

Including off-label drug indications in HTA jeopardizes patient health and discourages innovation



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SUMMARY

Introduction

The innovative development of anti-vascular endothelial growth factor (anti-VEGF) drugs is examined, together with the impact that these drugs have had on patient health. The health technology assessment (HTA) review of anti-VEGF drugs that took place in Canada in 2015 is considered from both innovation and patient health perspectives.

Anti-VEGF Drugs

Anti-VEGF drugs are used to treat retinal conditions such as the wet form of age-related macular degeneration (wAMD) which is responsible for 80-90% of the vision loss associated with AMD. Avastin, Lucentis and Eylea are anti-VEGF drugs. Avastin was developed as a systemic treatment for cancer. It was also considered for retinal conditions, but evidence showed that systemic exposure to Avastin increases the risk of thromboembolic events. Using knowledge gained from Avastin, decades of innovative research led to the development of Lucentis and Eylea, which are administered by intravitreal injection into the eye. Lucentis and Eylea are approved by Health Canada for retinal conditions, whereas Avastin is not. Avastin has a serious warning in its product monograph (or 'label') that it is 'not formulated and has not been authorized for intravitreal use'. Nevertheless, Avastin is prescribed off-label by clinicians to treat retinal conditions because it is less expensive than the other drugs.

Issue: including unapproved or off-label indications in the HTA

In early 2015, provincial governments requested that the Canadian Agency for Drugs and Technologies in Health (CADTH) compare Lucentis, Eylea and Avastin for retinal conditions, which meant that the HTA process that guides public drug plan coverage decisions would include a drug that did not have Health Canada safety approval for the indication being reviewed. CADTH also excluded some studies from its review that suggested greater safety risks with Avastin compared with Lucentis, predisposing the HTA review to the conclude that Avastin and Lucentis have similar efficacy and safety profiles. This led to a recommendation that Avastin can be used as the preferred initial anti-VEGF therapy over Lucentis or Eylea.

Conclusion

CADTH has changed the rules in the HTA process to accommodate provincial government cost-containment objectives, despite Health Canada's warnings of increased morbidity and mortality risks. Including off-label drug indications in HTA jeopardizes patient health and discourages innovation.

Introduction

Medications that cure or alleviate many of the diseases that were the scourge of humanity for millennia were developed during the twentieth century.¹ Disorders that remain without treatment, as well as those whose incidence has increased as human life has been extended, require significant scientific innovation that frequently demands major resources over an extensive period of time.

In this article, the innovative development of anti-vascular endothelial growth factor (anti-VEGF) drugs is examined, together with the impact that these drugs have had on patient health. The health technology assessment (HTA) review of anti-VEGF drugs that took place in Canada in 2015 is then considered from both product innovation and patient health perspectives.

Disease Process and Treatments

Angiogenesis is a normal physiological process in which new blood vessels form from pre-existing vessels that is vital for the growth and development of the human body and for wound healing. The fact that some tumours are highly vascularized, which was known 200 years ago,² led to the suggestion that newly formed blood vessels have an important pathogenic role in cancer development. Nevertheless, it was not until the time of the Second World War

that angiogenesis was recognized as being a fundamental step in the transition of tumours from a benign to malignant state.

Another 30 years were to elapse before the innovative idea of developing angiogenesis inhibitors to treat cancer was proposed,³ which resulted in significant activity in the field. However, a further two decades passed before the fundamental protein in tumour-induced angiogenesis (VEGF) was identified in 1989.⁴

After a murine monoclonal antibody targeting human VEGF was shown to inhibit tumour growth *in vivo* in 1993, the humanized variant bevacizumab (Avastin) was developed and clinical trials started in 1997. Avastin was approved for the treatment of metastatic colorectal cancer by the US Food and Drug Administration (FDA) in February 2004 and Health Canada in September 2005.

In 1948, an unknown 'Factor X' produced by the retina was suggested as being responsible for the retinal neovascularization that occurs in diabetic retinopathy.⁵ After much research, Factor X was identified as being VEGF.⁶ Neovascularization and leakage are prominent features of the wet form of age-related macular degeneration (wAMD), which is responsible for 80-90% of the vision loss associated with AMD.

¹ Rawson NSB (1990). Drug therapy: serendipity and science. *Can Pharmaceut J* 123: 493-502.

² Ferrara N (2002). VEGF and the quest for tumour angiogenesis factors. *Nat Rev Cancer* 2: 795-803.

