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Analogues for Ophthalmic Use



*Supporting Informed Decisions*

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**Canadian Agency for Drugs and Technologies in Health**

**Overview of Clinical and Cost-Effectiveness  
of Prostaglandin Analogues for Ophthalmic Use**

June 2007

We thank Lisa Hum for her assistance in creating this overview from a longer report authored by Hodge, *et al.*

This overview is based on the Technology Report commissioned by CADTH: Hodge WG, Lachaine J, Steffensen I, Murray C, Barnes D, Foerster V, Ducruet T, Mensinkai S. *Prostaglandin analogues for ophthalmic use: analysis of clinical and cost-effectiveness*. Ottawa: Canadian Agency for Drugs and Technologies in Health, 2007. Technology Report no. 89.

## Prostaglandin Analogues for Ophthalmic Use: Analysis of Clinical and Cost Effectiveness

### Technology and Condition

Prostaglandin analogues (PGAs) in the treatment of elevated intraocular pressure (IOP): bimatoprost, latanoprost, and travoprost

### Issue

PGAs are more costly than alternative agents for the lowering of IOP. One policy decision to be made is whether reimbursement of these agents as first-line therapy with no restrictions represents an optimal use of limited resources.

### Methods and Results

A systematic review of the clinical literature was conducted. Twenty-two RCTs comparing PGAs to alternative therapy in individuals >18 years old with elevated IOP who were treatment-naïve or who experienced appropriate washout before treatment were included. A cost-effectiveness analysis was conducted from the perspective of Canadian ministries of health. A decision-analytic model using a three-month time horizon calculated the associated costs and consequences of using latanoprost versus timolol, dorzolamide, and brimonidine; and travoprost versus timolol.

### Implications for Decision Making

- **Not all PGAs are the same.** There is evidence that latanoprost and travoprost reduce IOP more effectively than timolol. The same evidence does not exist for bimatoprost.
- **Timolol that is used as a first-line option could represent an optimal use of scarce resources.** For appropriate patients, it would be preferable, from a cost-effectiveness standpoint, to start treatment with timolol and reserve the PGAs as an alternative treatment or as add-on therapy for patients not achieving a clinical response with timolol.
- **PGAs may be cost-saving, depending on the alternative.** Compared to dorzolamide, latanoprost is more effective and less costly. Compared to brimonidine, latanoprost is associated with additional costs, at a lower cost per mm Hg reduced.
- **The long-term benefit from PGAs is unclear.** There is no evidence that greater reductions in IOP translate into reductions in visits to a physician or surgical procedures, or an increase in health-related quality of life.

This summary is based on a comprehensive health technology assessment available from CADTH's web site ([www.cadth.ca](http://www.cadth.ca)): Hodge WG, Lachaine J, Steffensen I, Murray C, Barnes D, Foerster V, Ducruet T, Mensinkai S. *Prostaglandin analogues for ophthalmic use: analysis of clinical and cost-effectiveness.*

# 1 Introduction

Glaucoma, which is a chronic ocular disorder characterized by slow and progressive degeneration of the optic nerve, can lead to total and irreversible blindness. It is one of the most common causes of blindness in industrialized countries. At least 300,000 Canadians are affected with glaucoma, with 50% of patients unaware of their disease.<sup>1</sup> Globally, an estimated 60.5 million people will have glaucoma by 2010, increasing to 79.6 million by 2020.<sup>2</sup> Once diagnosed, patients must be monitored and treated for the remainder of their lives.

The two types of glaucoma, open-angle glaucoma (OAG) and closed-angle glaucoma (CAG), can be primary (i.e., when the cause is unknown) or secondary (i.e., when the condition can be traced to a known cause). Primary open-angle glaucoma (POAG) is the most common form in Canada and other industrialized countries, accounting for 60% of glaucoma cases.<sup>3</sup> Pseudoexfoliation glaucoma and pigmentary glaucoma are the common forms of secondary OAG. Pseudoexfoliation glaucoma is associated with the production and deposition of material in the ocular tissue. Pigmentary glaucoma is a complication of pigmentary dispersion syndrome, a disorder that is characterized by the deposition of pigment granules in the eye.

