| December 2015 | Anti-vascular endothelial growth factor (VEGF) drugs for the treatment of retinal conditions [DRAFT] |
## ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMD</td>
<td>age-related macular degeneration</td>
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<tr>
<td>Anti-VEGF</td>
<td>anti-vascular endothelial growth factor</td>
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<td>BCVA</td>
<td>best corrected visual acuity</td>
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<td>CDEC</td>
<td>CADTH Canadian Drug Expert Committee</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>CNV</td>
<td>choroidal neovascularization</td>
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<tr>
<td>DME</td>
<td>diabetic macular edema</td>
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<tr>
<td>ETDRS</td>
<td>Early Treatment Diabetic Retinopathy Study</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>OR</td>
<td>odds ratio</td>
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<td>PM</td>
<td>pathologic myopia</td>
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<td>RCT</td>
<td>randomized controlled trial</td>
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<td>RVO</td>
<td>retinal vein occlusion</td>
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<tr>
<td>VA</td>
<td>visual acuity</td>
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<tr>
<td>Wet AMD</td>
<td>wet age-related macular degeneration</td>
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</table>
BACKGROUND

Retinal conditions have become an important health policy issue due to the large number of people affected by retinal conditions and the widespread adoption of effective but costly anti-vascular endothelial growth factor (anti-VEGF) drugs to treat these conditions. Anti-VEGFs are injected into the eye where they inhibit the abnormal angiogenesis 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, is compounded for intraocular injection and used in clinical practice to treat retinal conditions, although it is approved by Health Canada only to treat certain types of metastatic cancer. Due to their effectiveness and favorable 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**

<table>
<thead>
<tr>
<th>Product (Manufacturer/Distributor)</th>
<th>Generic Name</th>
<th>Health Canada-Approved Retinal Indications&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eylea (Regeneron/Bayer)</td>
<td>aflibercept</td>
<td>Neovascular (wet) AMD</td>
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<td></td>
<td></td>
<td>Visual impairment due to ME secondary to CRVO</td>
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<td></td>
<td></td>
<td>DME</td>
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<tr>
<td>Lucentis (Genentech/Novartis)</td>
<td>ranibizumab</td>
<td>Neovascular (wet) AMD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Visual impairment due to DME</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Visual impairment due to ME secondary to RVO</td>
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<tr>
<td></td>
<td></td>
<td>Visual impairment due to CNV secondary to PM</td>
</tr>
<tr>
<td>Avastin (Genentech/Hoffmann-La Roche)</td>
<td>bevacizumab</td>
<td>NA&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

AMD, age-related macular degeneration; 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.

<sup>a</sup> Source of information: Health Canada Drug Product Database.

<sup>b</sup> CADTH is not aware of regulatory filing to Health Canada for bevacizumab use in wet AMD, DME, BRVO, CRVO, or CNV due to PM.

Preamble to the Recommendations

There is considerable interest from jurisdictions who 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 better understanding the relative costs of these agents. The Committee appreciated that the cost of reimbursing the costliest of the anti-VEGFs 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 these needs, 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 several patient groups and other stakeholders (including manufacturers and individual clinicians) 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 are familiar with 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 AMD, DME, RVO, and CNV due to PM. While the absence of regulatory approval of a medicinal product is frequently associated with a dearth of clinical evidence regarding the effects of the product in populations that are not covered by the regulatory approval, this is not the case for bevacizumab, for which there is a relatively substantive evidence base available across several different retinal conditions. The Committee noted that all of the clinical studies that have assessed the efficacy and/or safety of bevacizumab in patients with retinal conditions were funded by independent research organizations and governmental support. In the absence of information from the manufacturer to the contrary, the Committee noted that the inclusion of bevacizumab in the scope of the therapeutic review was appropriate based on: the amount of clinical evidence available with which 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; and the desire of public payers to include bevacizumab as a viable treatment option in an objective assessment of the relative effects of anti-VEGF drugs for treating retinal conditions.

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 management of these conditions, particularly the appropriate preparation and handling of these agents.

**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 their 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. Considering all these views, CDEC identified a preferred treatment option for initial therapy based on a systematic review of clinical trials and an analysis of treatment costs.

**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. Ranibizumab or aflibercept can be used as alternative treatment options in patients who do not respond to bevacizumab treatment or are intolerant of bevacizumab.

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 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 studied, the Committee noted that patients could be assessed for treatment failure after at least 6 months of initial therapy. Treatment failure could be defined as not achieving an improvement in BCVA of at least 15 ETDRS letters compared to the baseline (pre-treatment) BCVA.

