Common Drug Review
Pharmacoeconomic Review Report

August 2015

Drug	ranibizumab (Lucentis) (10 mg/mL solution for intravitreal injection, 0.5 mg dose with monthly re-treatment as needed)
Indication	Visual impairment due to choroidal neovascularization (CNV) secondary to pathologic myopia
Listing request	As per indication
Manufacturer	Novartis Pharmaceuticals Canada Inc.

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 ophthalmology who provided input on the conduct of the review and the interpretation of findings.

Through the CADTH 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The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions.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
BSE	best seeing eye
CDR	CADTH Common Drug Review
CNV	choroidal neovascularization
CUA	cost-utility analysis
HUI3	Health Utilities Index Mark 3
ICUR	incremental cost-utility ratio
IOP	intraocular pressure
LYs	life-years
MCID	minimal clinically important difference
mCNV	myopic choroidal neovascularization
PAS	patient access scheme
PDT	photodynamic therapy
QALY	quality-adjusted life-year
QoL	quality of life
RANI	ranibizumab
RCT	randomized controlled trial
RVO	retinal vein occlusion
VA	visual acuity
VEGF	vascular endothelial growth factor
vPDT	verteporfin photodynamic therapy
WSE	worse seeing eye

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Ranibizumab (Lucentis)
Study Question	"To evaluate the incremental cost-utility ratio of Lucentis compared to standard of care (vPDT) for the treatment of visual impairment due to mCNV in Canada."
Type of Economic Evaluation	CUA
Target Population	Adults with CNV secondary to pathologic myopia (based on RADIANCE trial participants)
Treatment	Ranibizumab 0.5 mg in solution for intravitreal injection monthly as needed
Outcomes	QALYs; LYs
Comparator	Verteporfin photodynamic therapy (vPDT)
Perspective	Publicly funded health care system
Time Horizon	Lifetime (mean survival time approximately 28 years)
Results for Base Case	Ranibizumab is dominant vs. vPDT: $1,808 cost saving and additional 0.55 QALYs compared
Key Limitations	• Relative frequency of ranibizumab administration is uncertain. • Inclusion of non-health and non-vision costs is not appropriate. • Uncertainty that differences in VA between treatments are clinically relevant, and further uncertainty in translating BCVA to QoL. • Lack of high-quality data supporting the assumption that treatment modifies mortality and that use of ranibizumab leads to a mortality benefit compared with vPDT (0.12 LYs). • Long-term VA benefit and recurrence by treatment uncertain.
CDR Estimates	The cost of treatment with ranibizumab ($1,575 drug and $105 injection costs) is lower than vPDT ($1,703 drug and $330 PDT costs); as such, ranibizumab remains cost saving even under the assumption of no incremental VA benefit (equal mortality, no difference in QoL, no difference in VA-associated non-health and non-vision costs). Incremental cost savings are lost if drug acquisition costs of verteporfin decrease by more than 20%, or if frequency of ranibizumab administration is greater than the base case (without concomitant increase in overall frequency of vPDT administration).

BCVA = best corrected visual acuity; CDR = CADTH Common Drug Review; CNV = choroidal neovascularization; CUA = cost-utility analysis; LYs = life-years; mCNV = myopic choroidal neovascularization; QALYs = quality-adjusted life-years; QoL = quality of life; VA = visual acuity; vs. = versus; vPDT = verteporfin photodynamic therapy.

EXECUTIVE SUMMARY

Background

Ranibizumab (Lucentis) is being reviewed for the treatment of choroidal neovascularization (CNV) in patients with pathologic myopia. The recommended dose is 0.5 mg (0.05 mL of 10 mg/mL solution) administered by intravitreal injection to the affected eye. The drug acquisition cost for a single dose is $1,575. Ranibizumab has previously been reviewed by the CADTH Common Drug Review (CDR) for the treatment of diabetic macular edema, macular edema secondary to retinal vein occlusion, and age-related macular degeneration; the Canadian Drug Expert Committee (CDEC) recommended that ranibizumab be listed with criteria and/or conditions for all three indications.

The manufacturer submitted a cost-utility analysis[1] comparing ranibizumab (one injection with re-treatment as needed based on disease activity) versus verteporfin photodynamic therapy (vPDT) (the current standard of care in Canada) over a patient lifetime horizon, from a public payer perspective. Data from the RADIANCE randomized controlled trial (RCT),[2] VIP RCT[3] (vPDT versus sham) and observational trials[4] informed the model, based on the efficacy outcome of visual acuity (VA). Using observational data, each VA health state was assigned a utility value and health care costs, as well as a mortality risk.

Summary of Identified Limitations and Key Results

There were a number of parameters associated with uncertainty, specifically regarding the use and benefits of ranibizumab, as well as the clinical course of CNV. Under conservative assumptions regarding the clinical benefit of ranibizumab compared with vPDT (i.e., no clinical benefits in terms of VA), ranibizumab remains cost saving. While myopic choroidal neovascularization is largely considered a uniphasic disease, there are data to suggest recurrence does occur in a significant number of patients.[5] As there are no data to guide likely clinical and economic outcomes between the two treatment strategies, and the clinical expert suggested that the approach to treatment is unlikely to differ by treatment strategy, there may not be significant incremental clinical differences between treatments. Thus, neither reanalysis affects the likely cost savings with ranibizumab compared with vPDT.