³ Folkman J (1971). Tumor angiogenesis: therapeutic implications. *N Engl J Med* 285: 1182-6.

⁴ Ferrara N (2002). VEGF and the quest for tumour angiogenesis factors. *Nat Rev Cancer* 2: 795-803.

⁵ Michaelson IC (1948). The mode of development of the vascular system of the retina with some observations on its significance for certain retinal disorders. *Trans Ophthalmol Soc UK* 68: 137-80.

⁶ Ferrara N, Damico L, *et al* (2006). Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as a therapy for neovascular age-related macular degeneration. *Retina* 26: 859-870.

Avastin was considered for the treatment of wAMD and diabetic retinopathy, but the potential effects of prolonged systemic exposure to the drug, which has a long half-life, raised concerns. Moreover, initial clinical studies of Avastin in cancer patients showed signs of serious toxicity, such as bleeding. Later it became clear that Avastin in combination with chemotherapy in cancer patients doubled the risk of the incidence of thromboembolic events, such as acute myocardial infarction (AMI) and stroke, relative to chemotherapy alone and that risk factors include being aged 60 years or more and having a history of thromboembolic events. Safety concerns about Avastin led to the recognition of the need for a local (rather than systemic) anti-VEGF therapy for retinal conditions.

Studies began in 1996 that eventually resulted in the development of a humanized antigen binding fragment form from the same lineage as Avastin, known as ranibizumab (Lucentis).⁷ An Investigational New Drug application was filed with the FDA in October 1999 and the first trial of patients with AMD began in February 2000. After two successful pivotal randomized clinical trials, Lucentis was approved for the treatment of wAMD by the FDA in June 2006 and Health Canada in June 2007. Thus, more than a decade of research led to the commercialization of Lucentis.

Lucentis is reported to 'set the standard as regards the totality of evidence from randomized clinical trials demonstrating its efficacy and tolerability (particularly that of the monthly regimen) in the treatment of

neovascular AMD'⁸ providing 'safe and highly effective'⁹ therapy for wAMD. In addition to wAMD, Lucentis is approved for the treatment of visual impairment due to diabetic macular edema (DME), macular edema secondary to retinal vein occlusion, and choroid neovascularization secondary to pathologic myopia. The drug is administered by injection into the eye.

Despite concerns that Avastin's manufacturer had about its safe use in patients with retinal conditions, ophthalmologists at the University of Miami administered the drug intravenously to nine patients with neovascular AMD and found that the clinical benefits were similar to those of intravitreal Lucentis,¹⁰ although seven patients required new or revised anti-hypertensive medication.¹¹ Due to concerns about the serious thromboembolic adverse events of Avastin reported in patients with cancer, the Miami group converted the molar amount of Avastin to be injected into the eye using the same low volume as Lucentis and subsequently published two successful case reports.¹² These reports led to off-label use of

⁸ Frampton JE (2013). Ranibizumab: a review of its use in the treatment of neovascular age-related macular degeneration. *Drugs Aging* 30: 331-58.

⁹ Gibson JM, Gibson SJ (2014). A safety evaluation of ranibizumab in the treatment of age-related macular degeneration. *Expert Opin Drug Saf* 13: 1259-70.

¹⁰ Steinbrook R (2006). The price of sight – ranibizumab, bevacizumab, and the treatment of macular degeneration. *N Engl J Med* 355: 1409-12.

¹¹ Michels S, Rosenfeld PJ, *et al* (2005). Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration twelve-week results of an uncontrolled open-label clinical study. *Ophthalmology* 112: 1035-47.

¹² Rosenfeld PJ, Fung AE, *et al* (2005). Optical coherence tomography findings after an intravitreal injection of bevacizumab (Avastin) for macular edema from central retinal vein occlusion. *Ophthalmic Surg Lasers Imaging* 36: 336-9; Rosenfeld PJ, Moshfeghi AA, *et al* (2005).

⁷ Ferrara N, Damico L, *et al* (2006). Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as a therapy for neovascular age-related macular degeneration. *Retina* 26: 859-870.

intraocular Avastin for economic reasons in many countries,¹³ including Canada.