2. 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.

3. For all conditions, the Committee noted that patients could be considered as intolerant of initial therapy if any of the following adverse events occurred following the initiation of treatment:
   • Thromboembolism
   • An increase in intraocular pressure to ≥21 mmHg
   • Bacterial endophthalmitis
   • Retinal detachment

4. For patients with DME who cannot receive bevacizumab due to intolerance issues, the Committee recommends that aflibercept be considered in preference to ranibizumab.

5. The Committee noted that there is no information available in regards 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 warning against the intravitreal use of bevacizumab that reads “Eye Disorders: 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.”

6. The Committee noted the concerns expressed by stakeholders regarding the safety of bevacizumab to treat retinal conditions, but concluded 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 compared to ranibizumab or aflibercept.
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. Ranibizumab or aflibercept can be used as alternative treatment options in patients who do not respond to bevacizumab treatment or are intolerant of bevacizumab.

Of Note for Recommendation 1
1. For all conditions, the Committee noted that, based on the design of clinical trials and expert opinion, patients could be assessed for treatment failure after at least 6 months of initial therapy. Treatment failure could be defined as not achieving an improvement in BCVA of at least 15 ETDRS letters compared to the baseline (pre-treatment) BCVA. This is based on the threshold of 15 ETDRS letter 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.”
2. For patients with DME, the Committee recommends that aflibercept be considered in preference to ranibizumab when considering an alternative to bevacizumab treatment. This recommendation was based on the results of a study by Wells et al. that suggested that aflibercept may be more effective than bevacizumab and ranibizumab at improving visual acuity in DME patients. Specifically, Wells and colleagues reported that treatment of DME patients with aflibercept (13.3 letter improvement) improved visual acuity to a statistically significantly greater degree compared to treatment with ranibizumab (11.2 letter improvement) or bevacizumab (9.7 letter improvement; P<0.05 for both comparisons). Despite this statistically significant difference between aflibercept and the other treatments, 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. 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 vs. bevacizumab and ranibizumab, respectively. However, this difference is still smaller than the minimum clinically important difference of 10 to 15 letters. Therefore, it is not clear that the difference in the improvement in visual acuity between aflibercept and the other treatments is clinically meaningful. This 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. Nevertheless, the results of the Wells study suggest that when selecting between the remaining anti-VEGF drugs, aflibercept would be preferred over ranibizumab as it is associated with a small but significantly greater improvement in visual acuity, based on a comparison of aflibercept to 0.3 mg ranibizumab rather than the dose of 0.5 mg that is used in Canada.
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. 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 by discussing the molecular mechanisms that might cause ranibizumab 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 AMD**

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, OR: 1.13 [95% 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, 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, −0.53 to 0.64]). The results of the 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 assumes 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.

**DME**

The results of a single study by Wells et al. suggested that aflibercept is more effective than bevacizumab and ranibizumab at improving visual acuity in DME patients. However, clinical evidence from 5 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,
SMD: 0.16 [95% CI, –0.02 to 0.33]). The Wells et al.⁴ 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 to 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]). 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.

RVO
Clinical evidence from 9 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 ($1,989 per patient) while the two-year cost of aflibercept ($18,058 per patient) is $16,339 more than bevacizumab.

CNV due to PM
Clinical evidence from 3 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 to bevacizumab. Aflibercept was not compared directly to ranibizumab or bevacizumab in any of the included studies, but aflibercept was found to significantly improve visual acuity in CNV patients compared to 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., aflibercept was associated with greater improvements in vision in a subgroup of patients with relatively poor visual acuity at baseline compared to patients treated with bevacizumab or ranibizumab (see above). Given the difference in cost between aflibercept and bevacizumab, it is highly unlikely for aflibercept to 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 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, 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

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Note that supplemental information to support this statement is presented in the updated draft Science Report.
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 effectiveness and safety of anti-vascular endothelial growth factor (anti-VEGF) drugs (ranibizumab, bevacizumab, and aflibercept) compared to 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), 5 RCTs in patients with diabetic macular edema, 9 RCTs in patients with macular edema due to retinal vein occlusion, and 3 RCTs in patients with choroidal neovascularization due to pathologic myopia. 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 vs. bevacizumab and ranibizumab vs. 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 to 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 to bevacizumab and 2.1 (95% CI, 0.1 to 4.2) ETDRS letters compared to 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 to 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.

