. The clinical trial analysis assumed weighted average frequency of administration from the two aflibercept trials[4,5] and from the CRUISE[7,8] trial for ranibizumab: 8.4 injections in year 1 and 3.0 injections in year 2 for aflibercept, versus 8.8 injections in year 1 and 3.5 injections in year 2 for ranibizumab. The reimbursement-request analysis used the CDEC recommendation that reimbursement be limited to a maximum of 24 months and 12 vials for patients with CRVO[9] to assume that both drugs would be administered nine times in year 1 and three times in year 2.

The manufacturer reported, based on administration frequency from clinical trials, that use of aflibercept resulted in a savings of $3,174 per patient when compared with ranibizumab over two years (total cost per patient of $18,302 for aflibercept versus $21,476 for ranibizumab), while administration based on the reimbursement requests yielded a savings of $1,796 per patient receiving aflibercept compared with ranibizumab over 2 years ($19,216 for aflibercept versus $21,012 for ranibizumab) (Table 6).

Key Limitations

Assumption of Clinical Similarity is Uncertain

The manufacturer based its assumption of clinical similarity between aflibercept and ranibizumab on the results of a network meta-analysis (NMA)[6] including aflibercept, ranibizumab, and dexamethasone, all compared with sham treatment. While the NMA was relatively well conducted, unclear inclusion criteria relative to its systematic review, the small number of trials, and inadequately reported patient baseline characteristics all increase uncertainty in the findings. Additionally, given issues with small numbers, the validity of the NMA in the assessment of most harms outcomes was questionable and, as such, no conclusions can be reliably drawn (see CDR Clinical Review Report, Appendix 7).

Relative Frequency of Drug Use is Uncertain

The frequencies of drug use in the base case reflect the clinical trials included in the NMA. Relative costs between aflibercept and ranibizumab are sensitive to the frequency of use for each comparator. It is uncertain whether the frequencies assumed in either the clinical trial or the reimbursement-request analysis will be those used for CRVO in clinical practice. It is also unclear as to the extent that altering relative frequency between aflibercept and ranibizumab will impact relative clinical effectiveness and safety.

Two-Year Time Horizon

According to the CDR clinical expert, an estimated two-thirds of CRVO patients require treatment beyond year 2. A longer time horizon would increase costs for both aflibercept and ranibizumab; however, without further clinical data, it is not possible to predict if there would be a difference between the two drugs in the number of vials used after the second year. If the average number of vials used beyond year 2 is assumed to be similar between comparators, aflibercept would have a cost advantage because of its less expensive price per vial.

Issues for Consideration

Existence of Off-Label Comparators

While bevacizumab and triamcinolone are not indicated for the treatment of CRVO in Canada, they are used in clinical practice and may be of interest to jurisdictions that reimburse them for other eye conditions. In addition, there are jurisdictions in which triamcinolone is a full benefit and, as such, how it is used cannot be restricted. A 2012 NMA[10] (see CDR Clinical Review Report, Appendix 7) that included bevacizumab and triamcinolone did not find significant differences in the main efficacy outcomes between aflibercept, ranibizumab, and bevacizumab; however, a greater proportion of patients lost 15 or more letters of best-corrected visual acuity with triamcinolone compared with aflibercept and ranibizumab, and patients using aflibercept gained statistically significantly more letters than those using triamcinolone.

Results and Conclusions

The extent to which aflibercept is cost-saving when compared with ranibizumab is directly dependent on the frequency of administration and treatment drug costs. When the frequency of use is similar to what is observed in clinical trials, or when identical administration frequency is assumed based on CDEC's listing recommendation for ranibizumab, aflibercept is cost-saving compared with ranibizumab ($1,796 to $3,174 per patient over two years). While the frequency at which both comparators will be used in actual clinical practice for CRVO is uncertain, where clinical similarity between aflibercept and ranibizumab is assumed to hold despite differential administration, aflibercept remains cost-saving relative to ranibizumab if it is administered up to one additional time over two years, but not if it is administered 1.5 or more additional times (Table 7). These conclusions are based on the publicly available price of ranibizumab (price-reduction scenarios are explored in Appendix 1).

