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# PUBLIC REIMBURSEMENT OF PRESCRIPTION DRUGS USED FOR OFF-LABEL INDICATIONS IN ONTARIO

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## Abstract

### Background

A Canadian Agency for Drugs and Technologies in Health therapeutic review concluded that bevacizumab and ranibizumab have similar efficacy and safety in treating retinal conditions and recommended bevacizumab be used as preferred initial therapy based on a cost-saving perspective. Such use would be off-label because bevacizumab's Product Monograph (PM) has a serious safety warning that the drug is not formulated or authorized for intravitreal use.

### Objective

To evaluate whether the Ontario Public Drug Programs (OPDP) reimbursement is provided only for off-label use for serious conditions or when the drug's PM contains a serious safety warning.

### Methods

Comparisons were made between the OPDP reimbursement criteria for non-palliative drugs from its frequently requested Exceptional Access Program (EAP) list and for non-palliative injectable drugs from its Limited Use (LU) list and approved indications and serious safety warnings in the drugs' PMs.

### Results

Of 125 unique frequently-requested non-palliative EAP drugs, 12 included off-label use for serious conditions for which no alternative treatment exists. Eight of the 12 had serious safety warnings, but only one had a serious safety warning directly related to the OPDP-reimbursed off-label use. Of 29 non-palliative injectable LU drugs, one had off-label LU criteria allowing reimbursement for an unapproved indication and a serious safety warning unrelated to the reimbursable indication.

### Conclusion

Presently, OPDP only reimburse drugs for off-label use for the treatment of serious conditions for which no alternative treatment exists. OPDP should not diverge from this approach by allowing cost-savings to trump appropriate drug use.

### Keywords

Off-label drug use; drug reimbursement; drug coverage; Ontario

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In early 2015, the Canadian Agency for Drugs and Technologies in Health (CADTH) conducted a therapeutic review of the use of the anti-vascular endothelial growth factor (anti-VEGF) drugs aflibercept (Eylea), bevacizumab (Avastin) and ranibizumab (Lucentis) used for retinal conditions at the request of provincial governments.[1] A CADTH 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. Based on the review, CADTH concluded that bevacizumab and ranibizumab have similar efficacy and safety profiles in intravitreal treatment of retinal conditions, which justified its recommendation that bevacizumab be used as the preferred initial therapy for these conditions based on a cost-saving perspective.[2]

Bevacizumab has regulatory approval from Health Canada for the treatment of several types of cancer. However, regulatory approval for bevacizumab for intravitreal use for retinal conditions has not been sought from Health Canada. Moreover, bevacizumab's Product Monograph (PM) has a serious boxed safety warning explicitly stating that the drug is "not formulated and has not been authorized for intravitreal use."[3] The PM also notes that observational studies of unauthorized intravitreal use of bevacizumab have reported increased risks of intraocular inflammation, cataract surgery, hemorrhagic stroke, and overall mortality,[4,5] and that a randomized controlled clinical trial comparing unauthorized bevacizumab with authorized retinal treatment found an increased risk of serious systemic adverse events (the most frequent being myocardial infarction, cerebrovascular accident and hypertension) for bevacizumab.[6] The safety and efficacy of aflibercept and ranibizumab have been reviewed and approved by Health Canada for intravitreal use for retinal conditions. Both of their PMs have a caution that arterial thromboembolic events are adverse events potentially related to their use.[7,8]

Intravitreal use of bevacizumab for retinal conditions would be "off-label." Off-label use means that a prescription drug is being used for a condition for which the drug has not received approval from the relevant regulatory authority. Such use is common in many areas of medicine,[9] especially in psychiatric,[10] cancer,[11] and palliative care,[12] when patients have serious, life-threatening or severely debilitating conditions for which no alternative treatment exists. Off-label use of a drug in these circumstances may be the last and best hope for a patient, but in less serious conditions, off-label use may lead to greater harm than benefit.[13,14]