Whether ranibizumab is cost saving, and the extent of cost savings, depends on the frequency of ranibizumab dosing in actual practice as well as the cost of drug therapy (ranibizumab and verteporfin). The manufacturer assumes ranibizumab is administered 3.5 times in year 1 (from RADIANCE) versus 3.4 times for vPDT (from VIP; typically administered every three months) and once in year 2 (assumption) versus 1.7 times for vPDT (from VIP) with no treatment with either strategy thereafter. Sensitivity analyses varying the frequency of ranibizumab dosing resulted in ranibizumab being more expensive than vPDT when it is administered one or more additional times in year 1 (i.e., ≥ 4.5 times; at 4.5 threshold: plus $155, incremental cost-utility ratio [ICUR] $282 per quality-adjusted life-year [QALY]). While the drug and administration costs are favourable for ranibizumab (drug $1,575; intravitreal injection $105) compared with vPDT (drug $1,704; photodynamic therapy $330), ranibizumab also becomes more expensive if incremental drug or administration costs are modified (for example, a price reduction for verteporfin ≥ 20%).

Conclusions

For the treatment of CNV in pathologic myopia, the manufacturer's economic submission suggests that ranibizumab results in health care cost savings and better health outcomes compared with vPDT (dominant). Given the lower drug acquisition and administration costs for ranibizumab compared with vPDT, ranibizumab remains cost saving if observed VA differences do not result in clinical or subsequent health care cost differences. In this cost minimization scenario, ranibizumab becomes more costly if it is used with greater frequency, or if the cost of verteporfin is 20% less than the price suggested by the manufacturer.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer conducted a cost-utility analysis (CUA) comparing ranibizumab with verteporfin photodynamic therapy (vPDT) in patients with myopic choroidal neovascularization (mCNV).[1] Patient characteristics were based on trial participants in the RADIANCE[2] study. The economic submission utilized health states that were based on visual acuity (VA) (see Figure 1.). Starting VA distribution was obtained from RADIANCE trial participants, and progression through the VA health states was informed for ranibizumab from the RADIANCE trial[2] for months 1 to 12, and an open-label trial of ranibizumab for months 12 to 24.[4] VA progression for vPDT was from RADIANCE (months 1 to 3) and a two-year randomized controlled trial (VIP;[3] vPDT versus sham) for months 3 to 24. Each visual acuity health state was assigned a quality-of-life score for both the worse seeing eye (WSE) (from a study using contact lenses to change VA[6]) and the best seeing eye (BSE) (preference-based utility in patients with retinal vein occlusion[7]); both were adjusted for various factors in regression models. An increased mortality hazard was also assigned to health states with more severe VA loss based on an observational study assessing the risk of mortality with visual acuity. The model did account for BSE versus WSE by weighting the quality of life and the relative risk of mortality by the proportion of patients with BSE and WSE affected and treated. Fifteen per cent of patients were assumed to have bilateral disease; these patients were assumed to receive treatment separately for each eye in the reference case.

Frequency of administration of ranibizumab was obtained from Group 2 of the RADIANCE study[2] (administration on day 1, re-treatment based on observed disease activity) in the first year (3.5 administrations), and assumed one administration in the second year. The VIP trial[3] (vPDT versus sham) informed the frequency of vPDT in year one (3.4 administrations) and year two (1.7 administrations). Monitoring visits were also included according to clinical practice ([redacted]). The cost of administration and drug acquisition was based on the Ontario Schedule of Fees[8] and Benefits, and manufacturer-reported drug costs (ranibizumab and verteporfin). VA health state costs were assigned based on a Canadian observational study[9] that quantified resource utilization by three levels of visual acuity in patients with wet age-related macular degeneration (AMD), and included vision-related health care costs, non–vision-related health care costs, and non–medical-related costs. Adverse events that were common and likely to affect health or resource utilization were identified from the RADIANCE and VIP trial in the first year, consisting of conjunctival hemorrhage and increased intraocular pressure for ranibizumab, and visual disturbance and injection site adverse events for vPDT. These were assumed to cause transient and mild decrementing utility and minor additional resource utilization.

2. MANUFACTURER'S BASE CASE

The manufacturer's base case reported lower total costs with ranibizumab than vPDT of $19,334 versus $21,143 respectively, with incremental cost of –$1,808. Ranibizumab was associated with 11.64 quality-adjusted life-years (QALYs) versus 11.09 QALYs for vPDT, with incremental QALY gained of 0.55. Ranibizumab was dominant compared with vPDT when considering either QALYs or life-years (LYs) (see Table 9).

Drug acquisition costs were lower for the ranibizumab strategy, concordant with similar frequency of administration and unit costs ($1,575 versus $1,703 for ranibizumab and verteporfin, respectively). Further, administration costs are lower for the ranibizumab strategy (injection costs of $105 versus PDT costs of $330). Counterintuitively, costs due to visual impairment are greater for the ranibizumab strategy (see Table 10). As greater health care costs are assigned to more impaired VA (Manufacturer's Pharmacoeconomic submission,[1] Table 24) and treatment with ranibizumab is estimated to result in greater VA over time (see Figure 2), it is unclear why the submitted model results in higher costs for visual impairment with ranibizumab.

2.1 Summary of manufacturer's sensitivity analyses

The manufacturer conducted deterministic sensitivity analysis on several model parameters. The base-case results (and conclusion of dominance) were largely robust in analyses performed. When ranibizumab was administered 4.1 times in the first year (base case = 3.5) and 2.4 times in the second year (base case = 1), costs were greater for ranibizumab than vPDT (+$1,976) with an ICUR of $3,607/QALY.

