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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

Preservative-free latanoprost 50 µg/mL ophthalmic solution (Monoprost)

(Laboratoires Théa)

Indication: For the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

BAK	benzalkonium chloride
CDR	CADTH Common Drug Review
ICUR	incremental cost-utility ratio
IOP	intraocular pressure
ITC	indirect treatment comparison
OAG	open-angle glaucoma
OH	ocular hypertension
PGA	prostaglandin analogue
QALY	quality-adjusted life-year

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Preservative-free latanoprost (Monoprost)
Study Question	What is the cost-effectiveness of Monoprost compared with current prostaglandin analogues (PGA) in patients with ocular hypertension (OH) and open-angle glaucoma (OAG)?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Patients with OH and OAG
Treatment	Monoprost (50 mcg/mL)
Outcome	Quality-adjusted life-years (QALYs)
Comparators	Preserved PGAs: bimatoprost 0.01%, bimatoprost 0.03%, latanoprost, generic BAK-preserved latanoprost, travoprost, generic sofZia-preserved travoprost
Perspective	Canadian public health care payer
Time Horizon	Lifetime (41 years)
Results for Base Case	• Monoprost dominated (was less costly and more effective than) travoprost, branded BAK-preserved latanoprost, and bimatoprost 0.03%. • The ICURs for Monoprost were $21,178 per QALY compared with bimatoprost 0.01%; $139,148 per QALY compared with generic sofZia-preserved travoprost; and $217,790 per QALY compared with generic BAK-preserved latanoprost. • The manufacturer's sequential analysis indicated that Monoprost was the optimal therapy at a willingness to pay greater than or equal to $217,790 per QALY; if the willingness to pay is less than $217,791 per QALY, then generic BAK-preserved latanoprost is the optimal therapy. All other PGAs were dominated by generic BAK-preserved latanoprost.
Key Limitations	• There is uncertainty in the comparative clinical efficacy and safety of Monoprost compared with other PGAs, given the poor methodological quality and reporting limitations of the indirect treatment comparison (ITC). Although the ITC reported fewer hyperemia events in Monoprost, such pooled estimates may be inappropriate given the high levels of heterogeneity of hyperemia measurement. • The manufacturer used list prices for branded products, as opposed to the maximum price paid by the public drug plan (generally equivalent to the generic product). • The assumption of different adherence rates for preservative-free treatments was not appropriately justified and does not appear to be borne out based on trial data and other model assumptions. • The manufacturer's base case predominantly assessed the cost-effectiveness of Monoprost as first-line therapy. The cost-effectiveness of Monoprost compared with agents used after first-line therapy is currently unknown. • The model was not stable at the base case 5,000 iterations over multiple runs of the probabilistic analysis, increasing the uncertainty associated with the reported cost-effectiveness estimates. At 20,000 iterations, the model was stable. However, due to the long model run time, it was not feasible to test all reanalyses using such a large number of iterations.
CDR Estimate	• The CDR base case was undertaken based on revised comparator costs, equal adherence rates (67.5%), revising minor model errors, and increasing the number of iterations to 20,000. • Monoprost was the optimal therapy at a willingness to pay greater than or equal to $268,842 per QALY; if a decision-maker's willingness to pay is less than $268,842 per QALY, generic BAK-preserved latanoprost is the optimal therapy. All other PGAs were dominated. • The cost-effectiveness results are sensitive to hyperemia rate and mean IOP at 3 months across PGAs, IOP decrease in nonadherent patients, and transition probabilities from OH to OAG.

BAK = benzalkonium chloride; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; IOP = intraocular pressure; ITC = indirect treatment comparison; OAG = open-angle glaucoma; OH = ocular hypertension; PGA = prostaglandin analogues; QALY = quality-adjusted life-year.

Drug	Preservative-free latanoprost (Monoprost)
Indication	Reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Reimbursement Request	As per indication
Dosage Form	Solution / 50 µg/mL
NOC Date	2016-07-07
Manufacturer	Laboratoires Théa

Executive Summary

Background

Preservative-free latanoprost (Monoprost) is available as a sterile ophthalmic solution in a single-dose container (50 mcg/mL). Health Canada approved Monoprost for the reduction of intraocular pressure (IOP) in patients with ocular hypertension (OH) or open-angle glaucoma (OAG).[1] The manufacturer is requesting that Monoprost be reimbursed as per the Health Canada–approved indication. The recommended dose is one drop in the affected eye(s) once daily.[1] The manufacturer-submitted price was $20.54 per pack of 30 single-use containers, corresponding to a price of $0.68 per day.[2]