In the Canadian province of Ontario, the Ontario Public Drug Programs (OPDP) provide public drug insurance coverage to seniors, children and young adults, social assistance recipients and some special groups, such as cancer patients or when costs are deemed to be catastrophic.[15] The drugs covered by the OPDP are detailed in the Ontario Drug Benefit (ODB) Formulary in a General Benefit list and a Limited Use (LU) list.[16] As of April 30, 2018, the General Benefit list included over 4,500 products (about 700 unique drugs; with the exception of biosimilars, drugs with the same active ingredient were not considered unique irrespective of dose or route of administration) for which there are no reimbursement criteria and 938 LU products (191 unique drugs) for which reimbursement criteria are specified.

In addition, the OPDP have an Exceptional Access Program (EAP) through which patients may receive reimbursement for some drugs or indications not covered in the ODB Formulary, subject to patients satisfying reimbursement criteria.[17] These criteria set out the clinical conditions under which reimbursement will be approved. They frequently require patients to be at a particular point in the progression of the condition being treated and to have tried medications that are less expensive. The criteria for reimbursement of some drugs are complex, stringent and inconsistent with clinicians' views.[18] Over 1,000 products (234 unique drugs) were listed in the EAP as of April 30, 2018. However, the reimbursement criteria are only publicly available for a subset of the EAP drugs – those that are "frequently requested."[19] The latest list of frequently-requested EAP drugs requiring a formal application available as of April 30, 2018 was dated September 1, 2017. A shorter list of frequently requested drugs as part of the Telephone Request

Service program, under which requests are processed in real time, was dated August 2015.[20] The two lists were combined.

As far as we are aware, there has not been a thorough evaluation of the reimbursement of drugs for off-label use by the public payer in Ontario. We compared OPDP reimbursement criteria from the frequently-requested EAP list and the LU list with Health Canada-approved indications and serious boxed safety warnings in the drugs' PMs. The objective was to evaluate whether reimbursement was provided for off-label use for conditions that are serious (those that are life-threatening, e.g., myocardial infarction or cancer, or have the potential to negatively impact quality of life) for which there is no alternative therapy or when the PM contained a serious boxed safety warning against such use.

## METHODS

Since the guiding principles regarding pharmacotherapy in palliative care situations may be different from routine use cases for the same drugs, palliative care drugs were removed from both the frequently-requested EAP list and the LU list before commencing any analyses. In addition, the LU list was reduced to those drugs whose route of administration was by injection because the number of drugs in the LU list was substantial, anti-VEGF drugs are administered by injection, and injectables should require greater consideration of their safety before administration. The latest PMs for each of the included drugs were identified from Health Canada's online Drug Product Database.[21]

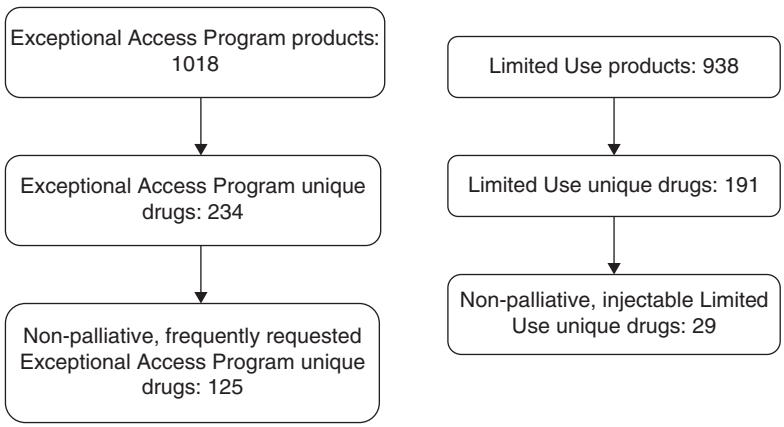
The OPDP reimbursement criteria for the drugs in the frequently-requested EAP list and the list of LU injectable drugs were compared with their Health Canada-approved indications and any serious boxed safety warnings in the PM to answer the following questions:

