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CADTH THERAPEUTIC REVIEW

Anti–Vascular Endothelial Growth Factor Drugs for the Treatment of Retinal Conditions — Recommendations Report

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Abbreviations

AMD	age-related macular degeneration
anti-VEGF	anti–vascular endothelial growth factor
BCVA	best corrected visual acuity
CDEC	CADTH Canadian Drug Expert Committee
CI	confidence interval
CNV	choroidal neovascularization
DME	diabetic macular edema
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
OR	odds ratio
PM	pathologic myopia
RCT	randomized controlled trial
RVO	retinal vein occlusion
VA	visual acuity
wet AMD	wet age-related macular degeneration

Background

Retinal conditions have become an important health policy issue due to the large number of people they affect, and the widespread adoption of effective but costly anti–vascular endothelial growth factor (anti-VEGF) drugs to treat these conditions. Anti-VEGFs are given by intravitreal injection (injection into the eye), where they inhibit the abnormal angiogenesis (new blood vessel formation) that underlies many diseases that affect the retina and cause vision loss. Ranibizumab was approved for intravitreal injection in 2006, and in 2011, aflibercept became the second anti-VEGF approved for treating retinal conditions. A third anti-VEGF, bevacizumab, can be prepared for intraocular injection and used in clinical practice to treat retinal conditions, although it is approved by Health Canada only for intravenous injection to treat certain types of metastatic cancer. Due to their effectiveness and favourable safety profile, the anti-VEGFs have quickly become established as the standard of care for the treatment of retinal conditions.

Table 1: Drugs Available for Retinal Conditions in Canada

Product (Manufacturer and Distributor)	Generic Name	Health Canada–Approved Retinal Indications[a]
Eylea (Regeneron/Bayer)	aflibercept	Neovascular (wet) AMD
		Visual impairment due to ME secondary to CRVO or BRVO
		DME
Lucentis (Genentech/Novartis)	ranibizumab	Neovascular (wet) AMD
		Visual impairment due to DME
		Visual impairment due to ME secondary to RVO
		Visual impairment due to CNV secondary to PM
Avastin (Genentech/Hoffmann-La Roche)	bevacizumab	NA[b]

AMD = age-related macular degeneration; BRVO = branch retinal vein occlusion; CNV = choroidal neovascularization; CRVO = central retinal vein occlusion; DME = diabetic macular edema; ME = macular edema; NA = not applicable; PM = pathologic myopia; RVO = retinal vein occlusion.
[a] Source of information: Health Canada Drug Product Database.[1]
[b] CADTH is not aware of regulatory filing to Health Canada for bevacizumab use in wet AMD, DME, BRVO, CRVO, or CNV due to PM.

NOTE:
The Canadian product monograph for Avastin (bevacizumab) includes the following warning:

"*AVASTIN is not formulated and has not been authorized for intravitreal use. Local and systemic adverse events have been reported in the post-market setting with unauthorized intravitreal use*."[2]

Preamble to the Recommendations

There is considerable interest from jurisdictions that participate in the CADTH review process in assessing the relative clinical effects of the different anti-VEGFs in patients with retinal conditions, as well as in better understanding the relative costs of these drugs. The CADTH Canadian Drug Expert Committee (CDEC; the Committee) appreciated that the total cost of reimbursing the costliest of the anti-VEGF therapies for treating retinal conditions is large and will continue to expand due to a growing proportion of older Canadians who are more likely to develop retinal conditions. Several jurisdictions within Canada have in place publicly funded access to bevacizumab for patients with retinal conditions. The Committee also noted that many ophthalmologists routinely use bevacizumab as an initial

therapeutic option for treating patients with retinal conditions. To address the needs of the jurisdictions, CADTH carried out a therapeutic review of the relative efficacy and safety of anti-VEGF drugs for treating retinal conditions, followed by an analysis of treatment costs.

The Committee considered the evidence and its limitations primarily from a population-based perspective. The anticipated benefits, harms, and costs of the anti-VEGF drugs, together with input from three patient groups and other stakeholders (including manufacturers, clinicians, and a clinical group) were considered in the development of recommendations by the Committee. In addition, the Committee relied on the clinical expertise and experience of three ophthalmologists from different regions of Canada who have experience in the management of patients with retinal conditions.

A challenging aspect of the process of developing recommendations for the use of anti-VEGF drugs to treat retinal conditions is the *lack of a review and approval by Health Canada for the use of bevacizumab to manage wet age-related macular degeneration (AMD), diabetic macular edema (DME), retinal vein occlusion (RVO), and choroidal neovascularization (CNV) due to pathologic myopia (PM)*. The Committee was aware throughout the review process that there is no information available with regard to regulatory review in Canada for the use of bevacizumab to treat wet AMD, DME, RVO, and CNV due to PM, and that the Canadian product monograph carries a statement cautioning against the intravitreal use of bevacizumab.

While the absence of regulatory approval of a medicinal product is frequently associated with a dearth of clinical evidence, this is not the case for bevacizumab, for which there is substantial evidence of efficacy in several different retinal conditions. This evidence was included in the Science Report[3] and, in addition, a targeted review of safety data regarding intravitreal use of bevacizumab was carried out and included in the Science Report to assess the potential harms associated with the use of bevacizumab for treating retinal conditions. None of the aforementioned evidence suggested that there is a higher risk for causing harm associated with intravitreal injection of appropriately prepared (i.e., in a sterile environment that ensures appropriate testing and handling of prepared doses) and handled bevacizumab aliquots compared with other anti-VEGFs. The Committee noted also that all clinical studies that have assessed the efficacy and/or safety of bevacizumab in patients with retinal conditions were funded by independent research organizations with government support. Recognizing the statement from Health Canada, the Committee believed that the inclusion of bevacizumab in the scope of the therapeutic review was appropriate for several reasons, including:

- Sufficient clinical evidence available to assess the relative effects of bevacizumab and other anti-VEGF drugs in treating retinal conditions;
- The widespread use of bevacizumab to treat patients with retinal conditions in Canada, which reflects the acceptance of this drug as a treatment option for retinal conditions; and
- The desire of public payers to include bevacizumab as a treatment option in an objective assessment of the relative effects of anti-VEGF drugs for treating retinal conditions.

The Committee noted that bevacizumab is currently being reimbursed by public payers for the treatment of retinal conditions in several jurisdictions in Canada, including British Columbia, Nova Scotia, New Brunswick, and Manitoba.[4-7] Alberta recently introduced a new program that will allow patients to choose, and physicians to prescribe, either ranibizumab or bevacizumab for the treatment of AMD, DME, RVO, and any other retinal condition that requires anti-VEGF treatment.[8-10]

The Committee noted that the administration of anti-VEGF drugs to patients with retinal conditions should be carried out only by ophthalmologists who have expertise and experience in the management of these conditions. All products should be handled appropriately, particularly for preparation of bevacizumab doses.