Cost-Comparison Table

Clinical experts have deemed the comparator treatments presented in Table 1 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 list prices, unless otherwise specified. Product listing agreements are not reflected in the table and, as such, may not represent the actual costs to public drug plans.

TABLE 1: COST-COMPARISON TABLE FOR CENTRAL RETINAL VEIN OCCLUSION MEDICATIONS

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; interval may be extended up to 3 months based on visual and anatomical outcomes	17,016 (12 injections) 12,762[b] (9 injections) 4,254[b] (3 injections)
Ranibizumab (Lucentis)	10 mg/mL (0.23 mL vial)	Intravitreal injection	1,575.00	0.5 mg monthly; treatment is continued until visual acuity is achieved (stable visual acuity for 3 consecutive months)	18,900 (12 injections) 14,175 (9 injections)[b] 4,725 (3 injections)[b]
Dexamethasone intravitreal implant (Ozurdex)	0.7 mg	Implant device	1,295.00[c]	0.7 mg not more than every 6 months[d]	1,295 (1 treatment) 2,590 (2 treatments)
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 mg every 6 weeks[f]	Up to 5,200[g]
Triamcinolone (Triesence)	40 mg/1 mL	Intravitreal injection	43.40[h]	1 mg to 4 mg every 3 months[i]	174

[a] Manufacturer's submission; also the Ontario Drug Benefit list price.
[b] Based on Canadian Drug Expert Committee recommendation for ranibizumab of maximum 12 injections over two years, assumed to be nine injections in year 1 and the remainder in year 2.
[c] Quebec Formulary price (January 2015).
[d] Monograph recommends a limit of two doses per patient; however, clinical practice may differ.
[e] *PPS Buyers Guide*, January 2014.
[f] Dose used in Epstein 2012[11,12] randomized trial.
[g] Maximum cost, which assumes that vials are not split between patients.
[h] McKesson Canada wholesale price (February 2015).
[i] SCORE (Standard Care versus Corticosteroid for Retinal Vein Occlusion) study dosing.
Source: Ontario Drug Benefit (February 2015), unless otherwise stated.

APPENDIX 1: PRICE-REDUCTION ANALYSIS

To explore the impact of variations in current or future prices for aflibercept and ranibizumab, the CADTH Common Drug Review ran a price-reduction analysis varying the cost of each comparator from its current price (Ontario Drug Benefit list price for ranibizumab; submitted marketed price for aflibercept) down to a 50% reduction.

TABLE 2: ESTIMATED ADDITIONAL COST (SAVINGS) PER VIAL FOR AFLIBERCEPT VERSUS RANIBIZUMAB AT VARIOUS PRICE REDUCTIONS

Percentage Reduction, Price per Vial[a]		Ranibizumab					
		0%, $1,575	**10%, $1,418**	**20%, $1,260**	**30%, $1,103**	**40%, $945**	**50%, $788**
Aflibercept	**0%, $1,418**	($157)	$1	$158	$316	$473	$631
	10%, $1,279	($299)	($141)	$16	$174	$331	$489
	20%, $1,134	($441)	($283)	($126)	$32	$189	$347
	30%, $993	($582)	($425)	($267)	($110)	$48	$205
	40%, $851	($724)	($567)	($409)	($252)	($94)	$63
	50%, $709	($866)	($709)	($551)	($394)	($236)	($79)

[a] Markups and dispensing fees not included.