- Are drugs reimbursed off-label only when the condition being treated is a serious disorder for which there is no alternative treatment?
- Does the PM contain a serious boxed safety warning against the off-label use of the drug?
- Is a different route of administration than that approved in the PM being used for off-label delivery of the drug?
- Are there any special monitoring requirements applicable either prior to or after off-label use?
- Is there any provision regarding informed consent to ensure that patients are aware they are receiving an off-label drug?

## RESULTS

One hundred and twenty-five non-palliative, unique frequently-requested EAP drugs and 29 non-palliative, unique injectable LU drugs were identified for inclusion in the analyses (Figure 1).

**FIG. 1** Flow diagram for the inclusion of drugs in the two analysis groups



**Frequently Requested Exceptional Access Program Drugs**

The OPDP reimbursement criteria were more restrictive than the PM indications for 52 drugs (41.6%) of the 125 frequently-requested EAP drugs, while the reimbursement criteria were the same for 61 drugs (48.8%). The reimbursement criteria for the remaining 12 drugs (9.6%) included off-label use (Table 1) for conditions considered to be serious disorders for which no alternative treatment would be appropriate.

**TABLE 1** Reimbursement Criteria and Safety Warnings For 12 Drugs on the Frequently Requested EAP List with Off-Label Use.

| Drug | Reimbursement Criteria | SSW | Off-label Use and SSW Information | Latest PM |
|---|---|---|---|---|
| Sirolimus (Rapamune); oral | Liver transplant or limb transplant where calcineurin inhibitors are not an option. | Yes | Prescriber required to explain why calcineurin inhibitors not an option. SSW: Lymphoma and hypersensitivity reaction risks. *Use in liver and lung transplants not recommended because safety in these uses has not been established.* | 2017 |
| Posaconazole (Posanol); oral | Prophylaxis of aspergillus and candida infections in patients who have recently undergone an allogenic bone marrow (stem-cell transplant) and have moderate to severe graft-versus-host-disease. Treatment of invasive aspergillosis refractory to voriconazole and mucormycosis refractory to amphotericin B. | Yes | Not indicated for treatment of mucormycosis. PM includes limited clinical trial information regarding efficacy in treating mucormycosis. SSW: Cardiovascular effects, hepatic toxicity and drug interactions. Unrelated to indication for mucormycosis treatment. | 2017 |
| Rosiglitazone (Avandia); oral | Patients with diabetes with inadequate glycemic control (A1C>7%) on maximum tolerated doses of other antidiabetic agents as part of dual or triple diabetes therapy. | Yes | Prescriber and patient must acknowledge that thiazolidinediones not indicated for triple therapy. SSW: Not recommended in patients with ischemic heart disease and should be used only when all other oral agents in mono-therapy or combination do not achieve adequate glycemic control. | 2017 |
| Mycophenolate mofetil (Cellcept and generics); oral | Solid organ transplants other than allogenic, renal, cardiac or hepatic transplants. Prophylaxis for limb rejection. Treatment of non-infectious ocular inflammation (uveitis, scleritis, and ocular mucous membrane pemphigoid). | Yes | SSW: Association with third trimester pregnancy loss and congenital malformation and increased susceptibility to infection and possible development of lymphoma may result from immunosuppression. Ocular indications are off-label but no concerns. | 2015–2018 |
| Darbepoetin (Aranesp); IV and SC | Anemia secondary to myelodysplastic syndrome where patient is not eligible under Special Drugs Program. | Yes | Myelodysplastic syndrome is not an approved indication. SSW: Not against use in myelodysplastic syndrome. | 2018 |