CADTH Canadian Drug Expert Committee Values and Preferences

The Committee sought to balance the concerns and needs of patients, as represented in the feedback received by CADTH, with the clinical and economic evidence. The Committee identified the values of efficacy, safety, cost, and patient perspectives as particularly important in making its recommendations. In considering the patients' perspectives, the Committee noted patients' preference for early intervention and individualized treatment to improve long-term outcomes and their concern that successful treatment could be jeopardized by delayed access and a lack of choice. For them, successful treatment is defined by what they say matters most: restoring vision and preventing further vision loss. Despite the strong opinion expressed by patient groups that recommending one drug in preference to another could be interpreted as limiting choice, the Committee noted that the exclusion of any consideration of cost disregards the opportunity cost of not funding other health care services, which was a value likely of importance to other patient groups.

Policy Questions

1. Based on clinical evidence and cost, which anti-VEGF drug(s) should be reimbursed for the treatment of neovascular (wet) AMD, DME, macular edema due to RVO, and CNV secondary to PM?
2. Are there subgroups within the aforementioned indications within which drug(s) identified in Question 1 should be reimbursed?
3. What is the preferred dosing regimen(s) for drug(s) identified in Question 1?

Summary of Recommendations

Recommendation 1:

For the treatment of patients with wet AMD, DME, RVO, or CNV due to PM, bevacizumab is the preferred initial anti-VEGF therapy, based on similar clinical effectiveness and lower cost compared with other anti-VEGF treatments. Ranibizumab or aflibercept can be used as alternative treatment options in patients who do not respond to bevacizumab (see Note 1) or in patients who experience thromboembolism following the initiation of bevacizumab treatment or who are at a high risk of cardiovascular adverse events (see Note 2).

Recommendation 2:

There are no specific recommendations for anti-VEGF therapy for any subgroups of patients within any of the conditions of interest.

Recommendation 3:

The frequency and dose of intravitreal injections of the anti-VEGF drugs should be determined by the treating ophthalmologist, but should not exceed that recommended for a particular retinal condition by the product monograph (if available) or that used in randomized clinical trials.

NOTES

1. For all retinal conditions considered, an inadequate response to treatment is defined as not achieving any improvement in best corrected visual acuity (BCVA) at 3 months or not achieving an improvement in BCVA at 6 months of at least 15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters compared with the baseline (pre-treatment) BCVA.
2. Individuals are considered to be at a high risk of cardiovascular adverse events if there is clinical evidence of atherosclerosis or they have had a previous myocardial infarction, have undergone coronary or arterial revascularization, or have a history of cerebrovascular disease (including transient ischemic attack) or peripheral arterial disease.[11]
3. The Committee noted that there was sufficient evidence available to conclude that the total number of injections of bevacizumab required to achieve a desired outcome will be similar to that for ranibizumab.
4. For patients with DME who cannot receive bevacizumab, there was evidence from a single randomized controlled trial (RCT)[12] that aflibercept could be considered as a preferable alternative treatment over ranibizumab in patients with poor visual acuity. However, due to several major limitations with this evidence (including the use of a lower dose of ranibizumab than that used in Canada), this evidence was insufficient to support a definitive recommendation by the Committee to use aflibercept in preference to ranibizumab in DME patients; rather, either aflibercept or ranibizumab is recommended as an alternative treatment in DME patients subsequent to bevacizumab treatment, and the selection of which one of these two alternatives should be used is at the discretion of the treating ophthalmologist.
5. The Committee noted the concerns expressed by stakeholders regarding the safety of bevacizumab to treat retinal conditions, but concluded that compared with ranibizumab or aflibercept, there was no evidence of an increased risk of cardiovascular or ophthalmic harm due to intravitreal injection of *properly prepared, stored, and handled aliquots of bevacizumab*.
6. The Committee emphasized that appropriate preparation, storage, and handling of bevacizumab aliquots is essential in jurisdictions that choose to follow the recommendation to fund access to bevacizumab for the treatment of retinal conditions. In addition, the Committee noted the need for quality control systems to be in place to monitor the safety of all anti-VEGF drugs used for intraocular injection.

NOTES (cont'd)

7. The Committee noted that including bevacizumab as a treatment option in its recommendations in the absence of regulatory approval for the use of bevacizumab to treat retinal conditions should not be interpreted as promoting 'off-label' use of bevacizumab, but rather as reflecting the current evidence-based expanded use of this product in clinical practice.
8. The Committee's recommendations were based on the body of clinical evidence within the Science Report and under the current pricing scenarios in Canada for the products reviewed. If important additional clinical evidence were to become available and/or if the pricing scenario were to change, CADTH could determine that these recommendations should be updated to reflect such new information, as appropriate.

Recommendations

Recommendation 1

For the treatment of patients with wet AMD, DME, RVO, or CNV due to PM, bevacizumab is the preferred initial anti-VEGF therapy, based on similar clinical effectiveness and lower cost compared with other anti-VEGF treatments. Ranibizumab or aflibercept can be used as alternative treatment options in patients who do not respond to bevacizumab (see Note 1) or in patients who experience thromboembolism following the initiation of bevacizumab treatment or who are at a high risk of cardiovascular adverse events (see Note 2).

NOTES

1. For all retinal conditions considered, an inadequate response to treatment is defined as not achieving any improvement in BCVA at three months or not achieving an improvement in BCVA at six months of at least 15 ETDRS letters compared with the baseline (pre-treatment) BCVA.
2. Individuals are considered to be at a high risk of cardiovascular adverse events if there is clinical evidence of atherosclerosis or they have had a previous myocardial infarction, have undergone coronary or arterial revascularization, or have a history of cerebrovascular disease (including transient ischemic attack) or peripheral arterial disease.

Of Note for Recommendation 1

1. For all conditions, the Committee noted that due to the design of clinical trials, there is limited available evidence to assess the association between an early response to treatment and long-term visual outcomes. Therefore, based on the available evidence, as well as the opinions of clinical experts, an inadequate response to treatment can be defined as follows: (1) the absence of any improvement in BCVA after three months of initial therapy compared with the baseline (pre-treatment) BCVA; or (2) not achieving an improvement in BCVA after six months of at least 15 ETDRS letters compared with the baseline (pre-treatment) BCVA. These two criteria allow for the switching of patients who do not experience any improvement to alternative treatments after a three-month period, as well as to allow sufficient time for patients who do experience an improvement at three months to gain the most from the current treatment before assessing whether switching treatments at six months would further generate additional improvement. The BCVA threshold at six months of 15 ETDRS letters is based on the threshold used as a primary outcome in many clinical trials, which is based on the following FDA guidance: "Improvement in best corrected distance visual acuity is considered to be clinically meaningful when the mean visual angle doubles in resolution capacity. On

a standard ETDRS … visual acuity chart, this change is equivalent to a 15-letter improvement."[13] In addition, feedback received from various stakeholders was taken into consideration in determining the two assessment periods.