The manufacturer submitted a cost-utility analysis based on a decision tree and a Markov model, comparing Monoprost with other prostaglandin analogues (PGAs) for the treatment of patients with OH or OAG (bimatoprost 0.01%, bimatoprost 0.03%, sofZia-preserved travoprost, and benzalkonium chloride [BAK]-preserved latanoprost). The analysis was carried out from the Canadian public payer perspective over a lifetime horizon (i.e., 41 years). Baseline characteristics were based on the pivotal trial of Monoprost, with patients entering the model at a mean age of 64 years.[3] All patients were assumed to have both eyes treated. A decision tree was used to reflect patients moving through alternative therapies, if they did not respond to their initial treatment, until they found an optimal treatment. The decision tree has a time horizon of one year.[3] At the end of the decision tree, patients entered the Markov model and cycled through the model at one-year cycles. The Markov model was used to predict the long-term progression of the disease through six health states: OH, mild OAG, moderate OAG, advanced OAG, blindness, and death.[3] The model assumed that changes in IOP affected only the risk of progression from OH to mild OAG but did not affect transition probabilities in the more severe health states (e.g., from the mild OAG to blindness health states).[3] The comparative safety and efficacy of first-line Monoprost compared with other available PGAs were obtained from a published indirect treatment comparison (ITC),[4] while the efficacy and safety of the second-line monotherapy and biotherapy were obtained from a different ITC (Orme et al.).[5] Health state utility values were derived from published literature, while the utility decrement due to hyperemia (10% decrease) was based on European expert opinion. Resource use and health system costs were derived from Canadian data sources.

In the manufacturer's probabilistic base-case analysis, Monoprost was associated with lower costs and greater gain in quality-adjusted life-years (QALYs) than all the branded PGAs except bimatoprost 0.01%, i.e., Monoprost is dominant. Compared with bimatoprost 0.01%, Monoprost was associated with an incremental cost-utility ratio (ICUR) of $21,178 per QALY gained. Compared with generic PGA therapies, the ICUR for Monoprost ranged from $139,148 per QALY (generic sofZia-preserved travoprost) to $217,790 per QALY (generic BAK-preserved latanoprost).[3]

Based on the manufacturer's sequential analysis, Monoprost was the optimal therapy at a willingness to pay greater than or equal to $217,790 per QALY. If the willingness to pay for one QALY is less than $217,791, generic BAK-preserved latanoprost is the optimal therapy. All other PGAs were dominated by generic BAK-preserved latanoprost.[3]

Summary of Identified Limitations and Key Results

CADTH Common Drug Review (CDR) identified several key limitations relating the manufacturer's model. First, there is uncertainty in the comparative efficacy and safety of Monoprost compared with other PGAs, given the poor methodological quality of the studies included in the published ITC. CDR did note that the point estimates from the ITC indicated that Monoprost may be less effective in reducing IOP than other PGAs, although these numerical differences were not statistically significant.

CDR also noted that the manufacturer incorrectly used the full price of the branded travoprost, BAK-preserved latanoprost, and latanoprost-timolol (second-line) treatments, as opposed to the price paid by the public payer, which is lower, given the availability of generic products. CDR revised the costs to align with the price paid by the public payer.

Furthermore, several assumptions had notable uncertainty, particularly the assumption that adherence will be greater with preservative-free treatments than with preserved treatments. This assumption was based on input from European experts, but no justification was provided for the difference in adherence rates. Data from the available trials indicated no difference in adherence, and the clinical expert consulted by CDR noted that the lack of difference in rates of ocular surface disease does not support the assumption of different adherence rates.

Finally, the manufacturer's base-case analysis was not reproducible over multiple model runs at 5,000 iterations, with the results varying notably. CDR increased the number of iterations to 10,000 and observed the same issue. The model results appeared to be stable at 20,000 iterations. However, due to the model run time, it was not feasible to use this number of iterations for the scenario analyses.

The CDR base case was undertaken using revised comparator costs and equal adherence rates (67.5%), correcting minor model errors, and increasing the number of iterations to 20,000. The CDR base case indicated that Monoprost was the optimal therapy at a willingness to pay greater than or equal to $268,842 per QALY; if a decision-maker's willingness to pay is less than $268,842 per QALY, generic BAK-preserved latanoprost is the optimal therapy. All other PGAs were dominated.

Conclusions

When considering all PGAs licensed in Canada, CDR found that Monoprost was not cost-effective compared with other PGAs, based on the CDR base case. A price reduction of more than 50% is required for Monoprost to achieve an ICUR of $50,000 per QALY compared with BAK-preserved latanoprost.

The results of CDR's revised base case should be interpreted with caution. There was significant uncertainty regarding the comparative safety and efficacy of Monoprost compared with other PGA therapies, particularly regarding the perceived benefits associated with a potential reduction in hyperemia.

There is limited evidence that Monoprost warrants a price premium over other available PGAs for the treatment of OH or OAG. A price reduction of approximately 65% is required for Monoprost to be priced equivalently to BAK-preserved latanoprost on a per drop basis.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a cost-utility analysis from the perspective of a Canadian health care payer with a lifetime horizon. The model compared Monoprost with four branded and two generic prostaglandin analogues (PGAs) licensed in Canada: bimatoprost 0.1%, bimatoprost 0.03%, latanoprost, and travoprost, as well as generic latanoprost and generic travoprost. Bimatoprost and latanoprost contain the preservative agent benzalkonium chloride (BAK), while travoprost contains the preservative sofZia.[3]

The target population was patients with ocular hypertension (OH) or open-angle glaucoma (OAG). The patient cohort was aligned with the safety population from the Monoprost group in the pivotal study[6] (mean age 63.4 years, 54% female, mean intraocular pressure (IOP) at baseline 24.1 mm Hg), while the distribution of disease severity was based on a Canadian cross-sectional study.[7] All costs and outcomes were discounted at an annual rate of 1.5%.[3] Patients were assumed to have both eyes treated throughout the model.