When a societal perspective was taken, including productivity costs lost due to decreased VA and assuming an average Canadian daily wage of $181.64, ranibizumab remained dominant with an incremental cost of –$12,605 and an incremental QALY of 0.548 when compared with vPDT.

Probabilistic sensitivity analysis was also conducted, with ranibizumab dominant in all iterations. Ranibizumab was considered cost-effective at any willingness-to-pay threshold 100% of the time.

3. LIMITATIONS OF MANUFACTURER'S SUBMISSION

- **Uncertainty in true incremental efficacy.** First, the conduct of the RADIANCE randomized controlled trial (RCT) permits head-to-head comparison of the two treatment options at three months only; relative efficacy is informed by data from a naive comparison of two separate trials after three months, and there is a scarcity of any data beyond two years. As such, there is significant uncertainty in relative efficacy beyond three months. Second, a minimal clinically important difference (MCID) of 10 letters in VA (Early Treatment of Diabetic Retinopathy Study [ETDRS] letters) is commonly cited; while the average VA change within the ranibizumab group is 10.5 letters to 10.6 letters, the incremental VA between ranibizumab and vPDT is below this MCID (8.5 letters to 8.6 letters) at three months. Therefore, the observed differences may be of questionable clinical relevance. This may overestimate the true clinical benefit of ranibizumab.

- **Uncertainty in assigning QoL to VA health states.** While numerical differences in disease-specific QoL instruments (National Eye Institute Visual Function Questionnaire 25 [NEI-VFQ-25]) were observed in the RADIANCE trial, Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH) and EuroQoL Questionnaire–5 Dimensions (EQ-5D) scores showed high variability and numerical differences. As such, a mapping exercise using other data sources and controlling for various factors was used. While there is face validity (worse VA associated with worse QoL), there is also uncertainty as to the true QoL difference by treatment strategy.
- **VA health state costs.** Direct non-medical (mean days lost, social benefits, etc.) and medical non-vision costs (falls, accidents, non-vision costs) are assumed to be larger for patients with a worse VA status. However, some costs (such as transfer payments) should not be included. Further, it is not clear that non-medical and non-vision costs are directly changed by VA status, as this relationship is obtained from observational data in a different patient group with a different underlying disease process. Of note, while patients in the ranibizumab group have better VA, the costs of visual impairment are unexpectedly greater for ranibizumab compared with vPDT.
- **Assumption of uniphasic disease and duration of incremental benefit.** While mCNV is commonly accepted as a uniphasic disease, there are data to suggest that recurrence is not uncommon (Kang).[5] However, the clinical expert indicates that recurrent disease would be approached similarly for both ranibizumab and vPDT treatments. As such, treatment costs are likely to be similar. The relative risk of recurrence and response to treatment of recurrent disease by treatment strategy are not known — if these differ by treatment, this may lead to differences in both cost and effectiveness. However, there are no data to inform in which direction differences might occur.
- **Drug acquisition and administration costs, and relative frequency of administration.** Drug and administration costs are favourable for ranibizumab (drug $1,575; intravitreal injection $105) compared to vPDT (drug $1,704; PDT $330). While verteporfin has been on the market for more than 10 years, its cost has not declined, and the factors responsible for this are not clear. Given that drug costs are a prime driver of overall and incremental costs, the relative frequency of administration may be a key driver. In the RADIANCE trial, Group I (administration on day 1 and at one month with re-treatment based on VA stabilization criteria), had 4.6 injections in year 1, and Group II (administration on day 1 re-treatment based on observed disease activity), had 3.4 in year 1 (reference case); year 2 frequency is based on opinion only. If frequency is greater, or more specifically, if relative frequency of administration of ranibizumab versus vPDT differs, cost savings may diminish or lead to ranibizumab becoming more costly.

3.1 CADTH Common Drug Review Analyses

1. **Equal mortality**. If no additional risk of mortality is assumed by VA status, ranibizumab remains dominant.
2. **Health state costs.** Direct non-medical (mean days lost, social benefits) and medical non-vision costs (falls, accidents, non-vision costs) are assumed to be larger for patients with a worse VA status. However, some costs (transfer payments) should not be included, and it is not clear that non-medical and non-vision costs are directly changed by VA status (based on observational data in a different patient group). Ranibizumab remains dominant (unexpectedly, the cost of visual impairment in the base case is greater for ranibizumab; therefore, exclusion of these costs leads to greater incremental cost savings with ranibizumab).
3. **Uncertainty in true incremental efficacy and subsequent impact on QoL- and VA status-associated costs**. A scenario considering equal efficacy (survival, and QoL) is plausible. Under this scenario (relative risk, RR = 1; QoL ignored) ranibizumab remains less costly (–$1,542).

4. **Other quality of life estimates**. Use of other sources to estimate QoL by VA status did not meaningfully change conclusions.
5. **Frequency of administration and drug acquisition costs.** (Table 11)
    a. The frequency of administration of ranibizumab in the second year is assumed to be once (versus vPDT 1.7 as per VIP study): if average frequency of administration of ranibizumab in the second year is ≥ 2.0, the ranibizumab strategy has slightly greater costs compared with vPDT (+$53).
    b. Relative frequency of administration of vPDT versus ranibizumab in year 1: if actual ranibizumab frequency is greater than trial (3.5), the cost savings diminish (and total costs become similar when frequency of ranibizumab in year 1 is ≥ 4.5). Group I in the RADIANCE trial (re-treatment based on stabilization of VA) had 4.6 injections — this would result in incremental costs of ranibizumab of $350 and an ICUR of $640/QALY gained. A threshold of 4.5 treatments in year 1 leads to ranibizumab being more expensive than vPDT.

    c. Drug costs of verteporfin: if drug acquisition costs of verteporfin are decreased by ~20% (from $1,703 to $1,378), there is no longer a cost savings with ranibizumab.