2. For patients with DME, the Committee determined that there was insufficient evidence to recommend that aflibercept be considered in preference to ranibizumab when considering an alternative to bevacizumab treatment. There is evidence from a study by Wells et al.[12] that suggested that aflibercept may be more effective than bevacizumab and ranibizumab at improving visual acuity in DME patients, particularly those with poor baseline visual acuity. Specifically, Wells and colleagues reported that treatment of DME patients with aflibercept (13.3 letter improvement vs. baseline) improved visual acuity to a statistically significantly greater degree compared to treatment with ranibizumab (11.2 letter improvement vs. baseline) or bevacizumab (9.7 letter improvement vs. baseline; $P < 0.05$ for both comparisons). Despite this, the difference *between treatments* of 2.1 to 3.6 letters is smaller than the minimum threshold required to be accepted as being a clinically meaningful difference, which is at least 10 to 15 letters.[12] The statistically significantly greater improvement in visual acuity that was observed in the aflibercept-treated patients was driven by a subgroup of patients who had worse visual acuity at baseline (an initial letter score < 69), and in these patients, there was a relative improvement in aflibercept-treated patients of 4.7 to 7.1 letters versus ranibizumab and bevacizumab, respectively. However, this difference is still smaller than the minimum clinically important difference of 10 to 15 letters. The apparent absence of clinically meaningful differences among the anti-VEGF drugs in DME patients supports the Committee's recommendation that bevacizumab be preferred as first-line treatment. However, in addition to the absence of a clinically meaningful difference between aflibercept and ranibizumab in the Wells study, the dose of ranibizumab used in the Wells study (0.3 mg) was lower than that used in Canada (0.5 mg), which likely biases the results in favour of aflibercept over ranibizumab. Therefore, the evidence available from the Wells study is insufficient to support a recommendation that aflibercept be used in preference to ranibizumab, although the Committee noted that the selection of aflibercept or ranibizumab as an alternative to bevacizumab in DME patients should be left to the discretion of the treating ophthalmologist.
3. The Committee's recommendation for CNV due to PM was based on evidence that bevacizumab and ranibizumab are equally efficacious in patients with CNV due to PM, and that aflibercept is also effective in treating CNV due to PM, based on the results of a sham-controlled study.[14] The Committee noted that there was less evidence included in the systematic review within the draft CADTH Science Report for CNV due to PM than for the other retinal conditions examined, and that the available evidence comprised relatively small numbers of patients. However, the Committee considered that this evidence was sufficient to support the recommendation.
4. The Committee noted the concerns expressed by stakeholders regarding the potential for bevacizumab to cause cardiovascular harm. The Committee considered the clinical evidence available from RCTs and uncontrolled studies, as well as discussed the molecular mechanisms that might cause bevacizumab to be associated with a higher risk of systemic adverse events than other anti-VEGF molecules. The Committee also considered whether intravitreal bevacizumab was safe to use in patients with a high risk of cardiovascular events, and noted that there is a lack of evidence of a significant, consistent association between intravitreal bevacizumab injection and cardiovascular events, particularly thromboembolic events. The Committee also noted that there is an absence of evidence to determine whether there is an elevated risk of cardiovascular harm within particular subgroups of patients stratified according to risk of a cardiovascular event. Nevertheless, the Committee noted that patients with a high risk of cardiovascular events could be considered for treatment with ranibizumab or aflibercept rather than bevacizumab, although this decision should be left to the discretion of the treating physician, taking into account also the needs and preferences of individual patients.

Reasons for Recommendation 1

Wet Age-Related Macular Degeneration

Clinical evidence from 13 RCTs of anti-VEGF drugs in patients with wet AMD, identified in the systematic search, along with the economic analysis, suggests that bevacizumab, ranibizumab, and aflibercept have similar efficacy and safety in patients with wet AMD, but the cost of treatment with bevacizumab is substantially less than the cost of treatment with ranibizumab or aflibercept.

The results of a meta-analysis of ranibizumab versus bevacizumab revealed no statistically significant differences with respect to the proportion of wet AMD patients who experienced a gain of ≥ 15 ETDRS letters (meta-analysis of eight RCTs, 2,950 patients, odds ratio [OR]: 1.13 [95% confidence interval (CI), 0.96 to 1.34]), a loss of ≥ 15 ETDRS letters (based on one RCT, 412 patients), or the mean difference in BCVA (seven RCTs, 2,769 patients, mean difference [MD]: 0.51 [95% CI, –0.82 to 1.83]). Similarly, the meta-analysis revealed no statistically significant differences between ranibizumab and aflibercept with respect to the proportion of patients who demonstrated a gain of ≥ 15 ETDRS letters (two RCTs, 1,815 patients, OR: 1.01 [95% CI, 0.75 to 1.37]), loss of ≥ 15 ETDRS letters (two RCTs, 1,815 patients, OR: 1.11 [95% CI, 0.72 to 1.71]), and difference in BCVA (two RCTs, 1,907 patients, MD: 0.10 [95% CI, –5.43 to 5.64]). The results of the network meta-analysis (NMA) suggested that there are no statistically significant differences among the anti-VEGF drugs with respect to their effects on improving vision, as reflected by the proportion of patients who report an increase in visual acuity of at least 15 ETDRS letters. There were no statistically significant differences in terms of harms (i.e., adverse events, serious adverse events, withdrawals due to adverse events and mortality) and harms of special interest (i.e., arterial thromboembolism, bacterial endophthalmitis, and retinal detachment) for the comparison of ranibizumab with bevacizumab or aflibercept with ranibizumab.

In wet AMD patients, bevacizumab was substantially less costly than either ranibizumab or aflibercept. Under base-case pricing and assuming that ranibizumab and bevacizumab are dosed monthly while aflibercept is dosed every two months after three initial monthly doses, the cost of two years of ranibizumab therapy ($39,360 per patient) was $35,963 more than the cost of two years of bevacizumab therapy ($3,397 per patient), while two years of aflibercept ($19,364 per patient) cost $15,967 more than bevacizumab.

Diabetic Macular Edema

The results of a single study by Wells et al.[12] suggested that aflibercept is more effective than bevacizumab and ranibizumab at improving visual acuity in DME patients. However, clinical evidence from five RCTs of anti-VEGF drugs in patients with DME, identified in the systematic search, along with the economic analysis, suggests that bevacizumab, ranibizumab, and aflibercept are all effective treatments for patients with DME, and the cost of treatment with bevacizumab is substantially less than the cost of treatment with ranibizumab or aflibercept.