The model used a decision tree and a cohort multi-state Markov model developed in Microsoft Excel. At the start of the model, patients with OH or OAG entered a decision tree and received one of the available PGAs as the first-line monotherapy. Based on the results of a published network meta-analysis and indirect treatment comparison (ITC),[4] these patients could experience full response, partial response, no response, or could not tolerate treatment. Responders continued the existing treatment, partial responders received additional therapies until laser therapy was required (second-line bi-therapy), and nonresponders and those who were intolerant to the first-line therapy switched to second-line monotherapy. The safety and efficacy of the second- and third-line therapies were based on another published ITC.[5] The model allowed a maximum of three consecutive lines of treatment in the decision tree before laser trabeculoplasty was performed. Response to therapy was assessed using IOP. For the first-line treatments, it was assumed that an IOP decrease of at least 25% from the baseline represented treatment response. If the IOP decrease was between 15% and 25%, this was considered a partial response. Any decrease lower than 15% represented nonresponse. For treatments prescribed after the first-line monotherapy, a decrease in IOP of 20% was considered a response.[3]

At the end of the first year, patients with OH or OAG entered a Markov model and could progress across six health states: OH, mild OAG, moderate OAG, advanced OAG, blindness, and death. The cycle length was one year.[3] The transition from OH to mild OAG depended on IOP and was based on a Dutch cost-effectiveness study that reported annual conversion rates in patients treated with timolol and latanoprost.[8] However, transition probabilities from mild OAG to the more severe glaucoma health states did not depend on the level of IOP and were constant over time. The manufacturer assumed that patients who adhered to the therapy had a slower increase in IOP and therefore slower progression from OH to mild OAG. Based on European expert opinion, adherence was assumed to be higher for preservative-free treatments compared with treatments with a preservative (80% versus 68%). Mortality rates were based on general Canadian population data. Health utility values attributed to the severity of disease were derived from a European study[9] that reported utility derived from the Health Utility Index Mark 3 (HUI-3), and the utility decrement associated

with hyperemia was based on European expert opinion. The manufacturer included treatment (drugs and laser) and disease progression costs. The manufacturer obtained direct health care costs from publicly available sources in Ontario. The costs specific to glaucoma health states were obtained from a Canadian cost study.[10] All costs were reported in 2016 Canadian dollars.

Manufacturer's Base Case

The manufacturer's probabilistic base-case analysis indicated that Monoprost was associated with lower costs and greater quality-adjusted life-years (QALYs) gained compared with the majority of the branded PGAs but was more costly than the generic PGAs. The incremental cost-utility ratios ICURs are reported in Table 2.

Table 2: Summary of Results of the Manufacturer's Base Case

	Total Costs ($)	Incremental Cost ($)[a]	Total QALYs	Incremental QALYs[a]	Incremental Cost per QALY[a]
Monoprost	24,830	–	13.1823	–	–
Bimatoprost 0.01%	24,393	–437	13.1617	–0.0206	$21,178
Bimatoprost 0.03%	24,918	88	13.1556	–0.0268	Monoprost dominates
Travoprost	28,421	3,591	13.1683	–0.0140	Monoprost dominates
Generic sofZia-preserved travoprost	22,876	–1,953	13.1683	–0.0140	$139,148
Latanoprost	25,059	229	13.1731	–0.0092	Monoprost dominates
Generic BAK-preserved latanoprost	22,827	–2,003	13.1731	–0.0092	$217,790

BAK = benzalkonium chloride; QALY = quality-adjusted life-year.

[a] Compared with Monoprost.

Source: Manufacturer's pharmacoeconomic submission.[3]

The manufacturer also reported the results of a sequential analysis. This involves comparisons of less costly comparators with the next most costly comparator and the exclusion of all comparators that are either dominated or subject to extended dominance. The sequential analysis indicated that Monoprost was the optimal therapy at a willingness to pay threshold greater than $217,790; if a decision-maker's willingness to pay for one QALY gained is less than $217,791, generic BAK-preserved latanoprost is the optimal therapy. All other PGAs were dominated, based on findings from the manufacturer's probabilistic analysis (Table 3, Figure 3).

Table 3: Results of Sequential Incremental Cost-Effectiveness Ratio Analysis From the Manufacturer's Base Case

	Total Costs ($)	Total QALYs	Incremental Cost per QALY Gained Versus Generic BAK-Preserved Latanoprost	Sequential ICUR ($/QALY)
Nondominated options				
Generic BAK-preserved latanoprost	$22,827	13.1731	–	–
Monoprost	$24,830	13.1823	$217,790	$217,790
Dominated options				
Generic sofZia-preserved travoprost	$22,876	13.1683	Dominated by generic BAK-preserved latanoprost	
Bimatoprost 0.01%	$24,393	13.1617	Dominated by generic BAK-preserved latanoprost	
Bimatoprost 0.03%	$24,918	13.1556	Dominated by generic BAK-preserved latanoprost	
BAK-preserved latanoprost	$25,059	13.1731	Dominated by generic BAK-preserved latanoprost	
sofZia-preserved travoprost	$28,421	13.1683	Dominated by generic BAK-preserved latanoprost	

BAK = benzalkonium chloride; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Note: All costs are presented in 2016 Canadian dollars.