Although neither necessary nor sufficient to cause glaucoma, high intraocular pressure (IOP) is recognized as the most important risk factor contributing to the development and progression of the disorder.<sup>4</sup> The elevated IOP that is observed in the classic presentation of POAG is thought to result from decreased drainage of aqueous humour, the fluid that fills the eye's anterior and posterior chambers. Pseudoexfoliation glaucoma and pigmentary glaucoma cause drainage obstruction, resulting in the elevation of IOP.

The main goal of current glaucoma treatment is to lower IOP, the only modifiable risk factor for progression. Approaches to reducing IOP are pharmacotherapy or surgery, with the former usually being the first line of treatment. Five classes of drugs are used to manage glaucoma and elevated IOP:<sup>4,5</sup> beta-adrenergic antagonists, adrenergic agonists, carbonic anhydrase inhibitors, cholinergics (acetylcholine receptor agonists), and prostaglandin analogues (PGAs).

PGAs are the newest class of glaucoma medications to be introduced on the Canadian market. PGAs are believed to lower IOP by increasing the outflow of aqueous humour. Although the mechanism of action is unclear, researchers hypothesize that PGAs exert their effect by binding to the prostanoid FP receptors of the ciliary body and up-regulating the production of metalloproteinase proteins involved in controlling extracellular permeability.<sup>5,6</sup> It has been shown that PGAs relax the ciliary muscle, facilitating uveoscleral outflow.<sup>7</sup>

Three PGAs are approved in Canada for the treatment of patients with elevated IOP or glaucoma (Table 1). The PGAs for ophthalmic use are open listed (i.e., drug plans provide unrestricted coverage) in all but two provincial drug plans. PGAs are more costly than alternative agents for the lowering of IOP. One policy decision to be made is whether to support continued open listing of these agents or restrict them to limited-use status.

**Table 1: Single-agent PGAs available in Canada for glaucoma treatment**

Generic Name, Trade Name (Manufacturer)	Date Approved in Canada	Dosage	Cost Per Unit* in C\$	Approved Dosage
latanoprost, Xalatan <sup>®</sup> (Pfizer Canada Inc.)	January 17, 2000	0.005% ophthalmic solution – 2.5 mL package	26.00	once daily
travoprost, Travatan <sup>®</sup> (Alcon Canada Inc.)	July 7, 2002	0.004% ophthalmic solution – 2.5 mL package	26.50	once daily
bimatoprost, Lumigan <sup>®</sup> (Allergan Inc.)	April 6, 2004	0.03% ophthalmic solution – 2.5 mL package	26.00	once daily

\*Cost and dosing information obtained from online Ontario Drug Benefit Formulary effective from April 4, 2006.<sup>8</sup>

## 2 Objective

The objective of the report *Prostaglandin analogues for ophthalmic use: analysis of clinical and cost-effectiveness* was to present a systematic review and economic evaluation of PGAs for the treatment of increased IOP, using evidence from published and unpublished randomized controlled trials (RCTs). Three questions were addressed.

- What is the effectiveness of using PGAs (bimatoprost, latanoprost, travoprost) as first-line agents for the lowering of ophthalmic IOP in patients with ocular hypertension and OAG, or isolated ocular hypertension?
- What is the effectiveness of using PGAs for the lowering of IOP in patients with ocular hypertension and OAG, or isolated ocular hypertension, who cannot use or have failed therapy with other IOP-lowering agents?
- What is the cost-effectiveness of using PGAs for ophthalmic use
  - as first-line agents
  - in patients with ocular hypertension and glaucoma, or isolated ocular hypertension, who cannot use or have failed other IOP-lowering agents?