The available evidence suggested that ranibizumab was not significantly different to bevacizumab with respect to vision gain (one RCT, 412 patients, OR: 1.18 [95% CI, 0.77 to 1.79]), vision loss (one RCT, 412 patients, OR: 1.00 [95% CI, 0.20 to 5.01]), mean BCVA (meta-analysis of two RCTs, 512 patients, standardized mean difference [SMD]: 0.16 [95% CI, –0.02 to 0.33]). The Wells et al.[12] RCT with 414 participants demonstrated that a significantly greater proportion of DME patients treated with aflibercept experienced an improvement of at least 15 ETDRS letter compared with bevacizumab-treated patients (OR: 0.56 [95% CI, 0.37 to 0.84]). Similarly, the difference in BCVA improvement from baseline was greater following aflibercept treatment compared with bevacizumab treatment (MD: –3.5 [95% CI, –5.7 to –1.4]). However, none of the differences between treatments in the number of ETDRS letters gained exceeded the threshold for clinical meaningfulness of 15 ETDRS letters. None of the reported harms, including arterial thromboembolism, bacterial endophthalmitis, and retinal detachment, occurred at significantly different frequencies among the anti-VEGF drugs.

In DME patients, bevacizumab was substantially less costly than either ranibizumab or aflibercept. Under base-case pricing and when considering frequencies derived from the aflibercept product monograph and

the RESTORE study, the two-year cost of aflibercept ($20,887 per patient) was $18,898 more than the two-year cost of bevacizumab ($1,989 per patient), while the two-year cost of ranibizumab ($18,160 per patient) was $16,171 more than bevacizumab.

Retinal Vein Occlusion

Clinical evidence from nine RCTs of anti-VEGF drugs in patients with RVO identified in the systematic search, along with the economic analysis, suggests that bevacizumab, ranibizumab, and aflibercept have similar efficacy and safety in patients with RVO, but the cost of treatment with bevacizumab is substantially less than the cost of treatment with ranibizumab or aflibercept.

Meta-analysis of two RCTs revealed no statistically significant differences between ranibizumab and bevacizumab with respect to the proportion of patients who experienced a gain of ≥ 15 ETDRS letters (OR: 1.067 [95% CI, 0.425 to 2.675]) and the mean difference in BCVA (MD: –0.8 [95% CI, –6.16 to 4.56]). There were no data comparing aflibercept to bevacizumab or ranibizumab for vision gain, loss, or mean BCVA. However, a meta-analysis of two studies suggested that aflibercept is associated with a statistically significantly greater improvement in vision compared with placebo (OR: 7.00 [95% CI, 3.90 to 12.60], two RCTs with 358 patients). In a single RCT with 77 patients, there were no statistically significant differences between ranibizumab and bevacizumab with respect to the frequencies of serious adverse events (OR: 2.11 [95% CI, 0.18 to 24.37]) and increased intraocular pressure (OR: 0.33 [95% CI, 0.01 to 8.44]). There were no data comparing aflibercept to bevacizumab or ranibizumab for any harms of interest, but there were no notable differences in the frequency with which aflibercept was associated with mortality (one RCT, 189 patients), arterial and venous thromboembolic events (one RCT, 188 patients), bacterial endophthalmitis (one RCT, 188 patients), increased intraocular pressure (one RCT, 172 patients), and retinal detachment (one RCT, 188 patients) compared with placebo. In addition, a meta-analysis of two RCTs (365 patients) suggested that aflibercept may be associated with a statistically significantly lower incidence of serious adverse events (OR: 0.26 [95% CI, 0.10 to 0.69], 365 patients) and withdrawals due to adverse events (OR: 0.14 [95% CI, 0.04 to 0.57]) compared with placebo.

In RVO patients, bevacizumab was substantially less costly than either ranibizumab or aflibercept. Under base-case pricing, when all anti-VEGF drugs are assumed to have nine injections in the first year and three in the second, the two-year cost of ranibizumab ($19,920 per patient) is $18,201 more than that of bevacizumab ($1,719 per patient) while the two-year cost of aflibercept ($18,058 per patient) is $16,339 more than bevacizumab.

Choroidal Neovascularization Due to Pathologic Myopia

Clinical evidence from three RCTs of anti-VEGF drugs in patients with CNV due to PM, identified in the systematic search, along with the economic analysis, suggests that bevacizumab, ranibizumab, and aflibercept have similar efficacy and safety in patients with CNV due to PM, but the cost of treatment with bevacizumab is substantially less than the cost of treatment with ranibizumab or aflibercept.

In patients with CNV due to PM, there were no statistically significant differences in the effects of ranibizumab and bevacizumab on the proportions of patients who experienced a gain of ≥ 15 ETDRS letters (meta-analysis of two RCTs, 80 patients, SMD: –0.13 [95% CI, –0.57 to 0.31]) or vision gain (one RCT, 32 patients, OR: 0.77 [95% CI, 0.19 to 3.17]) when comparing ranibizumab with bevacizumab. Aflibercept was not compared directly with ranibizumab or bevacizumab in any of the included studies, but aflibercept was found to significantly improve visual acuity in CNV patients compared with sham injection (one RCT, 32 patients, OR: 0.77 [95% CI, 0.19 to 3.17]). There were no data comparing any of the anti-VEGF drugs for any harms of interest.

In patients with CNV due to PM, bevacizumab was substantially less costly than either ranibizumab or aflibercept. Under base-case pricing, when all anti-VEGF drugs are assumed to have four injections over the first year of treatment, the one-year cost of ranibizumab ($6,720 per patient) is $6,140 more than the one-year cost of bevacizumab ($580 per patient), while the one-year cost of aflibercept ($6,092 per patient) is $5,512 more than bevacizumab.

Recommendation 2
There is no specific recommendation pertaining to anti-VEGF therapy for subgroups of patients within any of the conditions of interest.

Of Note for Recommendation 2
The Committee noted that in Wells et al.,[12] aflibercept was associated with greater improvements in vision in a subgroup of patients with relatively poor visual acuity at baseline compared with patients treated with bevacizumab or ranibizumab (see above). Given the difference in cost between aflibercept and bevacizumab, it is highly unlikely that aflibercept will realize the magnitude of clinical benefit to make it the most cost-effective treatment option.

Reasons for Recommendation 2
There was insufficient clinical evidence regarding the potential for differential efficacy, safety, and cost-effectiveness of the anti-VEGF drugs for any subgroups of patients in any of the conditions of interest.

Recommendation 3
The frequency and dose of intravitreal injections of the anti-VEGFs should be determined by the treating ophthalmologist, but should not exceed that recommended for a particular retinal condition by the product monograph (if available) or that used in randomized clinical trials.

