

## IN BRIEF A Therapeutic Review

# Anti–Vascular Endothelial Growth Factor Drugs for Retinal Conditions

## Key Messages

- Bevacizumab is the preferred, initial anti-VEGF treatment for patients with wAMD, DME, RVO, or CNV due to PM. This is an evidence-based expanded use of bevacizumab, not approved by Health Canada.
- Aflibercept and ranibizumab are appropriate second-line choices for patients who do not respond to, or are intolerant of, bevacizumab.
- Doses of bevacizumab intended for intravitreal injection should be prepared, stored, and handled by health care professionals with the appropriate expertise.

CNV = choroidal neovascularization; DME = diabetic macular edema; PM = pathologic myopia; RVO = retinal vein occlusion; VEGF = vascular endothelial growth factor; wAMD = wet age-related macular degeneration.

## Context

The retina is a light-sensitive layer of tissue at the back of the eye. It converts images into signals that are sent to the brain. Damage to the retina can cause permanent vision loss.

Several disorders of the retina involve abnormal angiogenesis, or blood vessel formation. The most common is the neovascular type (or “wet” type) of age-related macular degeneration (AMD). The macula is near the centre of the retina and damage to it results in central vision loss. AMD affects about 2 million Canadians and is the most common cause of blindness in industrialized countries.

Other retinal conditions involving abnormal angiogenesis include diabetic macular edema (DME), macular edema due to retinal vein occlusion (RVO), and choroidal neovascularization (CNV) secondary to pathologic myopia (PM).

## Drugs

Vascular endothelial growth factor (VEGF) is a protein that stimulates production of new blood vessels. A high intraocular level of VEGF appears to be a factor in these retinal conditions, so anti-VEGF drugs can be an effective treatment.

Three anti-VEGF drugs are routinely used in Canada for treatment of retinal conditions: aflibercept (Eylea), bevacizumab (Avastin), and ranibizumab (Lucentis). The drugs are given by intravitreal injection (injection into the eye).

## Issue

Although it is approved for intravenous use in treating certain types of cancer in Canada, the manufacturer of bevacizumab has not made a submission to Health Canada requesting approval to market bevacizumab for the treatment of retinal conditions. However, bevacizumab is widely used in clinical practice for the treatment of retinal conditions in Canada and throughout the world, and there is a substantial amount of evidence to support its intravitreal use for treating these conditions. To be complete and useful, CADTH’s review of anti-VEGF drugs needed to include this evidence-based expanded use (or “off-label” use) of bevacizumab.

## Methods

A systematic review of the clinical evidence and an economic analysis were conducted. Input from several patient groups, clinicians, and other stakeholders was considered and incorporated into the review. Three ophthalmologists with expertise in retinal diseases acted as advisors during the review. An expert committee made recommendations on the reimbursement of anti-VEGF drugs by public payers in Canada, but these recommendations are non-binding.

## Results

The review included 30 randomized studies: 13 for wet AMD (wAMD), 5 for DME, 9 for RVO, and 3 for CNV due to PM. Most studies measured vision gain or loss in terms of letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale. A gain of 15 or more ETDRS letters is considered to be clinically meaningful.

**Efficacy:** For wAMD, RVO, and CNV due to PM, there were no statistically significant differences in visual acuity for any comparisons of the three drugs. For DME, one study showed a greater improvement in visual acuity with aflibercept; this was a 2.1-letter gain compared with ranibizumab and a 3.6-letter gain compared with bevacizumab, so it was statistically significant but not clinically meaningful.

**Safety:** The bevacizumab product monograph does carry a warning against intravitreal use, so a supplemental safety review was conducted that looked at key safety concerns such as blood clots and eye infections. This review included observational and real-world studies, to complement the randomized trials included in the main review. (See Appendix 23 of the Science Report). Evidence from 24 studies suggests that, when prepared, stored, and handled

properly, intravitreal use of bevacizumab is unlikely to cause more harm than other anti-VEGF drugs. It is important to note that bevacizumab is not packaged for intravitreal injection; the vial contains a larger volume than would be used for a single intravitreal injection, and Health Canada labelling stipulates a single use per vial. There is no evidence to suggest that bevacizumab itself can cause more harm than the other drugs, but improper handling or storage can increase the risk of microbial contamination and therefore increase the risk of harm. Doses should be prepared, stored, and handled by health care professionals with expertise in sterile compounding procedures. Several Canadian jurisdictions already have systems in place to ensure that proper procedures are followed. In addition, there are existing systems to actively monitor the safety of intravitreal bevacizumab use.

**Cost:** As there was no difference in the clinical effects of the three drugs, the economic analysis compared the relative costs of each product. Costs of therapy depend on the condition being treated and the duration of therapy, but in general, total treatment costs are \$6,092 to \$20,887 for aflibercept; \$580 to \$3,397 for bevacizumab; and \$6,720 to \$39,360 for ranibizumab.

In summary, a review of the evidence suggests that all three anti-VEGF drugs have similar clinical effects, but the cost of bevacizumab is about one-tenth that of the other drugs. The committee viewed this as an important opportunity cost; in other words, funding the more expensive drugs without gaining additional health benefits for patients may mean there are missed opportunities to fund other health care services. Based on these findings, the committee recommended that bevacizumab be the preferred initial anti-VEGF therapy for each of the retinal conditions reviewed. Aflibercept and ranibizumab are appropriate second-line choices for patients who do not respond to, or are intolerant of, bevacizumab. The committee's suggestions for defining treatment failure or treatment intolerance are available in the full Recommendations report.

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