Source: Manufacturer's pharmacoeconomic submission.[3]

Summary of Manufacturer's Sensitivity Analyses

The manufacturer undertook scenario analyses varying the following parameters: discount rate (0% and 3%), time horizon (20 years), adherence (assumed similar adherence rate between patients receiving preservative-free and preserved treatments), disutility value (assumed no utility decrement due to hyperemia), long-term hyperemia (assumed no patient experiencing noticeable hyperemia in the long term), and impact of nonadherence on IOP (assumed no association between adherence rate and IOP).[3] The results of the scenario analyses suggested that the proportion of patients who experienced long-term hyperemia, disutility due to hyperemia, and IOP level at baseline for nonadherent patients were the three main drivers of the cost-effectiveness results.

The uncertainty around most input parameters was assumed to be 20% of their mean values. The uncertainty observed in the probabilistic results may not fully reflect the actual uncertainty around parameters used in the model. This arbitrary assumption of a certain feasible range is unlikely to be sufficient, since a parameter with low sensitivity, but high uncertainty, could easily have more impact on the model output than a more sensitive parameter estimated more precisely.

Limitations of Manufacturer's Submission

CDR identified the following key limitations of the manufacturer's model.

- **There is notable uncertainty in the comparative efficacy and safety of Monoprost compared with other PGAs.** The comparative efficacy (mean IOP at three months) and safety (hyperemia rate) of Monoprost compared with other PGAs as first-line treatment

was obtained from a published ITC. However, the CADTH Common Drug Review (CDR) Clinical Review team identified several limitations with the methodological quality of this ITC (see CDR Clinical Review Report). Importantly, the ITC did not report whether risk of bias of included studies was assessed. There was notable variation in the methods for measuring IOP and determining hyperemia across included studies. CDR tested the impact of this uncertainty by assuming no difference in mean IOP and hyperemia rates at three months across PGAs in scenario analyses. Despite these limitations, the ITC suggested Monoprost may be associated with a lower incidence of conjunctival hyperemia but may also be slightly less effective in lowering IOP compared with the comparator treatments (although the results were not statistically significant).

- **Incorrect pricing of comparator products.** The manufacturer used incorrect prices for branded travoprost, BAK-preserved latanoprost, and latanoprost-timolol, using the list price of these products, not the price paid by the public payer. CDR revised the costs to align with the price paid by the Ontario public drug plan. CDR noted some differences in the public price of the comparator treatments across the public drug plans.
- **Difference between adherence rates for preserved and non-preserved PGAs not justified.** The manufacturer assumed that 67.5% of patients on preserved treatments would be adherent, while 80% of patients on preservative-free treatments would be adherent. These rates were obtained through feedback from European clinical experts. However, justification for this assumption was not provided, and the data from studies of preservative-free treatments have not shown a significant reduction in the symptoms of ocular surface disease. Therefore, the assumption of greater adherence for preservative-free treatment is uncertain. The uncertainty inherent in this parameter has been addressed in scenario analyses through probabilistic methods.
- **Impact on hyperemia is uncertain.** The manufacturer obtained feedback from European experts regarding the impact of hyperemia, although whether these assumptions are generalizable to the Canadian setting is uncertain. The clinical expert consulted by CDR indicated, based on Canadian practice, that the assumption that 20% of patients who experience hyperemia during the decision tree phase of the model switch treatment was likely an overestimate. During the Markov model component, the manufacturer assumed that 5% of OH and OAG patients experienced hyperemia that had an impact on their quality of life (using a disutility value) and yet continued their treatment. This assumption has not been supported by published evidence. In the remaining 95% of patients, the manufacturer assumed that the hyperemia was transient and no disutility was applied.
- **Model lacked stability.** CDR noted that, at 5,000 iterations, the results varied notably upon different model runs. CDR increased the number of iterations to 10,000 and observed the same issue (CDR base case ranged from $235,000 per QALY to $285,000 per QALY over six model runs). The model results appeared to be stable at 20,000 iterations (based on three model runs). However, due to the model run time, it was not feasible to use this number of iterations to test the scenario analyses.

Other limitations identified by CDR include the following:

- **Use of multiple PGAs and use of Monoprost as subsequent PGA are uncertain.** The manufacturer's base case predominantly assessed the cost-effectiveness of Monoprost as the first-line therapy. It was assumed that Monoprost was equally effective as the other PGAs in subsequent lines of treatment. Although this is likely to be appropriate, according to feedback from the clinical expert consulted by CDR, it is

associated with some uncertainty, given that Monoprost has not been compared with other PGAs as subsequent therapy. Furthermore, based on feedback from the clinical expert consulted by CDR (and the European experts consulted by the manufacturer), the assumption that a patient might receive three different PGAs before an alternative treatment class/option is unlikely to reflect clinical practice. Due to the model structure, CDR was unable to test the impact of this limitation in the model.