Of Note for Recommendation 3
The Committee noted that the absence of regulatory approval for intravitreal use of bevacizumab posed a challenge for any recommendation regarding bevacizumab when used to treat retinal conditions. However, the Committee noted that there is a substantial body of evidence available regarding the frequency and dose at which bevacizumab has been administered in clinical studies of patients with retinal conditions.

Reasons for Recommendation 3
The Committee considered an analysis of the number of injections of bevacizumab used in studies in which bevacizumab was demonstrated to have similar clinical effects in patients with retinal conditions (supplemental information to support this statement is presented in the updated draft Science Report), and noted that there is no statistically significant difference between the maximum number of bevacizumab versus ranibizumab injections in clinical studies. Therefore, the Committee considered that it is reasonable to conclude that the total number of injections of bevacizumab required to achieve a desired outcome will be similar to that for ranibizumab. This was confirmed by the clinical experts, who in addition stated that patients were usually treated in practice with the minimum number of injections required to achieve and maintain a desired response.

Summary of The Evidence

Clinical Evidence
The Committee considered the results of a systematic review and meta-analysis, which was conducted to assess the efficacy and safety of anti–vascular endothelial growth factor (anti-VEGF) drugs (ranibizumab, bevacizumab, and aflibercept) compared with each other or placebo, for the treatment of retinal conditions. The systematic review included 30 parallel randomized controlled trials (RCTs) assessing the safety and efficacy of anti-VEGF drugs, including 13 RCTs in patients with wet age-related macular edema (wet AMD), five RCTs in patients with diabetic macular edema (DME), nine RCTs in patients with

macular edema due to retinal vein occlusion (RVO), and three RCTs in patients with choroidal neovascularization (CNV) due to pathologic myopia (PM). The pre-specified efficacy outcomes of interest included the proportion of patients reporting a gain or loss of 15 letters or more in best corrected visual acuity (BCVA), mean difference in BCVA at follow-up, legal blindness, and vision-related function (as measured by the National Eye Institute Visual Function Questionnaire). Safety outcomes of interest included adverse events (AEs), serious AEs, withdrawals due to AEs, mortality, arterial and venous thromboembolic events, bacterial endophthalmitis, increased intraocular pressure, and retinal detachment. Trials were excluded if patients were not randomized, if the anti-VEGF drug was not administered intravitreally, or if patients received surgery (e.g., cataract surgery).

In patients with wet AMD, the results of the meta-analyses suggest that there are no statistically significant differences in the effects of ranibizumab versus bevacizumab and ranibizumab versus aflibercept on visual acuity, although pairwise comparisons were not possible for all efficacy outcomes of interest. In addition, there were no data available comparing aflibercept and bevacizumab in the wet AMD population. Nevertheless, indirect comparisons of the anti-VEGF drugs via network meta-analysis (NMA), which allowed for comparison of treatments for which direct comparative data were not available, were consistent with the direct pairwise meta-analyses in suggesting that there are no statistically significant differences among ranibizumab, bevacizumab, and aflibercept with respect to the effects of these treatments on improving visual acuity and preventing loss of vision. Therefore, these findings suggest that there is no evidence of any clinically meaningful difference in the improvement of vision in wet AMD patients in response to treatment with ranibizumab, bevacizumab, or aflibercept.

In patients with DME, the meta-analysis did not reveal any significant differences between ranibizumab and bevacizumab with respect to the effects of these treatments on visual acuity and other vision-related outcomes. A single trial comparing aflibercept, bevacizumab, and ranibizumab suggested that aflibercept might be more efficacious in improving vision compared with the other two anti-VEGF treatments. However, the statistically significantly greater improvement in the difference in BCVA attributable to aflibercept reflects an absolute relative improvement of 3.5 (95% CI, 1.4 to 5.7) ETDRS letters compared with bevacizumab and 2.1 (95% CI, 0.1 to 4.2) ETDRS letters compared with ranibizumab, and this was not deemed a clinically meaningful difference.

There were a limited number of studies evaluating the efficacy of anti-VEGF drugs in patients with RVO and CNV due to PM. No studies directly compared aflibercept with bevacizumab or ranibizumab in either of these conditions. However, meta-analysis of evidence from two relatively small RCTs suggested that there is no statistically significant difference between bevacizumab and ranibizumab in terms of visual acuity in patients with RVO. Similarly, the effects of ranibizumab and bevacizumab on vision improvement were similar in a single study of patients with CNV due to PM.

For the comparative harms of anti-VEGF drugs among patients with wet AMD, the results suggest that ranibizumab, aflibercept, and bevacizumab have a similar safety profile. The same results were observed for the DME and RVO indication and no statistically significant results were observed across the single trials that reported the harms outcomes of interest. For DME and RVO, a meta-analysis was not possible across all of the harms outcomes examined because there were too few studies reporting on these. For CNV due to PM, none of the included studies reported on harms, which is an area for future research. Thus, these results should be interpreted with caution, given the paucity of harms data, and the fact that the included trials were not sufficiently powered to evaluate harms outcomes.
In addition to the safety data included in the main review and analysis, to further assess the potential for bevacizumab to cause cardiovascular and ophthalmic harm, we carried out a supplemental review of all relevant published studies, irrespective of design, that reported on the safety of intravitreal use of bevacizumab. The most credible evidence identified in our review suggests that intravitreal injection of bevacizumab is not associated with a significantly increased risk of cardiovascular harm compared with ranibizumab treatment. Similarly, the weight of evidence available suggests that the risk of ophthalmic harm due to intravitreal injection is similar for bevacizumab and ranibizumab.

Economic Evidence

While several economic studies were identified in the published literature that assessed the comparative costs or cost-effectiveness of anti-VEGF therapies for retinal diseases, very few of them were fully applicable to the research question of this review. In addition, no studies were conducted in a Canadian context. As no overall conclusions could be inferred from the available economic literature, the results of the current clinical review were used to inform the type of economic analysis required. Due to the lack of clinically meaningful differences found among the treatments in the systematic review and meta-analyses, a series of cost-minimization analyses were conducted for each indication.

In the base case, Ontario Drug Benefit Formulary list prices (2015) were used for ranibizumab ($1,575 per vial) and aflibercept ($1,418 per vial) as well as an assumed cost of $40 per dose of bevacizumab ($600 per 100 mg vial, assuming 15 doses obtained per vial, as a conservative estimate). A $105 fee for each intravitreal injection was also included and a 5% discount was applied to costs accrued in the second year of the two-year time horizon. Injection frequencies were taken from product monograph recommendations, where available; otherwise, they were taken from large clinical trials.