APPENDIX 2: REVIEWER WORKSHEETS

TABLE 3: SUMMARY OF MANUFACTURER'S SUBMISSION

Drug Product	Aflibercept (Eylea)
Treatment	Aflibercept 2 mg
Comparator(s)	Ranibizumab 0.5 mg
Study Question	What is the incremental cost-effectiveness of aflibercept compared with ranibizumab for the treatment of visual impairment due to macular edema secondary to CRVO?
Type of Economic Evaluation	Cost-minimization analysis
Target Population	Patients with visual impairment due to macular edema secondary to CRVO
Perspective	Public payer
Outcome(s) Considered	Direct costs (drug, administration, and monitoring costs)
Key Data Sources	
Cost	Ontario Drug Benefit Formulary list prices (drugs), Ontario Schedule of Benefits for Physician Services (administration and monitoring)
Clinical Efficacy	Unpublished NMA based on COPERNICUS, GALILEO, and CRUISE clinical trials
Harms	Unpublished NMA based on COPERNICUS, GALILEO, and CRUISE clinical trials
Time Horizon	Two years; 5% discount applied in year 2
Results for Base Case	**Base case (clinical trial frequencies):** Aflibercept (two-year total cost: $18,302) was $3,174 less expensive than ranibizumab (two-year total cost: $21,476) **Reimbursement-request analysis (identical frequencies; year 1 = 9 injections, year 2 = 3 injections):** Aflibercept (two-year total cost: $19,216) was $1,796 less expensive than ranibizumab (two-year total cost: $21,012)

CRVO = central retinal vein occlusion; NMA = network meta-analysis.

2. Manufacturer's Results

The manufacturer's model contains four main inputs: drug costs, taken from Ontario Drug Benefit Formulary list prices; frequency of injections, derived from the COPERNICUS,[4,13] GALILEO,[5] and CRUISE[7,8] trials in the base case; frequency of monitoring, again derived from these trials; and the cost per injection and monitoring visit, taken from the Ontario Schedule of Benefits for Physician Services[14] (Table 4).

TABLE 4: MANUFACTURER'S DRUG, ADMINISTRATION, AND MONITORING COSTS

Item	Cost	Source
Drug acquisition costs		
Aflibercept 2 mg	**$1,418 per vial**	Bayer
Ranibizumab 0.5 mg	**$1,575 per vial**	ODB list price (February 2015)
Administration		
Intravitreal injection	**$105.00**	ON SOB (code E149)
Monitoring visit costs		
Partial ophthalmology assessment	$28.95	ON SOB (code A234)
Optical coherence tomography	$35.00	ON SOB (code G821)
Tonometry	$5.10	ON SOB (code G435)
TOTAL monitoring visit costs	**$69.05**	

ODB = Ontario Drug Benefit; ON SOB = Ontario Schedule of Benefits for Physician Services 2014.[14]
Source: Manufacturer's pharmacoeconomic submission,[3] Tables 7 and 11.

The manufacturer presented two main analyses: the base-case analysis (or clinical trial analysis) and the reimbursement-request analysis. The clinical trial analysis used the weighted mean average injections for years 1 and 2 from the COPERNICUS[4,13] and GALILEO[5] trials for aflibercept (8.4 vials in year 1, 3.0 vials year 2), and from the CRUISE[7,8] trial for ranibizumab (8.8 vials in year 1, 3.5 vials in year 2). The reimbursement-request analysis used the Canadian Drug Expert Committee recommendation that a maximum of 12 vials for two years of ranibizumab be reimbursed for central retinal vein occlusion (CRVO) patients[9] to assume that patients would receive nine vials in year 1 and three vials in year 2 of either aflibercept and ranibizumab (see Table 5).