- **The annual probability of progressing to blindness from advanced OAG may be overestimated.** The clinical expert consulted by CDR indicated that the annual risk of blindness among patients with advanced OAG is approximately 1%, which was supported by Peters et al.,[11] reporting that the 10-year incidence of blindness from glaucoma was 26.5% for one eye and 5.5 % for both eyes. CDR assessed this limitation by reducing the annual risk of blindness to 1% in the CDR reanalyses, although this change appeared to have minimal impact on the ICUR.
- **The costs of ophthalmologist consultations and laser therapy may be overestimated.** The clinical expert consulted by CDR suggested that the costs of ophthalmologist consultations and laser therapy were too high and did not represent actual practice. CDR tested alternative costs in a scenario analysis.
- **The model assumed no drug wastage for all PGAs.** The manufacturer multiplied PGA costs per day by 30 days and 12 months to estimate the total costs of each PGA per year. This assumption may have minimal impact on Monoprost, given that this drug is packaged in single-use vials. For other PGAs, patients may need more than one drop if the dose is misapplied to the eye. Assuming no drug wastage would slightly underestimate the total costs of all PGAs. CDR was unable to test this limitation, as the submitted model only allows drug wastage in the decision tree component (first year) but not in a Markov model component.
- **Methods used to derive progression from OH to mild OAG were not transparent and may not be applicable to the Canadian population.** The manufacturer obtained IOP and annual transition probabilities from OH to mild OAG from a published cost-effectiveness study. Notably, this cost-effectiveness study did not provide the details of methods used to estimate or synthesize these transition probabilities from 11 cited references published between 1977 and 2003. There was also wide variation in interventions being evaluated in these cited references, including (but not limited to) topical timolol, timolol, betaxolol, and placebo. CDR was unable to assess the direct impact of this limitation because of the paucity of data. However, CDR assessed the uncertainty of this equation by refitting the IOP against transition probabilities from OH to mild OAG with a third-degree polynomial equation (transition probabilities = $-0.0000027105 \times IOP^3 + 0.0003087576 \times IOP^2 - 0.0063674411 \times IOP + 0.0351285220$). This equation has a slightly better fit than a second-degree polynomial that used in the submitted model ($R^2 = 0.99967$).

CDR detected minor errors in the submitted model relating to the cost calculations (e.g., using 30 days to represent a month), and estimation of standard deviations (linked to incorrect parameters) which were rectified in the CDR reanalyses.

CADTH Common Drug Review Reanalyses

CDR undertook the base-case reanalysis using the revised cost of the comparator treatments, as well as correcting the minor model errors, assuming equal adherence for preservative-free and preserved treatments (67.5%) and increasing the number of iterations to 20,000 to attempt to increase model stability. Subsequent scenario analyses were undertaken using 10,000 iterations.

Table 4: CDR Base Case

	Total Costs ($)	Total QALYs	Incremental Cost per QALY Gained Versus BAK-Preserved Latanoprost	Sequential ICUR ($/QALY)
Nondominated options				
Generic/branded BAK-preserved latanoprost	$22,759	13.1950	–	–
Monoprost	$24,795	13.2026	$268,842	$268,842
Dominated options				
Generic/branded sofZia-preserved travoprost	$22,804	13.1894	Dominated by BAK-preserved latanoprost	
Bimatoprost 0.01%	$24,341	13.1833	Dominated by BAK-preserved latanoprost	
Bimatoprost 0.03%	$24,874	13.1775	Dominated by BAK-preserved latanoprost	

BAK = benzalkonium chloride; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Note: All costs are presented in 2016 Canadian dollars.

CDR's revised base case ICUR (Table 4) was greater than the manufacturer's base case (Table 3).

Results of CDR reanalyses focusing on individual parameters are shown in Appendix 5. The most influential parameter was comparative hyperemia rates and mean IOP at three months across PGAs, IOP decrease in nonadherent patients, and transition probabilities from OH to OAG.

CDR undertook a price-reduction analysis based on the manufacturer's and CDR's revised base case, assuming proportional price reductions for Monoprost (Table 5). A price reduction for Monoprost of greater than 50% was required to achieve an ICUR of less than $50,000 per QALY compared with BAK-preserved latanoprost. A price reduction of between 60% and 70% was required for Monoprost to become less costly and more effective (dominant) than BAK-preserved latanoprost.

Table 5: CDR Reanalysis: Price-Reduction Scenarios

Sequential ICURs for Monoprost Versus All PGAs Licensed in Canada		
Price	**Manufacturer's Base Case**	**CDR's Revised Base Case**
Submitted	If WTP < $217,790: BAK-preserved latanoprost is optimal If WTP > $217,790: Monoprost is optimal	If WTP < $268,842: BAK-preserved latanoprost is optimal If WTP > $268,842: Monoprost is optimal
20% reduction	If WTP < $168,834: BAK-preserved latanoprost is optimal If WTP > $168,834: Monoprost is optimal	If WTP < $184,938: BAK-preserved latanoprost is optimal If WTP > $184,938: Monoprost is optimal
40% reduction	If WTP < $82,742: BAK-preserved latanoprost is optimal If WTP > $82,742: Monoprost is optimal	If WTP < $102,416: BAK-preserved latanoprost is optimal If WTP > $102,416: Monoprost is optimal
50% reduction	If WTP < $50,017: BAK-preserved latanoprost is optimal If WTP > $50,017: Monoprost is optimal	If WTP < $59,137: BAK-preserved latanoprost is optimal If WTP > $59,137: Monoprost is optimal
60% reduction	If WTP < $15,309: BAK-preserved latanoprost is optimal If WTP > $15,309: Monoprost is optimal	If WTP < $19,032: BAK-preserved latanoprost is optimal If WTP > $19,032: Monoprost is optimal
70% reduction	Monoprost is dominant	Monoprost is dominant

BAK = benzalkonium chloride; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; PGA = prostaglandin analogues; WTP = willingness to pay.