A second set of analyses using drug costs and fees as reimbursed by the British Columbia Provincial Retinal Disease Treatment Program was also conducted; results were similar, although the magnitudes of both the costs and incremental costs were smaller due to lower per-dose costs for each anti-VEGF drug and higher administration fees per injection.

Based on the current body of evidence, the indication for which there could be a difference in clinical efficacy is DME, where aflibercept had a statistically significant but clinically marginal advantage when compared with ranibizumab or bevacizumab for improvement in visual acuity in patients with low baseline vision as reported in Wells et al.[12] To explore the likelihood of aflibercept being cost-effective compared with bevacizumab for the treatment of DME or a subpopulation of DME, a threshold analysis was conducted to determine the minimum number of additional quality-adjusted life-years (QALYs) that aflibercept would have to yield compared with bevacizumab in order to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY. Under base-case pricing and aflibercept monograph–recommended dosing, the use of aflibercept would need to result in a gain of at least 0.3780 QALYs per patient over the two-year time horizon when compared with bevacizumab, which is more than what was observed in economic evaluations identified in the economic literature review between any anti-VEGF therapies, and between any therapy and no treatment, for any retinal indication.

Table 2: Summary of Base-Case Anti-VEGF Total and Incremental Costs (Per Patient) by Indication

Drug	Doses Per 2 Years[a]	Two-Year Total Cost	Cost Relative to Bevacizumab
Wet AMD[b]			
Bevacizumab	10 to 24	$1,422 to $3,397	Reference
Aflibercept	13	$19,364	$15,967 to $17,941
Ranibizumab	10 to 24	$16,480 to $39,360	$15,058 to $35,963
DME[c]			
Bevacizumab	14	$1,989	Reference
Aflibercept	14	$20,887	$18,898
Ranibizumab	11	$18,160	$16,171
RVO[d]			
Bevacizumab	12	$1,719	Reference
Aflibercept	12	$18,058	$16,339
Ranibizumab	12	$19,920	$18,201
CNV due to PM — 1 year only[a,e]			
Bevacizumab	4	$580	Reference
Aflibercept	4	$6,092	$5,512
Ranibizumab	4	$6,720	$6,140

AMD = age-related macular degeneration; CNV = choroidal neovascularization; DME = diabetic macular edema; PM = pathologic myopia; RVO = retinal vein occlusion; VEGF = vascular endothelial growth factor.
Note: The number of doses included in these analyses reflects product monograph recommendations or average use in a large clinical trial and should not be interpreted as reimbursement limits or as clinical advice. Costs include drug costs and fees for intravitreal injection, and a 5% discount was applied in the second year.
[a] CNV due to PM analysis was 1 year only.
[b] Ranibizumab and bevacizumab dosed monthly or every 3 months after 3 initial monthly injections as per ranibizumab monograph. Aflibercept dosed every 2 months after 3 monthly injections as per monograph.
[c] Aflibercept and bevacizumab dosed every 2 months after 5 initial monthly injections as per aflibercept monograph. Ranibizumab dosing based on rounded RESTORE trial mean. An alternate analysis was conducted using the Wells et al.[12] median number of doses over one year (ranibizumab & bevacizumab = 10 doses, aflibercept = 9 doses) where bevacizumab cost $12,257 less than aflibercept and $15,350 less than ranibizumab.
[d] All anti-VEGF drugs assumed to be dosed based on the rounded mean number of doses used in the COPERNICUS aflibercept trial.
[e] All anti-VEGF drugs assumed to be dosed based on the rounded mean number of doses used in the RADIANCE ranibizumab trial.

Limitations of the Evidence

There were generally few studies available with which to assess the relative effects of the anti-VEGF drugs in RVO and CNV due to PM. In many cases, the clinical evidence available comprised only one RCT, and there was a correspondingly higher degree of uncertainty associated with conclusions related to these analyses.

The RCTs included in the review were powered primarily to examine the efficacy of the anti-VEGF drugs and were therefore underpowered to examine relatively infrequent safety outcomes. The safety data derived from the included studies were supplemented by a review of safety evidence from studies that were not RCTs, including uncontrolled, observational, and/or retrospective studies, but there remains uncertainty regarding the real-world safety of the anti-VEGF drugs. This limitation does not only apply to bevacizumab, but is shared across all anti-VEGF drugs as a group.

There was generally a lack of sufficient data to inform recommendations for subgroups of patients. For instance, the dosing and frequency of injections used for the anti-VEGF drugs were not analyzed systematically, because very few studies reported sufficient information to conduct the pre-planned subgroup analysis based on these variables.

There were few data available regarding the appropriateness or effectiveness of switching patients among the anti-VEGF drugs, and the Committee therefore relied on the opinions of clinical experts to inform their recommendations.

It is not clear whether the assumptions made regarding the costs of the anti-VEGF drugs used in the analyses reflect the actual costs incurred by provincial, territorial, and federal drug plans and programs, because details related to cost are often not available publicly. Therefore, the estimates of actual costs incurred by drug plans or programs may over- or underestimate the true costs.

There is insufficient information on how treatments are administered in clinical practice (dose and frequency) for all the indications of interest. As a result, economic analyses were based on recommended dosing and dosing observed in clinical studies. Should more real-world information become available, the results of the analysis might need to be revised.

Discussion Points

Efficacy and Cost-Effectiveness

- During discussion of the economic analyses, the Committee noted that it did not consider it appropriate to view differences in costs among the anti-VEGF drugs in terms of potential savings to public payers, but rather as opportunity costs that reflect potentially uncaptured (lost) benefits.
- The Committee discussed the uncertainty regarding the actual costs of anti-VEGF treatment that is the result of details of negotiated prices not always made available publicly. They discussed how this uncertainty made it unclear how much lower the cost of reimbursing anti-VEGF treatment might be where bevacizumab is to be used instead of ranibizumab. Nevertheless, the Committee was very clear in its acceptance that the economic analyses demonstrated consistently and unequivocally that bevacizumab was the least costly option among the anti-VEGF drugs for each of the four retinal conditions.
- The Committee did not consider the potential savings due to the fractioning of single-use vials of ranibizumab or aflibercept to be relevant, but noted that individual public drug plans could determine for themselves whether this was something that would be appropriate and acceptable to them.
- The Committee stated that individual public plans should determine how best to implement the recommendations, and emphasized the need not to endorse one particular model of reimbursement.