TABLE 5: MANUFACTURER'S ADMINISTRATION AND MONITORING FREQUENCIES

Comparator	Year 1	Year 2	Source
Clinical trial analysis — number of vials			
Aflibercept 2 mg	8.4	3.0	COPERNICUS and GALILEO
Ranibizumab 0.5 mg	8.8	3.5	CRUISE
Reimbursement-request analysis — number of vials			
Aflibercept 2 mg	9	3	Assumption based on CDEC ranibizumab recommendation
Ranibizumab 0.5 mg	9	3	
Both analyses — number of monitoring visits			
Aflibercept 2 mg	12	5	COPERNICUS and GALILEO
Ranibizumab 0.5 mg	12	4	CRUISE

CDEC = Canadian Drug Expert Committee.
Source: Manufacturer's pharmacoeconomic submission,[3] Tables 8, 9, and 10.

Over two years, in the clinical trial analysis, the manufacturer's results indicate that aflibercept ($18,302) would save $3,174 per patient when compared with ranibizumab ($21,476). In the reimbursement-request analysis, the use of aflibercept ($19,216) was associated with a saving of $1,796 per patient when compared with ranibizumab ($21,012) over two years (see Table 6).

TABLE 6: RESULTS OF MANUFACTURER'S CLINICAL TRIAL AND REIMBURSEMENT-REQUEST ANALYSES

Comparator	Year 1 Drug Costs	Year 2 Drug Costs	Total Drug Costs	Administration Costs[a]	Total Costs
Clinical trial analysis					
Aflibercept 2 mg	$11,911	$4,051	$15,963	$2,339	$18,302
Ranibizumab 0.5 mg	$13,860	$5,250	$19,110	$2,366	$21,476
Difference (aflibercept minus ranibizumab)			**–$3,147**	**–$26**	**–$3,174**
Reimbursement-request analysis					
Aflibercept 2 mg	$12,762	$4,051	$16,813	$2,402	$19,216
Ranibizumab 0.5 mg	$14,175	$4,500	$18,675	$2,337	$21,012
Difference (aflibercept minus ranibizumab)			**–$1,862**	**$66**	**–$1,796**

[a] Administration includes both injection and monitoring costs.
Source: Adapted from manufacturer's pharmacoeconomic submission,[3] Tables 13 and 14. Costs are discounted 5% in the second year.

The manufacturer ran several sensitivity analyses: adjusting ranibizumab monitoring frequency to monthly for both years, adjusting aflibercept monitoring visits to occur only at time of injection visit, and assuming that six injections occur in each year for the reimbursement-request analysis. Aflibercept remained a cost saving in all of them.

3. CADTH Common Drug Review Results

The clinical expert consulted by the CADTH Common Drug Review (CDR) did not believe that the use of aflibercept would alter how CRVO patients are monitored in clinical practice relative to ranibizumab. Due to this expert opinion, along with the low cost of a monitoring visit ($69) relative to drug acquisition costs ($1,418 to $1,575 per vial), differences in monitoring frequency have limited impact on results and thus monitoring frequency is assumed to be similar between drugs and not included in CDR reanalyses. This also negates the minor issue of the manufacturer using code G821 (optical coherence tomography [OCT] for active management of retinal disease, $35) from the Ontario Schedule of Benefits for Physician Services, rather than code G822 (OCT for active management of neovascularization associated with retinal vein occlusion, $25).

The clinical expert consulted by CDR indicated that while aflibercept would initially be used in the manner described in the clinical trials and product monograph, unless clinicians perceived a clear difference between the two drugs, it is likely that aflibercept and ranibizumab will be used in a similar manner and frequency as clinical experience is gained with aflibercept, an assumption considered in the manufacturer's reimbursement-request analysis.

To explore the cost implications of changes in aflibercept frequency relative to ranibizumab, CDR ran a series of reanalyses holding ranibizumab usage at the frequency of the reimbursement-request scenario (nine times in year 1, three times in year 2), while aflibercept was assumed to vary across a range of frequencies over two years (Table 7). Due to its lower cost per vial, aflibercept is cost-saving in all scenarios where the number of vials used is equal to or less than ranibizumab (i.e., scenarios A, B, C, F, and K). Aflibercept remains cost-saving in scenarios that include up to one additional injection relative to ranibizumab over two years (i.e., scenarios D, G, I, and L); however, scenarios incorporating 1.5 or more additional injections over the two years (i.e., scenarios E, H, J, M, and N) led to additional cost compared with ranibizumab.