## 3 Clinical Review

### *Methods*

Published literature was obtained by cross-searching MEDLINE<sup>®</sup>, BIOSIS Previews<sup>®</sup>, ToxFile, and EMBASE<sup>®</sup>. Parallel searches were conducted on PubMed, the Cochrane database, and trial registries. Grey literature was obtained by searching specialized databases and the web sites of professional associations and regulatory, health technology assessment, and near-technology assessment agencies. The manufacturers of the pharmaceutical agents of interest to this report were contacted. Evidence permitted for review included RCTs if they involved humans older than 18 years, with elevated IOP, at least one PGA intervention, and treatment-naïve patients or patients with appropriate washout before treatment. RCTs were excluded if the comparator was not an IOP-lowering agent or placebo, or patients had CAG. Two reviewers independently screened titles and abstracts, and applied the selection criteria. Disagreements were resolved by consensus.

Validity assessment was performed by two reviewers using the Jadad scale,<sup>9</sup> which assesses the reporting of randomization, double-blinding, and withdrawals and dropouts. The weighted mean difference (WMD) and 95% confidence interval (CI) were calculated for continuous data. A chi-square test and an  $I^2$  test were used to test for statistical heterogeneity between studies. Sensitivity analyses were undertaken to evaluate the effect of validity assessment scores and intention to treat (ITT) analysis on IOP reduction.

## 4 Results

The literature search yielded 1,150 citations, of which 195 were retrieved for evaluation. Of the 195 reports, 26 reports of 22 unique RCTs involving 5,304 individuals were included. The kappa score was 0.90, indicating good agreement between reviewers. Of the 22 RCTs, 14 (64%) were given a high Jadad score ( $\geq 3$ ),<sup>10-23</sup> and eight studies (36%) were given a low Jadad score ( $\leq 2$ )<sup>24-31</sup>. All studies were parallel design except one<sup>14</sup> (cross-over).

Overall, 18 studies examined latanoprost,<sup>11-14,17-23,25-31</sup> four examined travoprost,<sup>10,15,16,18</sup> and one examined bimatoprost.<sup>24</sup> Latanoprost was compared to timolol,<sup>12,14,18-23</sup> betaxolol,<sup>25</sup> brimonidine,<sup>11,17,27,29</sup> dorzolamide,<sup>26,30,31</sup> dorzolamide+timolol,<sup>13</sup> and carteolol+pilocarpine.<sup>28</sup> Travoprost was compared to latanoprost and timolol,<sup>10,15,16,18</sup> and bimatoprost was compared to timolol.<sup>24</sup> The dosage for all treatments and comparators was the same across the included studies. Meta-analyses were performed for the IOP change from baseline, withdrawals due to adverse events (AEs), ocular hyperemia and all other ocular AEs, respiratory and cardiac AEs potentially related to timolol, and serious AEs.

### *Reduction in IOP*

Statistically significant reductions in mean IOP from baseline were seen in patients using latanoprost compared with timolol at three months [n=984; WMD -1.26 (95% CI: -1.63, -0.89)],<sup>12,14,18-20,23</sup> six months [n=1,178; WMD -1.06 (95% CI: -1.64, -0.48)],<sup>18,19,21-23</sup> and 12 months [n=424; WMD -1.04 (95% CI: -1.63, -0.46)].<sup>18,19</sup> The reduction in mean IOP from baseline was significant with latanoprost compared with dorzolamide at three months [n=328; WMD -2.64 (95% CI: -3.25, -2.04)].<sup>26,30,31</sup> When compared with brimonidine, the reduction in mean IOP from baseline was not significant in the latanoprost group at three months [n=471; WMD -1.04 (95% CI: -3.01, 0.93)].<sup>11,17,27</sup> In small, low Jadad score studies, latanoprost was superior to betaxolol<sup>25</sup> and similarly effective as carteolol+pilocarpine.<sup>28</sup> One large, high-quality RCT indicated that latanoprost was similarly effective as dorzolamide+timolol.<sup>13</sup>