Safety

- The Committee discussed the safety of the anti-VEGF drugs, and intravitreal bevacizumab, at length and in detail, including discussing the findings related to comparative safety presented in the draft Science Report, concerns raised by patients in their feedback to CADTH, issues brought forth by the manufacturers and other stakeholders in their feedback to CADTH, and additional evidence related to safety prepared by the research team for inclusion in the final Science Report. The Committee reviewed and discussed the precautionary statement related to intravitreal use of bevacizumab made in the product monograph for Avastin and reviewed the evidence cited as the genesis for this statement.
- The Committee discussed the challenges that arise as a consequence of not having guidance from the regulator regarding how bevacizumab might be used safely and effectively for intravitreal treatment of retinal conditions, despite its extensive use by ophthalmologists throughout the world for many years. The Committee used the latter fact, together with practice-based insights from Canadian clinical experts consulted during its discussion, to arrive at the consensus that extensive experience derived from clinical studies that have included intravitreal bevacizumab, and from the use of this product in practice in Canada, means that it is highly likely that ophthalmologists will be able to appropriately handle and administer aliquoted bevacizumab in practice.
- The Committee considered in particular evidence related to the potential for bevacizumab to cause ophthalmic harm. They discussed the clinical evidence available from RCTs as well as uncontrolled studies. The Committee noted that the available evidence was consistent with the view that bevacizumab per se is not more likely to cause ophthalmic harm than other anti-VEGF drugs, but

noted that the potential for causing ophthalmic harm could be potentially higher if appropriate procedures for preparing, storing, distributing, and otherwise handling bevacizumab were not followed. The Committee noted that there are already well-established systems in several jurisdictions to ensure that preparing bevacizumab for intravitreal injection is carried out appropriately, including having routine microbiological testing procedures to avoid contamination. The Committee noted that the existence of these procedures would mitigate the potential for contamination of aliquoted bevacizumab to cause ophthalmic side effects.

- The Committee noted that there was insufficient evidence to conclude that certain patients with high risk of cardiovascular events should be excluded from bevacizumab treatment.
- Given the concern raised by stakeholders regarding the insufficient data related to the relative safety of intravitreal injection of bevacizumab, the Committee suggested that payers should put in place or continue safety monitoring systems to capture and assess the rates of ophthalmic and cardiovascular AEs, as well as any other types of serious adverse event related to all anti-VEGF drugs used to treat retinal conditions.

Patient Considerations

- The Committee discussed whether making bevacizumab available to patients in addition to ranibizumab and aflibercept would represent an expansion of choice or would limit choice, given the desire expressed in the patient group feedback for patients, along with their doctors, to be able to individualize treatment options. The Committee recognized that individual patients may respond differently to different anti-VEGF drugs. The Committee discussed the concern of patients that recommending bevacizumab for the treatment of retinal conditions would limit patient choice. The Committee considered this issue to be attributable to reports and a perception that some patients were being given no choice other than treatment with bevacizumab. The Committee determined that patient choice should include all available treatments for which there is evidence of a favourable clinical benefit-risk profile, and that this was not congruent with excluding a treatment, such as bevacizumab, that is as effective as, but less costly than, other treatments.
- The Committee recognized that the safety of anti-VEGF drugs was a major concern for patients, particularly the safety of intravitreal bevacizumab. The Committee noted that many of the safety concerns raised by patients were not supported by high-quality evidence, and that several concerns were not limited to bevacizumab but applied to the anti-VEGF drugs as a class. Nevertheless, based on the concerns expressed in the patient input, the Committee considered it necessary to review additional evidence related to the relative safety of bevacizumab and discussed this at length (see above). While the Committee concluded that there is no credible, consistent evidence to suggest that properly prepared and handled aliquoted bevacizumab presents a greater risk of harm than other anti-VEGF drugs, it did include provisions in the recommendations to ensure that public payers that choose to reimburse bevacizumab for the treatment of retinal conditions have in place appropriate preparation, distribution, and storage procedures, as well as a system to monitor the safety of all anti-VEGF drugs, including bevacizumab.
- The Committee discussed the lack of detail about the sources of much of the information submitted in the patient group feedback received by CADTH; e.g., the number of patients who participated in focus groups or who responded to a survey or the names of any of the printed materials used by the patient groups. This lack of detail is one reason the Committee found it hard to determine how representative of patients with retinal conditions were the views and experiences reported in the groups' joint submission. This was especially true when one patient's or caregiver's experience was highlighted.
- The Committee noted that the relative costs of the anti-VEGF drugs and the cost of reimbursing such treatments were not raised as issues of major concern in the patient input received by CADTH. The Committee noted that where cost was mentioned in the patient input, it was in reference to the high cost of ranibizumab treatments that were not covered by a public plan or to the savings public plans would experience as a result of the expected less-frequent dosing required by aflibercept.
- If public drug plans follow the Committee's recommendation to reimburse bevacizumab for the treatment of retinal conditions, more patients will have access to a treatment that is readily available, effective, as safe as other anti-VEGF treatments, and substantially more affordable. The net benefits achieved would include (a) a greater number of patients with retinal conditions being treated effectively

than would be the case were bevacizumab not made available, and (b) the ability to invest any cost savings into improving management of retinal conditions and/or increase investment into other areas of public health care–related spending.

Other Discussion Points

- The Committee noted that there was no evidence that switching patients from one anti-VEGF to a different anti-VEGF would be clinically effective. The clinical experts provided anecdotal evidence that such switching of patients occurs in clinical practice and can improve outcomes in patients who do not respond to initial anti-VEGF therapy or experience a diminution in response to anti-VEGF therapy. Although they were not able to provide any data to support their observations, the clinical experts believe that switching patients from one anti-VEGF to a different anti-VEGF might be effective if refractoriness develops to the initial therapy. The clinical experts noted that this refractoriness did not apply to any one of the anti-VEGF drugs in particular.
- The Committee noted, based on the opinions and experience of clinical experts consulted during its deliberations, as well as on the concerns expressed by patients regarding the need for individualized treatment, that treatment with anti-VEGF drugs should be offered to individual patients based on their tolerability profile and response to treatment. Therefore, the Committee determined that it would be appropriate to leave the primary determination of injection frequency and number (duration of treatment) to the discretion of the treating ophthalmologist. Nevertheless, the Committee considered it reasonable and prudent, particularly from a safety perspective, to recommend that the maximum frequency of injections normally used in practice (based on guidance in the product monograph and randomized clinical trial data) not be exceeded. While the Committee included guidance in the recommendations as to the frequencies at which anti-VEGF drugs should be administered, they reached a consensus that any limits to the number of injections of anti-VEGF drugs that would be reimbursed should be determined by the public payers. In addition, the Committee noted that it is the purview of reimbursement agencies to monitor the frequencies with which anti-VEGF drugs are used in practice, relative to any reimbursement policy limitations on use.
- The Committee considered that the lack of clinical data for the RVO population relative to other retinal conditions was a concern, mainly due to the small number of patients included in the available clinical studies. The Committee noted that additional studies in this condition in particular are needed to reduce uncertainty regarding the relative effects of anti-VEGF drugs in this population.
- The Committee discussed at length the Wells et al. study[12] of DME patients (see above), and in particular the clinical relevance of the statistically significant differences in the effects of aflibercept versus the other anti-VEGF drugs. They sought to balance the evidence in favour of aflibercept with major limitations associated with this evidence, including the fact that the results of this trial have not been replicated independently and the absence of a precise estimate of the cost-effectiveness of aflibercept versus bevacizumab and ranibizumab in this population. Therefore, the Committee considered that recommending aflibercept over ranibizumab in DME patients could be justified by the available evidence, but that differences among the treatments were likely insufficient to justify the substantially higher cost of aflibercept.
- The Committee discussed the fact that bevacizumab is not approved for intravitreal injection in Canada. They reviewed and were satisfied with the eligibility of bevacizumab or any other unapproved treatment for inclusion in a CADTH therapeutic review and recommendations in light of the updated CADTH Therapeutic Review Framework. The Committee noted that other CADTH reviews have included unapproved treatments as comparators, if appropriate, and discussed the fact that inclusion of bevacizumab as a comparator in the Science Report reflected both the reality of the widespread use of the product in practice as well as a substantial body of clinical evidence regarding its use for treating retinal conditions. It also noted that the issue of lack of approval of bevacizumab for retinal conditions reflected unusually incongruent motivations on the part of public payers and the manufacturer of bevacizumab and ranibizumab, as evidenced by the fact that many of the clinical studies considered by the Committee in which bevacizumab was studied were funded independently of the manufacturer, by bodies such as the National Institutes of Health.