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 ranibizumab ($600 versus $1,575). However, there is a lack of data in this patient population, and it is not approved for use in Canada for this indication, where vPDT is the standard of care.
- Verteporfin drug acquisition costs are high and have not decreased over the past 10 years. It is not clear why costs have not decreased or what the factors surrounding this are.
- mCNV is uncommon (< 0.1% of the adult population).

4.1 Patient Input

Patients value the potential for improvement in VA with ranibizumab (versus vPDT) given the health, lifestyle, and economic burdens associated with reduced VA. Patients may also be able to engage in regular activities sooner with ranibizumab versus vPDT, given the need to avoid direct sunlight with vPDT. The economic submission includes QoL and costs of VA changes, and also includes productivity losses in sensitivity analysis.

5. CONCLUSIONS

For the treatment of CNV in pathologic myopia, the manufacturer's pharmacoeconomic submission suggests that ranibizumab results in health care cost savings and better health outcomes compared with vPDT (dominant). Given the lower drug acquisition and administration costs of ranibizumab compared with vPDT, ranibizumab remains cost saving if observed VA differences do not result in clinical or subsequent health care cost differences. In this scenario (assumption of no clinical benefit; i.e., cost minimization), ranibizumab is more costly if it is used with greater frequency than assumed, or if the drug costs of verteporfin decrease by more than 20%.

APPENDIX 1: COST COMPARISON

The comparators presented in the table below 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 list prices unless otherwise specified.

TABLE 2: COST COMPARISON TABLE FOR ANTI-VEGF THERAPIES FOR MCNV

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Per Unilateral Treatment ($)
Ranibizumab (Lucentis)	10 mg/mL	0.23 mL vial	1,575.00[ab]	0.5 mg intraocular injection as needed; not more than monthly	1 injection: 1,575
Verteporfin (Visudyne) plus PDT	2 mg/mL reconstituted NA	15 mg vial procedure	1,703.10[a] 330.00[c]	6 mg/m^2 body surface area by IV infusion	1 dose (infusion + PDT): 2,033
Non-indicated Therapies					
Aflibercept (Eylea)	40 mg/mL	0.05 mL vial	1,418.00[d]	2 mg intraocular injection as needed; not more than every 4 weeks	1 injection: 1,418
Bevacizumab (Avastin)	100 mg 400 mg	4 mL vial 16 mL vial	600.00[e] 2,400.00[e]	1.00 to 1.25 mg as needed; not more than monthly[e]	1 injection: up to 600
Pegaptanib sodium (Macugen)	0.3 mg	90 µL pre-filled syringe	1,013.91[f]	0.3 mg every 6 weeks	1 injection: 1,014

mCNV = myopic choroidal neovascularization; µL = microlitre; NA = not applicable; PDT = photodynamic therapy; VEGF = vascular endothelial growth factor.

[a] Manufacturer's submitted price; Lucentis price is consistent with the Ontario Drug Benefit list price; verteporfin price is consistent with the McKesson Canada wholesale price of $1,847.87 if an 8.5% markup is assumed.

[b] Ontario Drug Benefit Formulary (June 2014).

[c] Schedule of Benefits: Physician Services under the Health Insurance Act (May 1, 2014), Ministry of Health and Long-term Care, Ontario, code G460. Note that administration of bilateral PDT on the same day (code G461) is $500.

[d] Eylea submitted price; http://www.cadth.ca/media/cdr/complete/cdr_complete_SR0361-000_eylea_october_22_2014.pdf.

[e] Proactive Pharma Solutions Buyer's Guide (Jan 2014); vial division to reduce wastage may significantly reduce the cost per treatment of bevacizumab.

[f] Régie de l'assurance maladie du Québec (June 2014).

Note: It was assumed that partially used vials or syringes would result in drug wastage.

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 3: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS RANIBIZUMAB RELATIVE TO VPDT?

Ranibizumab vs. vPDT	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)		X				
Drug Treatment Costs Alone		X				
Clinical Outcomes		X				
QoL		X				
Incremental CE Ratio or Net Benefit Calculation	$1,808 cost savings 0.55 additional QALYs (0.12 additional LYs)					

CE = cost-effectiveness; LYs = life-year; NA = not applicable; QALYs = quality-adjusted life-years; QoL = quality of life; vs. = versus; vPDT = verteporfin photodynamic therapy.
Note: Based on manufacturer's results.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 4: 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 5: AUTHOR INFORMATION

Authors	Affiliations
Amy Lee, PhD Debbie Becker, MSc	Lead Analyst, Health Economics and Outcomes Research Director, Health Economics and Outcomes Research

	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

Ranibizumab for myopic choroidal neovascularization (mCNV) has recently been reviewed by the Institut national d'excellence en santé et en services sociaux (INESSS),[10] the National Institute for Health and Care Excellence (NICE),[11] and by the Scottish Medicines Consortium (SMC).[12]