| Drug | Reimbursement Criteria | SSW | Off-label Use and SSW Information | Latest PM |
|---|---|---|---|---|
| Epoetin alpha (Eprex); IV and SC | Anemia secondary to chronic renal disease, hepatitis C, myelodysplastic syndrome, major orthopedic surgery, chemotherapy-induced anemia or palliative cancer care where patient is not eligible under Special Drugs Program. | Yes | Myelodysplastic syndrome is not an approved indication<br>SSW: Not against use in myelodysplastic syndrome. | 2018 |
| Iron sucrose (Venofer); IV and IM | For iron-deficiency anemia where oral iron is not an option. | Yes | SSW: Hypersensitivity reactions. | 2013 |
| Lamivudine (Heptovir); oral | Chronic hepatitis B with clinical criteria specified. | Yes | SSW: HIV resistance, lactic acidosis and severe hepatomegaly with steatosis, and exacerbation of hepatitis. | 2018 |
| Acyclovir (Zovirax and generics); oral | Herpes simplex virus prophylaxis in post-kidney, heart and pancreas transplant patients and varicella zoster virus prophylaxis in stem cell transplant patients. | No | Indications are initial treatment of herpes genitalis, suppression of unusually frequent episodes of herpes genitalis, and acute treatment of herpes zoster and varicella. | 2014–2017 |
| Ambrisentan (Volibris); oral | NYHA class III or IV pulmonary arterial hypertension. | No | Indication is NYHA Class II or III, not III or IV. | 2016 |
| Dapsone; oral | *Pneumocystis* pneumonia prophylaxis in immunocompromised patients in whom trimethoprim/sulfamethoxazole is not an option; autoimmune diseases. | No | No concern regarding use in *Pneumocystis* pneumonia prophylaxis or autoimmune disease. PM indications: leprosy, dermatitis herpetiformis, actinomycotic mycetoma. | 2018 |
| Pioglitazone (Actos and generics); oral | For patients with diabetes with inadequate glycemic control (A1C>7%) on maximum tolerated doses of other antidiabetic agents as part of dual or triple diabetes therapy. | No | Prescriber and patient must acknowledge that thiazolidinediones not indicated for triple therapy. | 2013–2018 |

**EAP = Exceptional Access Program; IM = intramuscular; IV = intravenous; NYHA = New York Heart Association; PM = Product Monograph; SC = subcutaneous; SSW = serious safety warning.**

Although eight of the 12 frequently-requested EAP drugs had a serious safety warning, only one (sirolimus) was related to the OPDP-reimbursed off-label use. Sirolimus is reimbursed for liver or limb transplants where calcineurin inhibitors are not an option, despite this use being not recommended because safety and efficacy have not been established. However, prescribers are required to explain why calcineurin inhibitors are not an option.

Coverage is only available for off-label use once clinical criteria are satisfied and other treatment options have been demonstrably exhausted. The off-label use of the 12 drugs did not involve a different route of administration to the approved method. The only requirement for informed consent for off-label use was for rosiglitazone or pioglitazone in triple therapy for diabetes where both the prescriber and the patient must acknowledge their awareness that these drugs are not indicated for such use.

**Injectable Limited Use Drugs**

The LU criteria for all but one of the 29 injectable LU drugs (Figure 1) were in agreement with the Health Canada-approved indications (Table 2) in their PMs, which were all dated 2017 or 2018 except for testosterone enanthate (2014). Fourteen of the 28 drugs had a serious safety warning in their PM that was unrelated to the LU criteria.