Research Gaps

The Committee proposed that the following issues be addressed through research as a high priority in future to facilitate comparisons of the anti-VEGFs for treating retinal conditions.

The most important gap in the available evidence relates to safety comparisons. Safety outcomes are, in general, reported less frequently than efficacy outcomes in the studies included in the CADTH Science Report, rendering conclusions regarding the relative rates of individual AEs among patients treated with different anti-VEGF drugs uncertain. The studies that were included in the CADTH Science Report, by the nature of their design (RCTs), did not have sufficient statistical power to detect significant differences in the frequencies of relatively rare potential harms such as death and thromboembolic events. To supplement the safety data derived from RCTs included in the draft CADTH Science Report, the clinical research team conducted a review of clinical evidence regarding the relative safety of intravitreal use of bevacizumab. Nevertheless, larger randomized trials that follow patients with retinal conditions for several years are needed to properly assess the relative safety of the anti-VEGF drugs.

A second gap in the available evidence is the relatively smaller number of studies, and a correspondingly smaller number of patients studied, to allow for active comparisons of the three anti-VEGF drugs for conditions such as RVO and CNV due to PM. RCTs designed to examine directly the comparative efficacy of bevacizumab, ranibizumab, and aflibercept, such as the Wells et al.[12] study in DME patients, are needed for retinal conditions such as RVO and CNV due to PM.

The third gap in the available evidence is related to the safety of procedures used to prepare bevacizumab aliquots, as well as the distribution and storage of aliquoted bevacizumab. While there appear to be established, well-controlled procedures in place in those jurisdictions within which bevacizumab is used for intravitreal administration, the potential for increased risk of ophthalmic harms associated with this procedure suggests that active safety monitoring is essential.

Committee Members

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, Dr. Harindra Wijeysundera.

Two external clinical experts who are practising ophthalmologists participated in the discussion, but did not vote on the recommendations.

Regrets

None.

Conflicts of Interest

None.

References

1. Drug product database online query [Internet]. Ottawa: Health Canada; c2009 - [cited 2015 Dec 10]. Available from: http://webprod5.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp
2. [Pr]Avastin® (bevacizumab for injection) 100 and 400 mg vials (25 mg/mL solution for injection) [product monograph]. Mississauga (ON): Hoffmann-La Roche Limited; 2015 Sep 28.
3. Anti–vascular endothelial growth factor (VEGF) agents for the treatment of retinal conditions. Ottawa: CADTH; 2016 Apr. (CADTH therapeutic review; vol.3, no.2b).
4. Eye program expanded in British Columbia [Internet]. Victoria (BC): British Columbia Ministry of Health; 2013 Nov 16. [cited 2015 Dec 10]. Available from: http://www2.news.gov.bc.ca/news_releases_2013-2017/2013HLTH0116-001715.htm
5. Lucentis to be funded by N.S. [Internet]. [Toronto]: CBC News; 2010 Oct 20. [cited 2015 Oct 15]. Available from: http://www.cbc.ca/news/canada/nova-scotia/lucentis-to-be-funded-by-n-s-1.929833
6. Avastin® (bevacizumab) intravitreal injection project. Information for ophthalmologists. Fredericton (NB): Government of New Brunswick; 2014 Oct.
7. Eye Care Centre of Excellence. Age-related macular degeneration [Internet]. Winnipeg (MB): Misericordia Health Centre; c2003-2015. [cited 2015 Dec 10]. Available from: http://www.misericordia.mb.ca/Programs/ecDegeneration.html
8. Alberta approves use of cheaper alternative drug for eye treatment [Internet]. [Toronto]: CBC News; 2015 Sep 30. [cited 2015 Oct 15]. Available from: http://www.cbc.ca/news/canada/edmonton/alberta-approves-use-of-cheaper-alternative-drug-for-eye-treatment-1.3251388
9. Retina Anti-VEGF Program for Intraocular Disease (RAPID) program document. Edmonton (AB): Alberta Health; 2015 Sep.
10. Government introduces new eye care program, saving millions for patients and taxpayers [Internet]. Edmonton: Alberta Government; 2015 Sep 30. [cited 2015 Oct 8]. Available from: http://alberta.ca/release.cfm?xID=386013C86CA06-B059-36C8-B0F92434C5C65946
11. Anderson TJ, Gregoire J, Hegele RA, Couture P, Mancini GB, McPherson R, et al. 2012 update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. Can J Cardiol. 2013 Feb;29(2):151-67.
12. Diabetic Retinopathy Clinical Research Network, Wells JA, Glassman AR, Ayala AR, Jampol LM, Aiello LP, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med [Internet]. 2015 Mar 26 [cited 2015 Sep 24];372(13):1193-203. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4422053
13. FDA Cellular, Tissue, and Gene Therapies Advisory Committee. CTGTAC Meeting #52. Cellular and gene therapies for retinal disorders [Internet]. Rockville (MD): U.S. Food and Drug Administration; 2011 Jun 29. [cited 2015 Oct 15]. Available from: http://www.fda.gov/downloads/advisor.../ucm259087.pdf
14. Ikuno Y, Ohno-Matsui K, Wong TY, Korobelnik JF, Vitti R, Li T, et al. Intravitreal aflibercept injection in patients with myopic choroidal neovascularization: the MYRROR study. Ophthalmology. 2015 Jun;122(6):1220-7.