In November 2011, the FDA approved another anti-VEGF drug, aflibercept (Eylea), for wAMD and, two years later, Eylea was approved by Health Canada for wAMD, DME and macular edema secondary to retinal vein occlusion.¹⁴ Aflibercept, which was originally developed as an anticancer drug,¹⁵ is a pharmacologically engineered protein that blocks the effect of VEGF by acting as a decoy receptor. The drug is available in an intravenous form for oncology indications and an iso-osmotic ultra-purified formulation for intravitreal injection.¹⁶ As with Lucentis, over a decade of research was required to bring Eylea to patients.

Optical coherence tomography findings after an intravitreal injection of bevacizumab (Avastin) for neovascular age-related macular degeneration. *Ophthalmic Surg Lasers Imaging* 36: 331-5.

¹³ Jansen RM (2013). The latest on the Avastin-Lucentis debacle. *Med Law* 32: 65-77.

¹⁴ Semeraro F, Morescalchi F, *et al* (2013). Aflibercept in wet AMD: specific role and optimal use. *Drug Des Devel Ther* 7: 711-22; Sophie R, Akhtar A, *et al* (2012). Aflibercept: a potent vascular endothelial growth factor antagonist for neovascular age-related macular degeneration and other retinal vascular diseases. *Biol Ther* 2: 3.

¹⁵ Holash J, Davis S, *et al* (2002). VEGF-Trap: a VEGF blocker with potent antitumor effects. *Proc Natl Acad Sci USA* 99: 11393-8.

¹⁶ Keane PA, Sadda SR (2012). Development of anti-VEGF therapies for intraocular use: a guide for clinicians. *J Ophthalmol* 483034.

Impact of vision loss on patients

The retinal conditions for which Lucentis and Eylea are approved have a major impact on affected patients and their families. Although each disease has different complications, they all can cause vision loss.

Vision loss presents many challenges in patients' lives, but in particular it leads to:

- A decrease in patients' quality of life¹⁷ due to difficulties performing tasks that utilize central vision, such as reading, watching television, recognizing people, reading facial features, and interacting with family and friends (reading difficulty is particularly challenging due to the broad impact that it has on other activities).
- A loss of independence due to the inability to drive, which affects many aspects of life, such as maintaining a job and travelling to doctor appointments, and leads to difficulties with daily living, such as housework and household repairs.
- Poor depth perception and balance leading to frequent falls and injuries (adults with vision loss have nearly three times the risk of falling¹⁸ and an increased risk of hip

¹⁷ Lotery A, Xu X, *et al* (2007). Burden of illness, visual impairment and health resource utilization of patients with neovascular age-related macular degeneration: results from the UK cohort of a five-country cross-sectional study. *Br J Ophthalmol* 91: 1303-7.

¹⁸ Cruess A, Zlateva G, *et al* (2007). Burden of illness of neovascular age-related macular degeneration in Canada. *Can J Ophthalmol* 42: 836-43; Soubrane G, Cruess A, *et al* (2007). Burden and health care resource utilization in neovascular age-related macular degeneration. *Arch Ophthalmol* 125: 1249-54; Szabo SM,

fracture¹⁹ when compared with age-matched controls; in turn, hip fracture increases the risk of death²⁰).

- Loss of friends and social supports leading to isolation and depression (adults with vision loss experience a significantly higher rate of depression and anxiety²¹).

Vision loss is, therefore, a devastating diagnosis because it impacts almost every task and activity related to daily living and increases the risk of morbidity and mortality. In every case, early diagnosis and an individualized approach to treatment are essential to effectively combat rapid vision deterioration.

Vision loss also has a major cost to society. A study conducted by the Canadian National

Janssen PA, *et al* (2010). Neovascular AMD: an overlooked risk factor for injurious falls. *Osteoporos Int* 21: 855-62; Wood JM, Lacherez P, *et al* (2011). Risk of falls, injurious falls, and other injuries resulting from visual impairment among older adults with age-related macular degeneration. *Invest Ophthalmol Vis Sci* 52: 5088-92.

¹⁹ Wysong A, Lee PP, *et al* (2009). Longitudinal incidence of adverse outcomes of age-related macular degeneration. *Arch Ophthalmol* 127: 320-7.

²⁰ Abrahamsen B, van Staa T, *et al* (2009). Excess mortality following hip fracture: a systematic epidemiological review. *Osteoporos Int* 20: 1633-50.