In the comparisons of travoprost and timolol, a statistically significant reduction in mean IOP from baseline was seen with travoprost at three months [n=951; WMD -1.21 (95% CI: -1.58, -0.85)]<sup>10,15,18</sup> and at six months [n=1,178; WMD -0.92 (95% CI: -1.25, -0.60)].<sup>15,16,18</sup> Bimatoprost showed statistically significant IOP reductions relative to timolol at the six-month follow-up (10.6 versus 7.5 mm Hg, p=0.003), although the evidence was limited to one small (n=60), low-quality study.<sup>24</sup>

### *Withdrawals due to AEs and serious AEs*

Withdrawals due to AEs were significantly higher in patients who received travoprost than in patients who received timolol, although this difference was small [risk difference (RD) 0.02 (95% CI: 0.01, 0.04)].<sup>15,16,18</sup> There were no other significant differences between PGAs and comparators.

There were no significant differences in the withdrawals due to AEs between PGAs and comparators.<sup>11,13-19,21-23,26,28-30</sup>

### *Ocular hyperemia and other ocular AEs*

In comparisons of latanoprost versus timolol, significant RDs were found in favour of timolol for ocular hyperemia [n=1,274; RD 0.09 (95% CI: 0.06, 0.12)]<sup>12,18-20,22,23</sup> and for other ocular AEs, excluding hyperemia [n=1,526; RD 0.06 (95% CI: 0.00, 0.12)].<sup>12,18,20-23</sup> In comparisons of travoprost versus timolol, significant RDs were found in favour of timolol for ocular hyperemia [n=1,364; RD 0.29 (95% CI: 0.25, 0.33)]<sup>10,15,16,18</sup> and for other ocular AEs [n=1,364; RD 0.15 (95% CI: 0.07, 0.23)].<sup>10,15,16,18</sup> A comparison of latanoprost versus brimonidine showed a significant RD in favour of latanoprost for ocular AEs, excluding hyperemia [n=803; RD 0.11 (95% CI: 0.05, 0.16)].<sup>11,17,29</sup>

### *Respiratory and cardiac AEs potentially related to timolol*

A meta-analysis of four studies involving 971 patients showed that, compared to latanoprost, timolol significantly increased the risk of respiratory and cardiac AEs [RD 0.02 (95% CI: 0.00, 0.03)].<sup>12,18,20,22</sup>

## 5 Economic Analysis

### *Literature Search*

Published literature was obtained by cross-searching MEDLINE<sup>®</sup>, BIOSIS Previews<sup>®</sup>, ToxFile, and EMBASE<sup>®</sup>, using a filter to restrict results to relevant economic records. A parallel search on PubMed and the Cochrane database was also conducted. Regular alerts were established to capture new studies and updates. A search was run on the Health Economic Evaluations Database (HEED) using a parallel-search strategy.

Of 65 articles retrieved, five<sup>32-36</sup> were considered to be eligible evidence for review. Eligible evidence for review included economic evaluations comparing PGAs with other IOP-lowering medications as first-line treatment. Two reports that were based on the results of published studies estimated the proportion of patients achieving IOP targets.<sup>35,36</sup> One study<sup>35</sup> found latanoprost to be less effective and more costly than bimatoprost. The other study<sup>36</sup> concluded that the most cost-effective strategy is to use timolol as first-line therapy and add bimatoprost if the IOP target is not met. Two additional studies used a retrospective chart review to compare latanoprost and beta-blockers,<sup>33</sup> and bimatoprost.<sup>32</sup> In one study, patients on latanoprost had better persistence of treatment and lower IOP compared with bimatoprost or beta-blockers, but beta-blockers led to lower overall costs.<sup>32</sup> The authors of the fifth study<sup>34</sup> performed cost-effectiveness and cost utility analyses in five European countries, comparing travoprost, latanoprost, and timolol in advanced glaucoma. Travoprost dominated latanoprost in all countries except France in the cost-effectiveness and cost-utility analyses.