TABLE 6: OTHER HEALTH TECHNOLOGY ASSESSMENT FINDINGS

	INESSS (Oct. 2014)	NICE (Nov. 2013)	SMC (Oct. 2013)
Treatment	Ranibizumab 0.5 mg for mCNV versus vPDT		
Price	$1,575 Cost + administration: $1,750 Cost vPDT: $2,103	£742.17 not including PAS (~C$1,346)[a]	~£742 not including PAS (~C$1,346)[a]
Similarities With CDR submission	CUA; used data from RADIANCE, details not reported.	CUA appears identical to CDR submission with exceptions listed below.	Uncertain, likely similar to NICE submission, details not reported.
Differences From CDR submission	Unknown; likely similar to CDR submission.	• WSE utilities calculated from Czoski-Murray 2009 rather than from Canadian Balshaw 2012 • Costs of drugs, health care utilization, adverse events, and blindness from UK sources • Discount rate 3.5% (vs. 5%).	Uncertain, likely similar to NICE submission.
Manufacturer's Results	RANI dominated vPDT.	RANI dominated vPDT, yielding 0.43 more QALYs while costing £2,761 less over a lifetime. Robust to deterministic and probabilistic SA.	RANI dominated vPDT and remained dominant through range of SA, unless cost of RANI monitoring increased to 8 times base case.
Issues Noted by the Review Group	Noted RANI would be an additional treatment option to the widely used bevacizumab.	• Failed to include bevacizumab as comparator despite available trial evidence and clinical practice. • Uncertainty in continued treatment effect. • Source of HRQoL data in model. • Overestimation of cost of blindness. • Uncertainty that trials adequately sized to reliably populate a 64-cell transition probability matrix. • Lifetime maintenance of treatment benefit optimistic.	• vPDT considered an appropriate comparator, but experts suggested VEGF-A inhibitors unlicensed for mCNV more frequently used in clinical practice. • Indirect comparison naive for months 4 through 12. • Opportunity cost of clinic time to administer and monitor RANI given capacity constraints may not be fully reflected in base case. • Cost of blindness high vs. recent RANI submission for BRVO.

	INESSS (Oct. 2014)	NICE (Nov. 2013)	SMC (Oct. 2013)
Results of Reanalyses by Review Group	Not reported.	Using Brown 1999 utility values, increasing year 2 RANI dose, lowering costs and mortality multiplier of blindness, and correcting manufacturer's calculation errors led to RANI dominating vPDT (0.344 incremental QALYs, £2,474 less). Using Czoski-Murray 2009 utility values yielded an incremental QALY gain for RANI vs. vPDT of 0.266.	Not reported.
Recommendation	Listed for mCNV for patients who meet specific clinical criteria.	An option for treating mCNV with the discount agreed upon in the PAS.	Accepted for use, contingent upon the availability of the PAS in NHS Scotland.

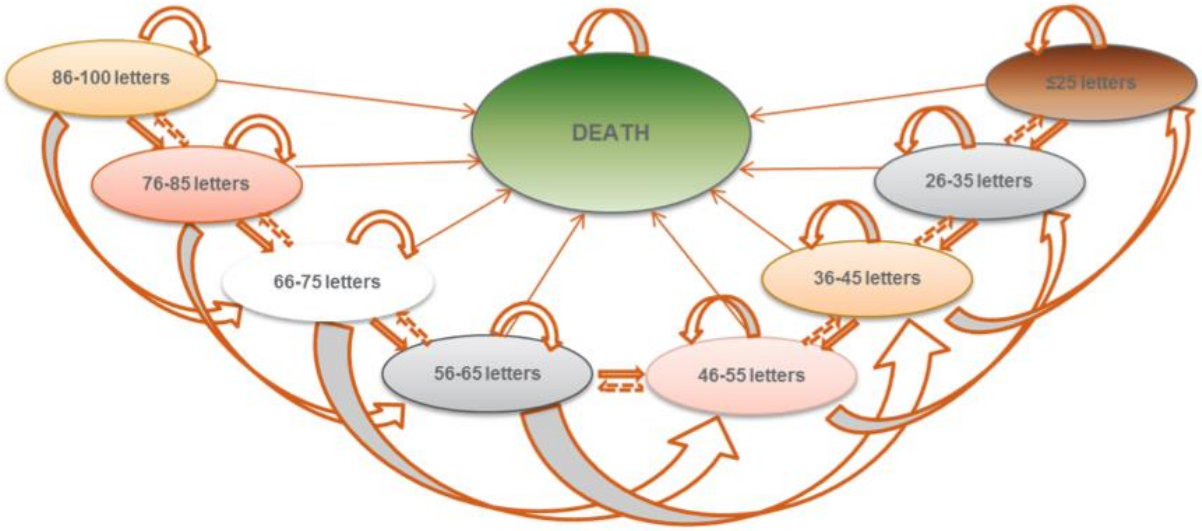
BRVO = branch retinal vein occlusion; C$ = Canadian dollars; CDR = CADTH Common Drug Review; CUA = cost-utility analysis; HRQoL = health-related quality of life; mCNV = myopic choroidal neovascularization; NICE = National Institute for Health and Care Excellence; PAS = patient access scheme; QALY = quality-adjusted life-year; RANI = ranibizumab; SA = sensitivity analysis; UK = United Kingdom; VEGF-A = vascular endothelial growth factor A; vPDT = verteporfin photodynamic therapy; vs. = versus; WSE = worse seeing eye.