CDR also considered an analysis assuming equal treatment efficacy and safety, assessing the cost of each treatment per drop (Table 6). The results suggest that a price reduction of approximately 65% is required to be equivalent to the least costly PGA on a per drop basis. However, CDR acknowledges the uncertainty regarding the number of drops per bottle; therefore, the results of this analysis should be interpreted with caution.

Table 6: CDR Scenario Analysis: Price per Drop

Drug	Cost per Pack ($)	Drops per Pack	Cost per Drop ($)	Price Reduction Required for Monoprost for It to Be Equivalent
Monoprost	20.5350	30	0.6845	N/A
Bimatoprost 0.01%	27.5808	45	0.6129	10%
Bimatoprost 0.03%	58.0800	80	0.7260	N/A
Generic/branded sofZia-preserved travoprost	10.0660	40	0.2517	63%
Generic/branded BAK-preserved latanoprost	9.5830	40	0.2396	65%

BAK = benzalkonium chloride; N/A = not applicable.

Note: Based on Ontario costs.

Issues for Consideration

- Drop size/total drops per bottle varies among treatments: There is variability in drop volume among comparator treatments. As Monoprost is available as a single-dose vial, wastage may be minimized compared with comparator treatments.
- Use of Monoprost in practice: The clinical expert consulted by CDR noted that there is a high probability that the drug will be used as first-line therapy, which may add to the cost of treatment for OH or OAG, given the disparity between the submitted price of Monoprost and the amount public drug plans pay for other PGAs.

Patient Input

No patient input was received for this submission.

Conclusions

When considering all PGAs licensed in Canada, CDR found that Monoprost was not cost-effective compared with other PGAs based on the CDR base case. A price reduction of more than 50% is required for Monoprost to achieve an ICUR of $50,000 per QALY compared with BAK-preserved latanoprost.

The results of CDR's revised base case should be interpreted with caution. There was significant uncertainty regarding the comparative safety and efficacy of Monoprost compared with other PGA therapies, particularly regarding the perceived benefits associated with a potential reduction in hyperemia.

There is limited evidence that Monoprost warrants a price premium over other available PGAs for the treatment of OH or OAG. A price reduction of approximately 65% is required for Monoprost to be priced equivalently to BAK-preserved latanoprost on a per drop basis.

Appendix 1: Cost Comparison

The comparators presented in Table 7 and Table 8 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice, rather than actual practice. Comparators are not restricted to drugs but may include devices or procedures. Costs are manufacturer's list prices unless otherwise specified. Existing Product Listing Agreements are not reflected in the table; as a result, costs may not represent the actual costs to public drug plans.

Table 7: Cost Comparison Table for Prostaglandin Analogues for Ocular Hypertension or Open-Angle Glaucoma

Drug / Comparator	Dosage Form	Size	Price per Bottle	Price ($/mL)	Recommended Dose[a]	Cost per Day ($)
Latanoprost 50 mcg/mL (Monoprost)	**Ophthalmic solution, single-use containers**	**30 containers, 0.2 mL**	**20.5350[b]**	**3.422**	**One drop daily**	**0.6845**
Prostaglandin Analogues						
Bimatoprost 0.03% (Vistitan)	Ophthalmic solution	3 mL 5 mL	27.5808 45.9680	9.19	One drop daily	0.5253
Bimatoprost 0.01% (Lumigan RC)	Ophthalmic solution	5 mL 7.5 mL	58.0800 87.1200	11.62	One drop daily	0.6638
Latanoprost 0.005% (generics)	Ophthalmic solution	2.5 mL	9.5830	3.83	One drop daily	0.2190
Travoprost 0.003% (Izba)	Ophthalmic solution	5 mL	20.1300[c]	4.03	One drop daily	0.2301
SofZia-preserved travoprost 0.004% (generics)	Ophthalmic solution	2.5 mL 5 mL	10.0660 20.1320	4.03	One drop daily	0.2301

Note: All prices are from the Ontario Drug Benefit Formulary (accessed May 12, 2017) unless otherwise indicated and do not include dispensing fees. Assumes drop sizes were the same across treatments (35 drops/mL). Daily cost assumes treatment of both eyes.

[a] Recommended dose is for each affected eye.

[b] Manufacturer-submitted price.

[c] IQVIA Delta PA wholesale price (Nov. 2017).