²¹ Augustin A, Sahel JA, *et al* (2007). Anxiety and depression prevalence rates in age-related macular degeneration. *Invest Ophthalmol Vis Sci* 48: 1498-1503; Cruess A, Zlateva G, *et al* (2007). Burden of illness of neovascular age-related macular degeneration in Canada. *Can J Ophthalmol* 42: 836-43; Evans JR, Fletcher AE, *et al* (2007). Depression and anxiety in visually impaired older people. *Ophthalmology* 114: 283-8; Soubrane G, Cruess A, *et al* (2007). Burden and health care resource utilization in neovascular age-related macular degeneration. *Arch Ophthalmol* 125: 1249-54; van der Aa HPA, Comijs HC, *et al* (2015). Major depressive and anxiety disorders in visually impaired older adults. *Invest Ophthalmol Vis Sci* 56: 849-54.

Institute for the Blind (CNIB), using 2012 data, estimated the direct health costs of vision loss in Canada due to AMD and diabetic retinopathy to be \$1.8 billion and \$412 million per year, respectively.²² When indirect expenses of \$860 million and \$364 million are included, the total financial costs of these disorders are \$2.6 billion and \$776 million. In addition, the CNIB estimated the cost of falls, depression, hip fractures and nursing home admissions associated with vision loss to be \$25.8 million, \$175.2 million, \$101.7 million and \$713.6 million, respectively. These costs are so large that just a small reduction in vision loss would lead to a significant impact. Therefore, there is an obvious economic benefit to sight-saving and restoring therapies.

Before anti-VEGF drugs were available, patients were treated with cold laser, photodynamic laser therapy and verteporfin (Visudyne). These therapies had limited effectiveness. Patients found them painful and they left scarring. Anti-VEGF drugs provided the first opportunity to improve visual outcomes in patients diagnosed with wAMD and other retinal conditions.²³

If administered within a window of 'treatability,' anti-VEGF drugs can prevent further vision loss and even restore some lost sight. However, this window is relatively short and, if missed, the delay can mean the

²² Canadian Council of the Blind, Canadian National Institute for the Blind, and the Foundation Fighting Blindness (2015). Patient summary. <https://www.cadth.ca/anti-vascular-endothelial-growth-factor-drugs-retinal-conditions>.

²³ Keane PA, Tufail A, *et al* (2011). Management of neovascular age-related macular degeneration in clinical practice: initiation, maintenance, and discontinuation of therapy. *J Ophthalmol* 752543.

difference between retaining vision and becoming blind.²⁴

Despite the sight-saving opportunities presented by anti-VEGF drugs, their delivery by an injection into the eye is a frightening prospect for many patients that may prevent some from accessing therapy. Patients want pharmaceutical companies to continue their innovative research in the hope that it leads to less invasive treatments.

Patients report experiencing ocular side effects with anti-VEGF drugs, such as eye pain, dizziness, blurred vision, headaches, bleeding in the eye, floaters, temporary blindness, elevated inner eye pressure, greying vision, and ‘itchy eyeball.’ These side effects often fail to prompt patients to seek treatment with an alternative anti-VEGF drug because they feel that other options are not available to them due, in part, to coercive insurance access policies. However, when a drug has side effects or limited effectiveness, switching to another drug often provides a better outcome. Therefore, patients need unrestricted access to all anti-VEGF drugs.

HTA review of anti-VEGF drugs

Insurers’ criteria that require patients to use older, often less effective drugs before allowing access to new innovative drugs in an attempt to contain costs, negate the benefits that patients can receive from innovation. A recent example of this is the recommendation from Canadian Agency for Drugs and Technologies in Health (CADTH) therapeutic review²⁵ of drugs for pulmonary arterial hypertension (PAH) that sildenafil or tadalafil (both available as generic products and, therefore, cheaper) be the preferred initial therapy for adults at a certain disease stage,²⁶ rather than more expensive and innovative drugs. This has the potential to delay access to more effective drugs by which time the patient’s health has deteriorated.

In early 2015, provincial governments requested CADTH to conduct a therapeutic review of the use of Lucentis, Eylea and Avastin for retinal conditions. Up to now, therapeutic reviews have been performed to provide recommendations at the time of a new drug submission to CADTH. However, CADTH changed its rules to allow a review to be done at any time and to extend the scope to include ‘evidence-based expanded use (i.e. for a clinical

²⁴ Angiogenesis Foundation (2012). Advocating for improved treatment and outcomes for wet age-related macular degeneration. http://www.mdffoundation.com.au/resources/Australia_AMD_Whitepaper.pdf.