APPENDIX 5: REVIEWER WORKSHEETS

Manufacturer's Model Structure

A Markov model consisting of health states defined by best corrected visual acuity (BCVA) status (as well as death) was used to track health outcomes and costs related to myopic choroidal neovascularization (mCNV) and its treatment (Figure 1). Patients may transition between health states every three months. The initial distribution of patients was informed by baseline characteristics of patients enrolled in the RADIANCE trial.

FIGURE 1: MODEL STRUCTURE (FROM MANUFACTURER'S PHARMACOECONOMIC SUBMISSION, PAGE 22)



Visual acuity (VA) progression for ranibizumab was informed by the RADIANCE trial for the first 12 months, a long-term (three-year) open-label trial in a cohort of patients with mCNV for months 12 to 24. VA progression for verteporfin photodynamic therapy (vPDT) was obtained from the RADIANCE trial for months 1 to 3; a 24-month randomized controlled trial (RCT) (vPDT versus sham) for months 4 to 24. The probability of transitioning between VA health states was calculated by estimating the probability of change dependent on the patients' current VA health status (as opposed to a constant transition probability independent of current VA status; this was tested in sensitivity analysis). After 24 months, it was assumed that the difference in BCVA between the two treatment groups would persist but that the decline in VA would occur, based on observational data of a cohort of patient with choroidal neovascularization (CNV) followed for 36 to 258 months (mean 86 months) (Yoshida 2003[13]) equally in both treatment groups.

Mortality probability was informed by Canadian life tables, and based on observational data (Christ 2008[14]) demonstrating an increased risk of mortality with worsening BCVA (in both best seeing eye [BSE] and worse seeing eye [WSE]), a hazard ratio (HR) was applied (based on the weighted average of patients in whom disease was in the BSE or WSE).

Quality of life was assigned using data that assessed utility in 202 patients with retinal vein occlusion (RVO) using the Health Utilities Index Mark 3 (HUI3). A regression model estimated utility accounting for

age, visual acuity in both the affected and unaffected eye (note that RVO could occur in BSE or WSE), and time since onset to predict utility in each of the health states for the WSE.

Effectiveness was informed by using data from the study eye only, although the proportion of patients where the study eye was the BSE (versus WSE) was accounted for by weighting of QoL and the RR of mortality by the proportion of patients with BSE as the study eye.

Internal validity (logic, programming, etc.) as well as face validity was conducted by internal and external reviewers, and applicability to the Canadian setting was validated by two Canadian retina specialists.

TABLE 7: DATA SOURCES

Data Input	Description of Data Source	Comment[a]
Efficacy	Ranibizumab: RADIANCE RCT for 0 to 12 months; open-label treatment trial (Franqueira) for 12 to 24 months. vPDT: RADIANCE RCT for 0 to 3 months; VIP trial vPDT vs. sham 4 to 24 months.	Relative efficacy informed by head-to-head RCT for 0 to 3 months only.
Natural History	Relative efficacy between groups maintained beyond 24 months. Decline in BCVA for both groups informed by observational trial (Yoshida 2003[13]).	
Utilities	BSE utility estimated from a TTO study assessing QoL in subject with simulated VA loss (contact lenses) and adjusted for clinical and demographic factors in regression model. WSE estimated using regression analysis of data from study that examined association of HUI3 (utility measure) in patients with RVO by VA status, and accounting for VA in affected and unaffected eye.	Uncertainty in true associates of utility and BCVA; complicated by VA in BSE and WSE. The model did account for BSE versus WSE by weighting the QoL by the proportion of patients with BSE and WSE affected.
Resource Use	Treatment for mCNV with either ranibizumab or vPDT is episodic. Frequency of treatment for ranibizumab from the RADIANCE trial was used in the first year (3.5), and it was assumed that 1 additional treatment occurred in the second year. vPDT is typically provided every 3 months in patients who have not completely responded; frequency of vPDT was obtained from the VIP trial in year 1 (3.4) and year 2 (1.7). No further treatments occurred for either strategy beyond 2 years. Additional monitoring (clinic visits) occurred in patients treated with ranibizumab to monitor response ([redacted]).	Treatment and monitoring frequency for both strategies has face validity as per clinical expert, but lacks data to inform long-term use.
Adverse Events (indicate which specific adverse events were considered in the model)	Relatively common adverse events that were likely to affect health or resource utilization were obtained from the first year of the RADIANCE and VIP trial for ranibizumab and vPDT. Conjunctival hemorrhage (8.5%) and increased IOP (4.2%) for ranibizumab and visual disturbance (14.8%) and	No suggestion that significant AEs occur beyond 1 year.

Data Input	Description of Data Source	Comment[a]
	injection site AEs (9.9%) for vPDT were included. These were assumed to cause transient and mild decrements in utility (0 to 0.02) and minor additional resource use ($0 to $165).	
Mortality	All cause mortality modelled using annual rates based on Canadian life tables. The HR of mortality by BCVA for both BSE and WSE from an observational study (Christ 2008[14]) was applied based on the weighted average of patients affected in the BSE vs. WSE.	No RCT data supporting that interventions to improve or preserve VA affect mortality; observational data may be prone to bias.
Costs		
Drug	Ranibizumab ($1,575) and verteporfin ($1,704) provided by manufacturer.	
Administration	Intravitreal injection ($105) and PDT ($330) from Ontario Schedule of Fees & Benefits, as well as monitoring (OCT) ($25 to $35) and ophthalmologist assessment ($58).	
AEs	Conjunctival hemorrhage, visual disturbance and injection site AEs (non-ocular) were assumed to be self-limited and incur no cost. Increased IOP assumed topical drops and ophthalmologist visit ($165).	
Health state	The cost of visual impairment was adapted from a Canadian observational study enumerating resource utilization by 3 levels of VA in patients with wet-AMD, and applied only to patients with disease affecting the BSE (as patients who are affected in the WSE may compensate by vision in the BSE).	Some costs are not clearly direct health care costs (i.e., social benefits are a transfer payment); unclear if resource use may be influenced by other confounders.
Indirect costs	Assessed in sensitivity analysis and include workforce productivity losses, as well as caregiver time. Based on review by Lachaine.	