Only one drug (tacrolimus) had off-label LU criteria that allow reimbursement for its use in bone marrow transplant, which is not an approved indication in its PM. Tacrolimus has a serious safety warning in its PM, but it is not related to the reimbursable indication, and it is administered as specified in the PM. Coverage for tacrolimus is only available for off-label use once clinical criteria are satisfied and other treatment

**TABLE 2** Reimbursement Criteria and Safety Warnings for 29 Injectable Drugs on the Limited Use List

| Generic Name | Brand name | Limited Use criteria are to restrict coverage to: | Off-label | Serious safety warning (SSW) | SSW related to covered indication |
|---|---|---|---|---|---|
| Tacrolimus | Prograf | Approved indication *and bone marrow transplant* | Yes | Yes | No |
| Adalimumab | Humira | Approved indication | No | Yes | No |
| Botulinum toxin type A | Botox | Approved indications | No | Yes | No |
| Clostridium botulinum neurotoxin type A | Xeomin | Approved indications | No | Yes | No |
| Dalteparin sodium | Fragmin | Specific patients | No | Yes | No |
| Darbepoetin alfa | Aranesp | A specific indication | No | Yes | No |
| Epoetin alfa | Eprex | A specific indication | No | Yes | No |
| Filgrastim | Neupogen | Approved indications | No | Yes | No |
| Ganciclovir sodium | Cytovene | A specific indication | No | Yes | No |
| Infliximab | Inflectra | Specific context of approved indications | No | Yes | No |
| Insulin aspart | NovoRapid | Specific context of approved indications | No | Yes | No |
| Interferon alfa-2b | Intron A | Approved indications | No | Yes | No |
| Etanercept | Brenzys | Specific context of approved conditions | No | Yes | No |
| Etanercept | Enbrel | Specific context of approved indication | No | Yes | No |
| Aflibercept | Eylea | Approved indication | No | No | No |
| Denosumab | Prolia | Specific patients | No | No | No |
| Enoxaparin | Lovenox | Specific patients | No | No | No |
| Evolocumab | Repatha | Specific indication | No | No | No |
| Fondaparinux sodium | Arixtra | Specific indication | No | No | No |
| Ixekizumab | Taltz | Specific indication | No | No | No |

| Generic Name | Brand name | Limited Use criteria are to restrict coverage to: | Off-label | Serious safety warning (SSW) | SSW related to covered indication |
|---|---|---|---|---|---|
| Nadroparin calcium | Fraxiparine | Specific patients | No | No | No |
| Ocriplasmin | Jetrea | Approved indication | No | No | No |
| Ranibizumab | Lucentis | Approved indications | No | No | No |
| Secukinumab | Cosentyx | Specific context of approved indication | No | No | No |
| Testosterone cypionate | Depo-Testosterone | Approved indication | No | No | No |
| Testosterone enanthate | Delatestryl | Approved indication | No | No | No |
| Tinzaparin sodium | Innohep | Specific patients | No | No | No |
| Ustekinumab | Stelara | Specific context of approved indication | No | No | No |
| Zoledronic acid | Aclasta | Specific patients | No | No | No |

options have been exhausted. There is no requirement for informed consent for its off-label use.

## CONCLUSION

The results of this investigation demonstrate that non-palliative drugs on the frequently-requested EAP lists and non-palliative injectable drugs on the LU list are reimbursed for off-label use *only* when the condition being treated is a serious disorder for which there is no alternative treatment. Only two drugs had criteria that allowed reimbursement for an indication not in their Health Canada-approved PM. Although eight of the EAP drugs and one of the LU drugs that had off-label reimbursement carry a serious safety warning, only one warning (for sirolimus) related directly to the off-label use. None of the drugs were reimbursed for a route of administration different from that indicated in the PM. Informed consent to ensure that patients are aware they are receiving an off-label drug is only required for two EAP drugs.

This analysis is limited by the lack of complete reimbursement criteria for all drugs in the EAP and the exclusion of oral and topical LU drugs. In addition, it is unknown to what extent drugs on the General Benefit list are reimbursed for off-label use.

Presently, OPDP only reimburse drugs for off-label use in situations where the condition being treated is a serious disorder for which alternative treatment is not available and only one orally administered frequently-requested EAP drug has a reimbursable use that is contrary to a serious safety warning. OPDP should not diverge from this approach by allowing cost savings to trump the appropriate use of drugs.

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