### *Canadian Economic Evaluation*

The cost-effectiveness of PGAs was assessed using a decision-analytic model. Latanoprost was compared with timolol, dorzolamide, and brimonidine; travoprost was compared to timolol. The target population included patients over 18 years of age with elevated IOP and treated with a PGA or other glaucoma medication available in Canada. Effectiveness was measured by IOP reduction from baseline at three-month follow-up and by the incidence of study withdrawals due to AEs (unspecified time frame). The analysis was performed from the perspective of a public third-party payer (ministry of health) and only

costs assumed by a ministry of health were considered – specifically, medications used to reduce IOP and number of visits to a physician for the initial prescribing of treatment and for managing AEs. Probabilistic and univariate sensitivity analyses were conducted to assess the uncertainty and the robustness of the study results, including the impact of patients’ non-persistence on cost-effectiveness. Sensitivity analyses were performed with six- and 12-month endpoints, when available.

### ***Base Case***

Compared with timolol, latanoprost and travoprost were associated with increased costs and improved effectiveness (i.e., ICERs of C\$34.48/mm Hg reduced and C\$39.06/mm Hg reduced respectively). Compared with brimonidine, latanoprost had an ICER of C\$16.17/mm Hg reduced. Latanoprost was more effective and less costly than dorzolamide.

Base case results did not change from the probabilistic sensitivity analyses conducted on the reduction of IOP. Relative to dorzolamide, latanoprost remained in all cases a dominant strategy, and a positive ICER was found for all other comparisons.

### ***Sensitivity analyses for six- and 12-month endpoints***

Data were available on IOP reduction at six and 12 months. ICERs were calculated comparing timolol versus latanoprost and travoprost respectively. Compared with timolol, latanoprost had ICERs of C\$81.80 at six months and C\$168.06 at 12 months. At six months, travoprost had an ICER of \$110.61 compared with timolol.

### ***Persistence with treatment***

Cost-effective analyses were performed using estimates of persistence with a PGA from a study that assessed the proportion of patients who were persistent with their treatment after two years.<sup>37</sup> All other parameters were the same as in the base-case analyses. As was observed with the base-case analyses, latanoprost was a dominant strategy compared to dorzolamide (Table 2). All other ICERs remained positive, although they were lower than those estimated in the base case.

## **6 Limitations**

Clinical effectiveness data were derived from studies of mainly Caucasians and may not be representative of Canadian glaucoma patients. Different racial groups may have differential responses to IOP-lowering agents. In addition, the cost-effectiveness may vary in subgroups of patients with different diagnosis and treatment experience. Subgroup analysis was impossible because of insufficient data. These factors limit the generalizability of our findings.

IOP fluctuates during a 24-hour period, but four trials obtained only one IOP measurement. A clinically significant response, defined as reaching a target IOP or achieving a 20% or greater than 20% reduction in IOP from baseline, was evaluated in four RCTs. The short duration of follow-up and the use of IOP as a surrogate marker of damage make it difficult to extrapolate results to long-term clinical outcomes. With respect to cost-effectiveness analyses, it would have been preferable to evaluate IOP-lowering agents over a longer time, as patients diagnosed with glaucoma are usually treated for the remainder of their lives. Because the clinical outcomes in the retained studies were limited solely to the reduction of IOP, and the relationship between IOP reduction and changes in health-related quality of life are unclear, it is impossible to derive usable values for performing a cost-utility analysis.