TABLE 7: CDR SENSITIVITY ANALYSES REGARDING RELATIVE FREQUENCY AND COSTS OF TREATMENTS

Scenario	Assumed Frequency of Aflibercept		Cost of Aflibercept ($)	Cost of Ranibizumab ($)	Relative Cost (Savings) With Aflibercept ($)
	Year 1	Year 2			
A	7	4	16,463	19,920	(3,457)
B	7	5	17,913		(2,007)
C	8	4	17,986		(1,934)
D	8	5	19,436		(484)
E	8	5.5	20,162		242
F	9	3	18,058		(1,862)
G	9	4	19,509		(411)
H	9	4.5	20,234		314
I	9.5	3.5	19,545		(375)
J	9.5	4	20,270		350
K	10	2	18,131		(1,789)
L	10	3	19,581		(339)
M	10	3.5	20,307		387
N	10	4	21,032		1,112

CDR = CADTH Common Drug Review.

Note: Ranibizumab assumed to be used nine times in year 1 and three in year 2. Monitoring costs not included (assumed equal and thus negated). A 5% discount applied in year 2; $105 administration cost applied to each injection. These sensitivity analyses are not meant to imply clinical equivalence or inform clinical practice.

The Canadian Institute for Health Information National Prescription Drug Utilization Information System Database (NPDUIS) was queried regarding the per-patient utilization of ranibizumab. Information was received regarding claims in Alberta, New Brunswick, Ontario, Prince Edward Island, and Saskatchewan.[15] In 2013, an average of 5.24 claims were made per ranibizumab beneficiary across these five provinces. While it is not possible to identify indication or timing of treatment initiation from these data, assuming an average of 5.24 injections per year for CRVO patients (for both aflibercept and ranibizumab) leads to an estimated saving of $1,606 per patient using aflibercept over two years (monitoring costs not included).

TABLE 8: KEY LIMITATIONS

Identified Limitation	Description	Implication
Clinical similarity to comparators uncertain	The manufacturer based its assumption of clinical similarity between AFL and RAN on the results of an NMA[6] that included AFL, RAN, and DEX, all compared with sham treatment. While the NMA was relatively well conducted, unclear inclusion criteria relative to its systematic review, the small number of trials, and inadequately reported patient baseline characteristics all increase uncertainty in the results compared with those which could come from a head-to-head trial.	Uncertainty in relative efficacy is increased. Results for most adverse events had such wide credible intervals that conclusions could not be drawn.
Uncertainty in frequency relative to comparator	The frequencies in the economic base-case analysis are based on those in the clinical trials included in the NMA. As the main cost driver in the analyses (along with price per vial), the results are very sensitive to the frequency of administration. It is uncertain whether the frequencies assumed in either the clinical trial or the reimbursement-request analysis will be those used for CRVO in clinical practice.	There is uncertainty in frequency of both comparators that will be used in clinical practice for this indication. CDR ran analyses holding RAN use steady and altering AFL use (Table 7); however, the comparative efficacy at these altered frequencies is unknown.
Clinical use extending past two years	While clinical data are available for only 2 years, the expert CDR consulted estimated that as many as two-thirds of CRVO patients require further treatments for recurrences after 2 years.	A longer time horizon would increase costs for both comparators; however, without further clinical data, it is not possible to predict whether there would be a difference in the number of vials used for each comparator after the second year. If the average number of vials used beyond year 2 is assumed to be similar, AFL would have a cost advantage due to its less expensive price per vial.

AFL = aflibercept; CDR = CADTH Common Drug Review; CRVO = central retinal vein occlusion; DEX = dexamethasone; NMA = network meta-analysis; RAN = ranibizumab.

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