²⁵ A therapeutic review is an evidence-based assessment of publicly available sources regarding a therapeutic category or a class of drugs to support drug listing and policy decisions and to encourage optimal therapy.

²⁶ CADTH (2015). Drugs for pulmonary arterial hypertension: comparative efficacy, safety and cost-effectiveness – recommendations report. https://www.cadth.ca/sites/default/files/pdf/TR0006_PA_H_Recs_Report.pdf.

indication not included in an approved Health Canada product monograph).²⁷

Furthermore, CADTH decided to include only randomized clinical trials in its therapeutic review.²⁸ Randomized trials of Avastin and Lucentis have shown that these drugs have similar efficacy and safety in the treatment of retinal conditions but, as CADTH acknowledged in its review, the trials are not large enough to provide appropriate guidance about safety risks.²⁹ Some large-scale real-world observational studies that included thousands of patients suggest greater safety risks with Avastin compared with Lucentis.³⁰ The exclusion of observational studies predisposed CADTH's therapeutic review to produce the conclusion that Avastin and Lucentis have similar efficacy and safety profiles in the treatment of retinal conditions – a conclusion that justifies the recommendation that Avastin can be used as 'the preferred initial anti-VEGF therapy' for retinal conditions.³¹

²⁷ CADTH (2015). Updates to the therapeutic review framework. <https://www.cadth.ca/updates-therapeutic-review-framework>.

²⁸ CADTH (2015). Anti-vascular endothelial growth factor drugs for retinal conditions: a therapeutic review. https://www.cadth.ca/sites/default/files/pdf/TR0009_Anti-VEGF_Protocol_e.pdf; CADTH (2015). Anti-vascular endothelial growth factor (VEGF) drugs for retinal conditions: draft science report. https://www.cadth.ca/sites/default/files/pdf/TR0009_Anti-VEGF_Science_Report-Draft.pdf.

²⁹ Solomon SD, Lindsley K, *et al* (2014). Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. *Cochrane Database Syst Rev* 8: CD005139.

³⁰ Gower EW, Cassard S, *et al* (2011). Adverse events rates following intravitreal injection of Avastin or Lucentis for treating age-related macular degeneration. *Invest Ophthalmol Vis Sci* 52: 6644.

³¹ CADTH (2015e). Anti-vascular endothelial growth factor (VEGF) drugs for the treatment of retinal conditions: draft recommendation report.

Quotas already exist in Alberta and British Columbia, where government payments to retinal specialists are significantly less if they do not prescribe Avastin to 70-80% of their patients.³² The CADTH recommendation is likely to lead to more provinces setting fixed quotas for retinal specialists to prescribe Avastin over Lucentis or Eylea.

While the safety and efficacy of Lucentis and Eylea for intravitreal use for retinal conditions have been reviewed and approved by Health Canada, Avastin is not approved for retinal conditions. Moreover, its Product Monograph has a serious black-boxed warning explicitly stating that the drug is 'not formulated and has not been authorized for intravitreal use'³³ and an alert was issued by Health Canada in 2011 concerning reports of cases of severe eye inflammation leading to blindness following unauthorized use of Avastin.³⁴ Avastin also has a serious warning about gastrointestinal perforation as well as other cautions about the potential for AMI, stroke, hypertension, heart failure, hemorrhaging and death.

Nevertheless, Avastin has been found to be effective for the treatment of retinal conditions and is much less expensive than Lucentis and Eylea. Consequently, Avastin is being used off-

https://www.cadth.ca/sites/default/files/pdf/TR0009_Anti-VEGF_Recommendation_Report-Draft.pdf.

³² Gerein K (2015). Alberta health minister announces new eye-care program. *Edmonton Journal* Sep 30. <http://edmontonjournal.com/news/politics/alberta-health-minister-announces-new-eye-care-program>.

³³ Health Canada (2015). Avastin product monograph. <http://webprod5.hc-sc.gc.ca/dpd-bdpp/info.do?code=75642&lang=eng>.

³⁴ Health Canada (2011). Avastin (bevacizumab) – reports of cases of severe eye inflammation leading to blindness following use in the eye. <http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2011/14095a-eng.php>.

label in Canada and other countries.³⁵ Although the rate of adverse events following off-label drug use has been shown to be significantly higher than the rate for approved use,³⁶ off-label use of drugs is an accepted medical practice, especially in the treatment of children or situations where unusual measures are required. However, it is usually only done for medical reasons, whereas off-label Avastin use for retinal conditions is encouraged for cost-containment purposes.