<b>Table 2: ICERs – Base case and with persistence data</b>						
<b>Comparison</b>	<b>Base Case</b>			<b>With Persistence Data</b>		
	<b>Change in Cost (C\$)</b>	<b>Change in mm Hg Reduction</b>	<b>ICER (C\$/mm Hg reduced)</b>	<b>Change in Cost (C\$)</b>	<b>Change in mm Hg Reduction</b>	<b>ICER (C\$/mmHg reduced)</b>
timolol latanoprost	43.33	1.26	34.48	40.27	1.80	22.42
brimonidine latanoprost	22.84	1.41	16.17	21.72	1.54	14.07
dorzolamide latanoprost	-22.97	2.63	latanoprost dominant	-14.10	2.77	latanoprost dominant
timolol travoprost	40.02	1.02	39.06	37.60	1.75	21.53
timolol latanoprost (6 months)	87.85	1.07	81.80	81.66	1.71	47.46
timolol latanoprost (12 months)	176.39	1.05	168.06	163.98	1.59	103.36
timolol travoprost (6 months)	79.26	0.72	110.61	74.37	1.49	49.77

Relying on results from clinical trials may not reflect experiences in real life. In real life, persistence with treatment may be lower, and the incidence of AEs may be lower, given the patient selection criteria imposed by research protocols (although AEs are more likely to be reported because of the requirements of clinical trials). The incidence of AEs could affect the relative cost-effectiveness of treatments.

There was a lack of head-to-head studies comparing IOP-reducing agents, with timolol being the only comparator consistently used. The lack of available clinical data limited the scope of the economic evaluation to some of the IOP-lowering agents that are available in Canada and to their use as single-therapy, first-line agents, which is often not the case in clinical practice.

## 7 Health System Implications

It is estimated that the number of Canadians afflicted with vision loss will increase from 67,900 blind and 319,000 visually impaired persons in 2001, to 120,000 and 600,000 respectively in 2026 – an increase of 86% in the number of Canadians with significant vision loss.<sup>38</sup> Because glaucoma is the second most frequent cause of visual disability in Canada, cost-effective therapeutic options and correct policy decisions for therapeutic eye care are challenges.

The maximum effectiveness in glaucoma control requires the balancing of potential beneficial and adverse outcomes from treatment with tolerability and quality of life. The primary approach for disease management in patients with glaucoma is maximal use of drug therapy for the greatest reduction in IOP. The introduction of newer drug therapies may reduce or delay the requirement for more invasive treatments, such as surgery. The long-term benefits of avoiding or delaying surgery are unclear.

A potential increase in drug costs associated with newer therapies may be offset by incremental benefits, such as reductions in the number of visits to a physician and surgical procedures. These have implications for the patient, health care providers, and payers. A clear value must be established to gain acceptance and utilization from providers, and unrestricted reimbursement from payers.

## 8 Conclusion

As first-line therapy, latanoprost, travoprost, and bimatoprost all showed statistically significant reduction in IOP relative to timolol, although for bimatoprost, the evidence was limited to one small study of potentially limited validity. Compared with timolol, PGAs reduced the average IOP by 0.92 mm Hg to 1.48 mm Hg. Latanoprost was found to be significantly superior to dorzolamide, betaxolol, or combined therapy with carteolol+pilocarpine. One large, high-quality RCT indicated that latanoprost was similarly effective to combined therapy with dorzolamide+timolol. Latanoprost was not found to significantly reduce IOP compared with brimonidine. Neither travoprost nor bimatoprost were compared with other IOP-reducing agents. One study, which compared latanoprost versus brimonidine, examined a PGA as second-line therapy. Although long-term studies are lacking, current studies suggest that PGAs are well tolerated.

For the treatment of glaucoma and elevated IOP, latanoprost is a dominant strategy compared to dorzolamide and is cost-effective compared to brimonidine if it is assumed that reductions in IOP directly correspond to health benefit and that no threshold value for IOP reduction exists. Latanoprost and travoprost are more effective than timolol, but more expensive. From a cost-effectiveness standpoint, where timolol is not contraindicated, it would be preferable to start treatment with timolol and reserve the PGAs as alternative treatment or as add-on therapy for patients not achieving a clinical response with timolol. The better treatment persistence associated with PGAs improves their cost-effectiveness.

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