AE = adverse event; AMD = age-related macular degeneration; BCVA = best corrected visual acuity; BSE = best seeing eye; HR = hazard ratio; HUI3 = Health Utilities Index Mark 3; IOP = intraocular pressure; mCNV = myopic choroidal neovascularization; OCT = optical coherence tomography; PDT = photodynamic therapy; QoL = quality of life; RCT = randomized controlled trial; RVO = retinal vein occlusion; TTO = time trade-off; VA = visual acuity; vPDT = verteporfin photodynamic therapy; vs. = versus; WSE = worse seeing eye.

TABLE 8: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
Incremental differences in VA by treatment strategy are clinically important and lead to meaningful changes in QoL.	Not definitively established.
Patients with better VA as a result of treatment strategy will decrease the risk of mortality.	Not definitively established.
Patients with better VA as a result of treatment strategy will incur lower health care costs.	While reasonable assumption for medical vision-related costs, not clear for non-visual costs.
Frequency of administration of ranibizumab and vPDT are similar in the first and second year, and are not used subsequently.	Unknown. The clinical expert indicates that this is a reasonable assumption.

QoL = quality of life; VA = visual acuity; vPDT = verteporfin photodynamic therapy.

Manufacturer's Results

The manufacturer's base case reported lower total costs with ranibizumab than with PDT of $19,334 versus $21,143, respectively, with incremental costs of $1,808. Ranibizumab was associated with 11.64 QALYs versus 11.09 QALYs for vPDT, with an incremental QALY gained of 0.55. Ranibizumab was dominant compared with vPDT when considering either QALYs or LYs.

TABLE 9: SUMMARY OF MANUFACTURER'S RESULTS

	Ranibizumab	vPDT	Incremental
Total Costs	$19,334	$21,143	–$1,808
QALYs	11.64	11.09	0.55
LYs	14.42	14.30	0.12
ICUR			Ranibizumab dominant

ICUR = incremental cost-utility ratio; LYs = life-years; QALYs = quality-adjusted life-years; vPDT = verteporfin photodynamic therapy.
Source: Manufacturer's Pharmacoeconomic Submission.[1]

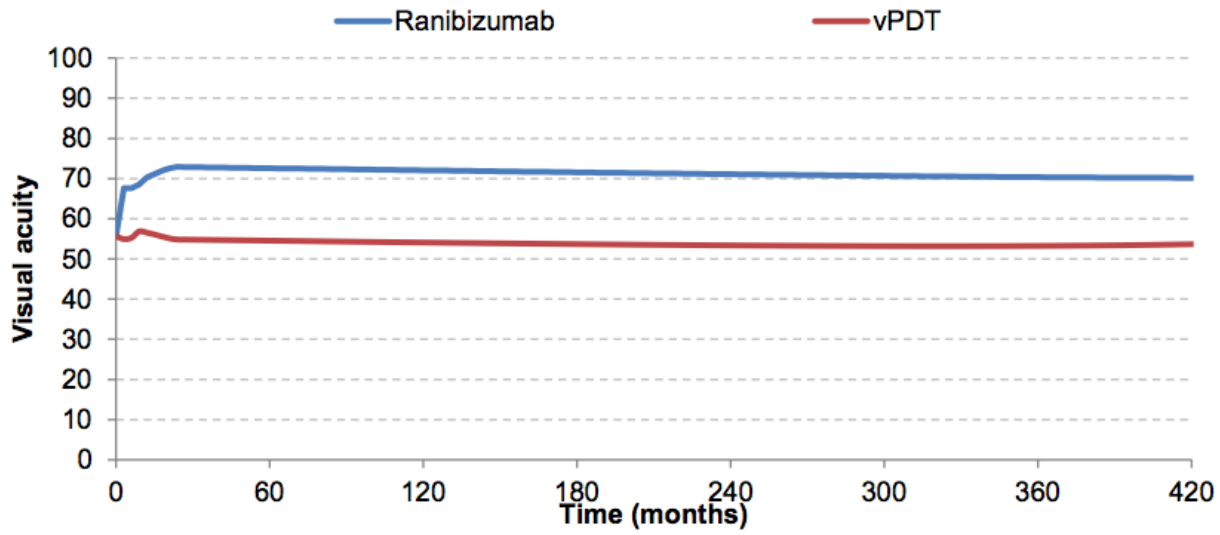
Disaggregated costs are shown in Table 10. Drug acquisition costs were lower for the ranibizumab strategy, concordant with similar frequency of administration and unit costs ($1,575 versus $1,703 for ranibizumab and verteporfin, respectively). Further, administration costs are lower for the ranibizumab strategy (injection costs of $105 versus PDT costs of $330). Counterintuitively, costs due to visual impairment are greater for the ranibizumab strategy. As greater health care costs are assigned to more impaired VA and treatment with ranibizumab is estimated to result in greater VA over time, it is unclear why the model results in higher costs for visual impairment with ranibizumab.