Since Avastin is supplied in large vials suitable for oncology treatment, its use for retinal conditions requires either repeated extraction of the small doses needed for intravitreal use from the large vial or appropriately sized doses for intravitreal use being prepared by a compounding pharmacy. The former approach increases the risk of infection, while the latter requires using companies such as the one that supplied erroneously diluted oncology drugs.³⁷

The use of Avastin for wAMD and other retinal conditions means that the drug is being used for indications for which there is no regulatory approval, is inappropriately formulated and is administered in an unauthorized manner. In addition, use of Avastin as a first-line drug for retinal conditions increases the risk that the treatability window in which Lucentis or Eylea are at their most effective is missed.

³⁵ Jansen RM (2013). The latest on the Avastin-Lucentis debacle. *Med Law* 32: 65-77.

³⁶ Eguale T, Buckeridge DL, *et al* (2016). Association of off-label drug use and adverse drug events in an adult population. *JAMA Intern Med* 176: 55-63.

³⁷ Babbage M (2013). Diluted chemo drugs administered to Ontario patients didn't accurately describe saline 'overfill.' *National Post* May 6. <http://news.nationalpost.com/news/canada/diluted-chemo-drugs-administered-to-ontario-patients-didnt-accurately-describe-saline-overfill>.

The safety risks of Avastin appear to be greater than those of the other drugs, especially in patients who already have risk factors for thromboembolic events. The risks of Avastin therapy are not properly understood, but they are being shouldered by physicians and patients,³⁸ not Health Canada, CADTH or the provinces. If patients are required to use Avastin as first-line therapy or (especially) are to be transferred from Lucentis or Eylea to Avastin, they should be informed of the risks and sign a consent form before treatment.

To summarize, the recommendation for the first-line use of Avastin for retinal conditions:

- Undermines the Health Canada regulatory approval process established to assess the efficacy and safety of medications and exposes patients to potentially increased risks.
- Overrides expert medical opinion from making patient-appropriate treatment decisions.
- Manipulates the HTA process by revising the rules for therapeutic reviews to allow assessments of drugs used for indications without regulatory approval.
- Means that step therapy will be introduced which has the potential to delay access to Lucentis and Eylea for some patients beyond the window of treatability and lose the opportunity for the prevention of further vision loss and restoration of some lost sight.
- Increases the risk for thromboembolic events in patients already at a higher risk, e.g. elderly overweight diabetics.

³⁸ Jansen RM (2013). The latest on the Avastin-Lucentis debacle. *Med Law* 32: 65-77.

Conclusion

Innovation is the life-blood of brand-name pharmaceutical companies. Without innovation, they would cease to exist. For patients, innovation in drug development means that they have access to therapies for conditions for which there was no prior treatment or the current treatment has limited effectiveness. Moreover, despite frequent claims to the contrary, a higher level of innovation is not related to an increased risk of serious safety issues identified after regulatory approval.³⁹

As the extensive research programs that brought Lucentis and Eylea to patients demonstrate, innovation requires a major investment of resources and time by pharmaceutical companies. Consequently, a company that has developed a new innovative drug needs to recuperate its investment over the limited patent life that regulatory agencies allow in order to be able to continue its research programs. Restricted access to drugs significantly limits a company's ability to recover its outlay to allow it to continue innovation (in the case of retinal disorders towards less invasive therapies) and prevents patients from benefiting from scientific advancement.

The blatant manipulation of the HTA process seen in the change in the rules for CADTH therapeutic reviews to achieve provincial government cost-containment objectives is an abuse of the system that significantly increases patients' risk of morbidity and mortality. By delaying access to the benefits of innovative

drugs, it implies that innovation and patient health are considered to have a lower priority than cost-containment. Moreover, it sets a sinister precedent for the use of the HTA system to promote preferential off-label prescribing for economic reasons in any national Pharmacare scheme.

The new Liberal federal government claims to support evidence-based science and greater transparency in government decisions. Any increased federal funding to provincial and territorial governments for healthcare should be conditional on patient access to innovative beneficial drugs being unrestricted by a manipulated HTA process and any decisions that delay, restrict or deny access to drugs should be based on valid, comprehensive scientific and medical evidence.

³⁹ Mol PGM, Arnardottir AH, *et al* (2013). Post-approval safety issues with innovative drugs: a European cohort study. *Drug Saf* 36: 1105-15.

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