**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). 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 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 the Protocol T trial. To explore the likelihood of aflibercept being cost-effective compared to 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 (WTP) 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 to 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*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Doses per 2 years(^a)</th>
<th>Two-year total cost</th>
<th>Cost relative to bevacizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Wet AMD(^a)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>10 to 24</td>
<td>$1,422 to $3,397</td>
<td>Reference</td>
</tr>
<tr>
<td>Aflibercept</td>
<td>13</td>
<td>$19,364</td>
<td>$15,967 to $17,941</td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>10 to 24</td>
<td>$16,480 to $39,360</td>
<td>$15,058 to $35,963</td>
</tr>
<tr>
<td><strong>DME(^b)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>14</td>
<td>$1,989</td>
<td>Reference</td>
</tr>
<tr>
<td>Aflibercept</td>
<td>14</td>
<td>$20,887</td>
<td>$18,898</td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>11</td>
<td>$18,160</td>
<td>$16,171</td>
</tr>
<tr>
<td><strong>RVO(^c)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>12</td>
<td>$1,719</td>
<td>Reference</td>
</tr>
<tr>
<td>Aflibercept</td>
<td>12</td>
<td>$18,058</td>
<td>$16,339</td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>12</td>
<td>$19,920</td>
<td>$18,201</td>
</tr>
<tr>
<td><strong>CNV due to PM – one year only(^d,e)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>4</td>
<td>$580</td>
<td>Reference</td>
</tr>
<tr>
<td>Aflibercept</td>
<td>4</td>
<td>$6,092</td>
<td>$5,512</td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>4</td>
<td>$6,720</td>
<td>$6,140</td>
</tr>
</tbody>
</table>

*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.

\(^a\) Ranibizumab and bevacizumab dosed monthly or every three months after three initial monthly injections as per ranibizumab monograph. Aflibercept dosed every two months after three initial monthly injections as per monograph.

\(^b\) Aflibercept and bevacizumab dosed every two months after five initial monthly injections as per aflibercept monograph. Ranibizumab dosing based on rounded RESTORE trial mean. An alternate analysis was conducted using the Protocol-T trial 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.

\(^c\) All anti-VEGF drugs assumed to be dosed based on the rounded mean number of doses used in the COPERNICUS aflibercept trial.

\(^d\) All anti-VEGF drugs assumed to be dosed based on the rounded mean number of doses used in the RADIANCE ranibizumab trial.

\(^e\) CNV due to PM analysis was one year only.

**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 they 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 to be used instead of ranibizumab. Nevertheless, the Committee was very clear in their 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 discussed 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, arguments related to safety 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 (warning) 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 their discussion, to arrive at the consensus that extensive experience derived from clinical studies that have included intravitreal bevacizumab, and more importantly 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 compounding 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 adverse events, 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 favorable 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 agents 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 compounded and handled aliquoted bevacizumab presents a significantly greater risk of harm than other anti-VEGF drugs, it did include provisions in the recommendations to ensure that public payers who 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, 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, about the sources of much of the information submitted in the patient group feedback received by CADTH. 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.
- Although, as noted above, the Committee did not use cost as the primary driver for their recommendations, 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.
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 their deliberations, as well as on the concerns expressed by patients regarding the need for individualized treatment, that treatment with anti-VEGF drugs should be appropriate 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, particular 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 agents 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\(^4\) 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 in preference to 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 independent of the manufacturer, by bodies such as the NIH.
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-VEGs 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 adverse events 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 Protocol T 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 suggest that active safety monitoring is essential.

Committee Members
Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), 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. James Silvius, Dr. Adil Virani, Dr. Harindra Wijeysundera.

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

Regrets
None.

Conflicts of Interest
None.
About this document
The Therapeutic Review Recommendations or Advice are formulated following a comprehensive evidence-based review of the medication’s efficacy or effectiveness and safety and an assessment of its cost-effectiveness. Therapeutic Review clinical and economic reports are based on published information available up to the time that CDEC made its recommendation. Input from stakeholders, such as drug manufacturers, patient groups, and health-related professional associations or organizations, is considered in the preparation of this recommendation document.

CDEC is a Committee of the Canadian Agency for Drugs and Technologies in Health (CADTH). It makes recommendations and provides advice to Canadian jurisdictions to use in making informed decisions. It is made up of experts in drug evaluation and drug therapy, and public members.

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The Therapeutic Review Framework describes the Therapeutic Review process in detail. 

6
REFERENCES


2. 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.