TABLE 10: SUMMARY OF MANUFACTURER'S RESULTS FOR DISAGGREGATED COSTS

	Ranibizumab	vPDT	Incremental
Treatment	$6,782	$8,262	–$1,480
Administration	$851	$2,050	–$1,199
Monitoring	$380	$196	$185
Bilateral	$1,145	$1,547	–$402
AE	$7	$0	$7
Visual Impairment	$10,170	$9,088	$1,082

AE = adverse event; vPDT = verteporfin photodynamic therapy.
Source: Manufacturer's Pharmacoeconomic Submission.[1]

FIGURE 2: MODEL ESTIMATED VISUAL ACUITY OVER TIME



vPDT = verteporfin photodynamic therapy.
Source: Manufacturer's Pharmacoeconomic Submission.[1]

The manufacturer conducted deterministic sensitivity analysis on several model parameters. The base-case results (and conclusion of dominance) were largely robust in analyses performed. When ranibizumab was administered 4.1 times in the first year (base case 3.5) and 2.4 times in the second year (base case 1), costs were greater for ranibizumab ($1,976) with an ICUR of $3,607/QALY.

Probabilistic sensitivity analysis was also conducted, and ranibizumab was dominant in all iterations, and was cost-effective at any willingness-to-pay threshold 100% of the time.

CADTH Common Drug Review Reanalysis

1. **Equal mortality**. Given the absence of reliable data that treatment in this patient population modifies the risk of mortality (mediated by incremental differences in BCVA), equal risk of mortality was assumed. Ranibizumab remains dominant.
2. **Health state costs.** Direct non-medical (mean days lost, social benefits) and medical non-vision costs (falls, accidents, non-vision costs) are assumed to be larger for patients with a worse VA status. However, some costs (transfer payments) should not be included, and it is not clear that non-medical and non-vision costs are directly changed by VA status (based on observational data in a different patient group). Ranibizumab remains dominant (unexpectedly, the cost of visual impairment in the base case is greater for ranibizumab; therefore, exclusion of costs leads to greater incremental cost savings with ranibizumab).
3. **Uncertainty in true incremental efficacy and subsequent impact on QoL and VA status– associated costs**. First, the conduct of the RADIANCE RCT permits head-to-head comparison of the two treatment options at three months only; relative efficacy is informed by data from two separate trials after three months, and there is a scarcity of any data beyond two years. As such, there is significant uncertainty in relative efficacy beyond three months. Second, an MCID of 10 VA (ETDRS letters) is commonly cited; while the average VA change within the ranibizumab group is 10.5 to 10.6, the incremental VA between ranibizumab and vPDT is below the MCID (8.5 to 8.6) at three months. Therefore, the observed differences may be of questionable clinical relevance. As such, a scenario considering equal efficacy (survival and QoL) is plausible. Under this scenario (RR = 1; QoL ignored) ranibizumab remains less costly (–$1,542).
4. **Recurrent disease**. The long-term trajectory of mCNV is not well described. While most experts describe it as a uniphasic disease, there have been reports of recurrence in up to 46% (Kang 2013).[5] There are no data to suggest disparate probability of recurrence by initial treatment (ranibizumab versus vPDT), and clinical expert opinion indicates that choice of treatment strategy is unlikely to lead to long-term differences in recurrence (or health and resource use implications). As such, no reanalysis was performed.
5. **Frequency of administration and drug acquisition costs.**
    a. The frequency of administration of ranibizumab in the second year is assumed to be once (versus vPDT 1.7 as per VIP study). If average frequency of administration is greater, costs for ranibizumab increase; incrementals are greater for ranibizumab if the frequency is ≥ 2.0 in the second year.
    b. Relative frequency of administration of vPDT versus ranibizumab in year 1. If actual ranibizumab frequency is greater than trial (3.5), the cost savings diminish (and total costs become similar when frequency of ranibizumab in year 1 is 4.5). Group I in the RADIANCE trial (re-treatment based on stabilization of VA) had 4.6 injections, leading to incremental costs of ranibizumab of $350 and ICUR of $640/QALY gained.
    c. Drug costs of verteporfin. If drug acquisition costs of verteporfin are decreased by ~20% ($1,703 to $1,378), there is no longer cost savings with ranibizumab.

TABLE 11: CADTH COMMON DRUG REVIEW REANALYSES

	Incremental Cost	Incremental QALYs	ICUR
Base Case	**–$1,808**	**0.55**	**Ranibizumab dominant**
Equal mortality	–$1,542	0.41	Ranibizumab dominant
Non-medical & non-visions health costs excluded	–$2,416	0.55	Ranibizumab dominant
Equal mortality No difference in QoL	–$1,542	0	Ranibizumab less costly
Frequency of Administration in Year 2 (Base Case 1.0)			
1.7 (vs. 1.7 vPDT)	–$505	0.55	Ranibizumab dominant
2.0 (vs. 1.7 vPDT)	$53	0.55	$98/QALY gained (threshold)
Frequency of Administration in Year 1 (Base Case 3.5)			
4.6 (vs. 3.4 vPDT)	$350	0.55	$640/QALY gained
4.5 (vs. 3.4 vPDT)	$155	0.55	$282/QALY gained (threshold)

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; QoL = quality of life; vPDT = verteporfin photodynamic therapy; vs. = versus.

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