Table 8: Other Eye Drops for Ocular Hypertension or Open-Angle Glaucoma

Drug / Comparator	Dosage Form	Size	Price per Bottle	Price ($/mL)	Recommended Dose[a]	Cost per Day ($)
Alpha-2 Adrenergic Agonists						
Apraclonidine 0.5% (Iopidine)	Ophthalmic solution	5 mL	23.8300[b]	4.77	One drop two to three times daily	0.5447 to 0.8170
Brimonidine P 0.15% (generic)	Ophthalmic solution	5 mL 10 mL 15 mL	9.3675[b] 18.7350[b] 28.1025[b]	1.87	One drop three times daily	0.3212
Brimonidine 0.2% (generic)	Ophthalmic solution	5 mL 10 mL 15 mL	5.7750[b] 11.5500[b] 17.3250[b]	1.16	One drop twice daily	0.1320
Beta Blockers						
Betaxolol 0.25% (Betoptic S)	Ophthalmic solution	10 mL	25.5800	2.56	One drop twice daily	0.2923
Levobunolol 0.5% (Betagan)	Ophthalmic solution	10 mL	35.2580	3.53	One drop twice daily	0.4029
Timolol 0.25% (generic)	Ophthalmic solution	5 mL 10 mL	4.8390 9.6780	0.97	One drop twice daily	0.1106
Timolol 0.5% (generic)	Ophthalmic solution	5 mL 10 mL	6.0725 12.1450	1.21	One drop twice daily	0.1388
Carbonic Anhydrase Inhibitors						
Brinzolamide 1% (Azopt)	Ophthalmic solution	5 mL	17.7800	3.56	One drop two to three times daily	0.4064 to 0.6096
Dorzolamide 2% (generic)	Ophthalmic solution	5 mL	15.35	3.07	One drop three times daily	0.5263
Miotics						
Pilocarpine 1% (Isopto Carpine)	Ophthalmic solution	15 mL	3.5100	0.23	Two drops three to four times daily	0.0401 to 0.0535
Pilocarpine 2% (Isopto Carpine)	Ophthalmic solution	15 mL	4.0995	0.27		0.0469 to 0.0625
Pilocarpine 4% (Isopto Carpine)	Ophthalmic solution	15 mL	4.6590	0.31		0.0532 to 0.0710
Dual Therapies						
Brimonidine/timolol 0.2%/0.5% (Combigan)	Ophthalmic solution	10 mL	43.6145	4.36	One drop twice daily	0.4985
Brinzolamide/brimonidine 1.0%/0.2% (Simbrinza)	Ophthalmic solution	10 mL	46.8100	4.68	One drop twice daily	0.5350
Brinzolamide/timolol 1%/0.5% (Azarga)	Ophthalmic solution	5 mL	23.3500	4.67	One drop twice daily	0.5337
Dorzolamide/timolol 2%/0.5% (generics)	Ophthalmic solution	10 mL	20.9510	2.10	One drop twice daily	0.2394

Drug / Comparator	Dosage Form	Size	Price per Bottle	Price ($/mL)	Recommended Dose[a]	Cost per Day ($)
Latanoprost/timolol 50 mcg/5 mg/mL (generics)	Ophthalmic solution	2.5 mL	11.0700	4.43	One drop daily	0.2530
Travoprost/timolol (DuoTrav PQ)	Ophthalmic solution	5 mL	68.0600	13.61	One drop daily	0.7778

Note: All prices are from the Ontario Drug Benefit Formulary (accessed May 12, 2017) unless otherwise indicated and do not include dispensing fees. Assumes drop sizes were the same across treatments (35 drops/mL). Daily cost assumes treatment of both eyes.

[a] Recommended dose is for each affected eye.

[b] Saskatchewan formulary (Nov. 2017).

Appendix 2: Summary of Key Outcomes

Table 9: When Considering Only Costs, Outcomes and Quality of Life, How Attractive Is Monoprost Relative to Other PGAs Licensed in Canada?

Monoprost Versus Other PGAs Licensed in Canada	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	N/A
Costs (total)				X		
Drug-treatment costs alone				X		
Clinical outcomes			X			
Quality of life			X			
Incremental CE ratio or net benefit calculation	• Monoprost was the optimal therapy at a willingness to pay threshold greater than or equal to $268,842 per QALY. • If a decision-maker's willingness to pay for one QALY gained is less than $268,842, generic BAK-preserved latanoprost is the optimal therapy. • All other PGAs were dominated.					

BAK = benzalkonium chloride; CE = cost-effectiveness; N/A = not applicable; PGA = prostaglandin analogue; QALY = quality-adjusted life-year.

Note: Based on the CDR base case.

Appendix 3: Additional Information

Table 10: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?			X
Comments	As noted in the limitations section, CDR has concerns about the uncertainty in the comparative safety and efficacy of Monoprost and other PGAs and about the method used to derive annual progression from OH to mild OAG. The model contains some coding errors (e.g., the same input parameters were referred to multiple cells). This made it challenging to assess the validity of the manufacturer's results and undertake CDR reanalyses. Because of lack of model stability, CDR was unable to replicate several scenario analyses conducted by the manufacturer.		
Was the material included (content) sufficient?		X	
Comments"	The manufacturer did not provide sufficient details regarding data source(s) or methods used to calculate the number of drops per container.		
Was the submission well organized and was information easy to locate?		X	
Comments	None		

Table 11: Author Information

Authors of the pharmacoeconomic evaluation submitted to CDR

☐ Adaptation of global model/Canadian model done by the manufacturer

☒ Adaptation of global model/Canadian model done by a private consultant contracted by the manufacturer

☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the manufacturer

☐ Other (please specify)

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document			X
Authors had independent control over the methods and right to publish analysis	X		

Appendix 4: Summary of Other Health Technology Assessment Reviews of Drug

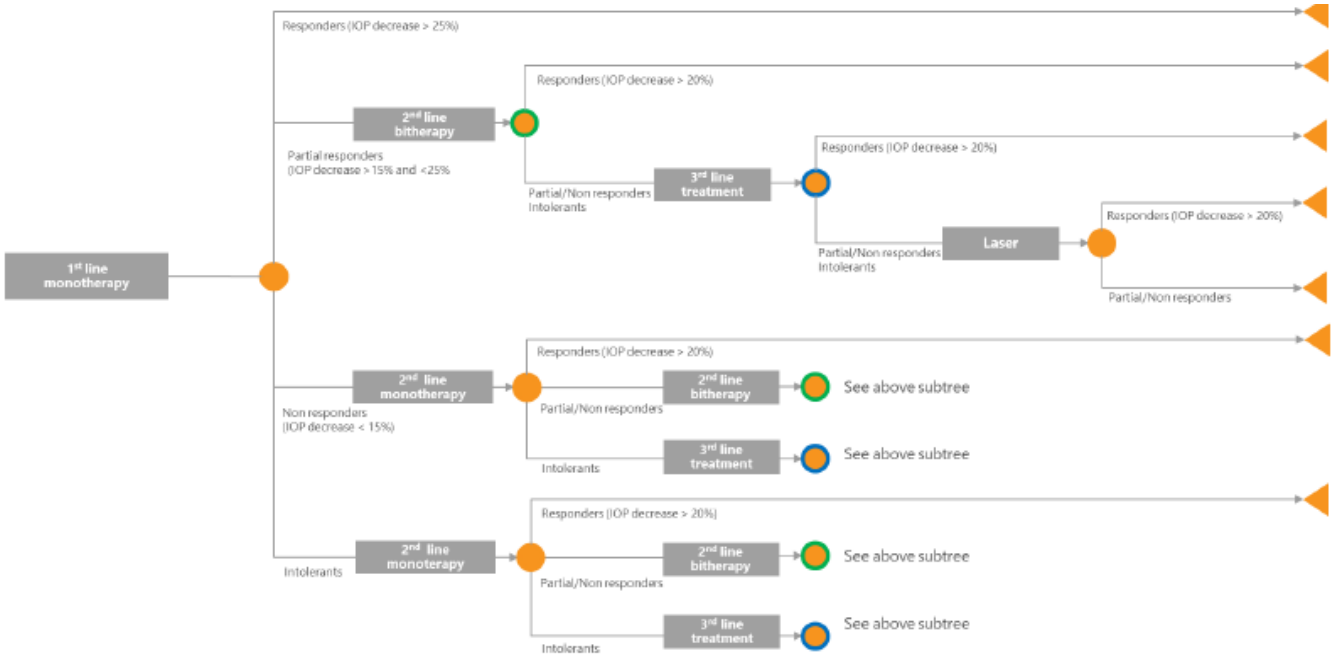
Monoprost has been reviewed by other Health Technology Assessment agencies, including the Scottish Medicines Consortium (SMC) and Haute Autorité de Santé (HAS) in France, for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. SMC recommended Monoprost be reimbursed in patients who have proven sensitivity to the preservative benzalkonium chloride, noting that “this preparation is substantially more expensive than the equivalent generic multi-dose eye drop preparation with preservative.”[12] HAS also recommended Monoprost be reimbursed for first-line treatment of open-angle glaucoma or ocular hypertension at a reimbursement rate of 65%, noting the benefits of a preservative-free product compared with products with preservative.[13]

Appendix 5: Reviewer Worksheets

Manufacturer's Model Structure

The manufacturer used a decision tree to estimate therapeutic adjustments during the first year of treatment, based on intraocular pressure (IOP) response and adverse events (Figure 1). In the decision-tree portion, the manufacturer assumed that patients would have a follow-up consultation every 2.4 months to assess the IOP response and tolerability of initial treatment. At these visits, patients were categorized into four groups based on their IOP response and the occurrence of hyperemia: responders (IOP decrease > 25%), partial responders (IOP decrease > 15% and < 25%), nonresponders (IOP decrease < 15%), and intolerants (Figure 1).[3] The patient cohort was aligned with the safety population from the Monoprost group in the pivotal study[6] (mean age 63.4 years, 54% female, mean IOP at baseline 24.1 mm Hg), while the distribution of disease severity was based on a Canadian cross-sectional study.[7] Treatment effects representing efficacy and safety of Monoprost compared with other prostaglandin analogues (PGAs) were derived from a network meta-analysis that reported the difference in mean IOP at three months following the initiation of the first-line PGA comparators. A microsimulation was used to estimate the rate of responders; IOP was assumed to follow a gamma distribution (shape parameter =1/θ, scale parameter =θ). The standard deviation of each PGA comparator was assumed to be equal to that observed for Monoprost (14.3% of the mean), as standard deviations were not reported in the network meta-analysis.

Figure 1: Decision-Tree Structure Representing Response to and Tolerability of Prostaglandin Analogues



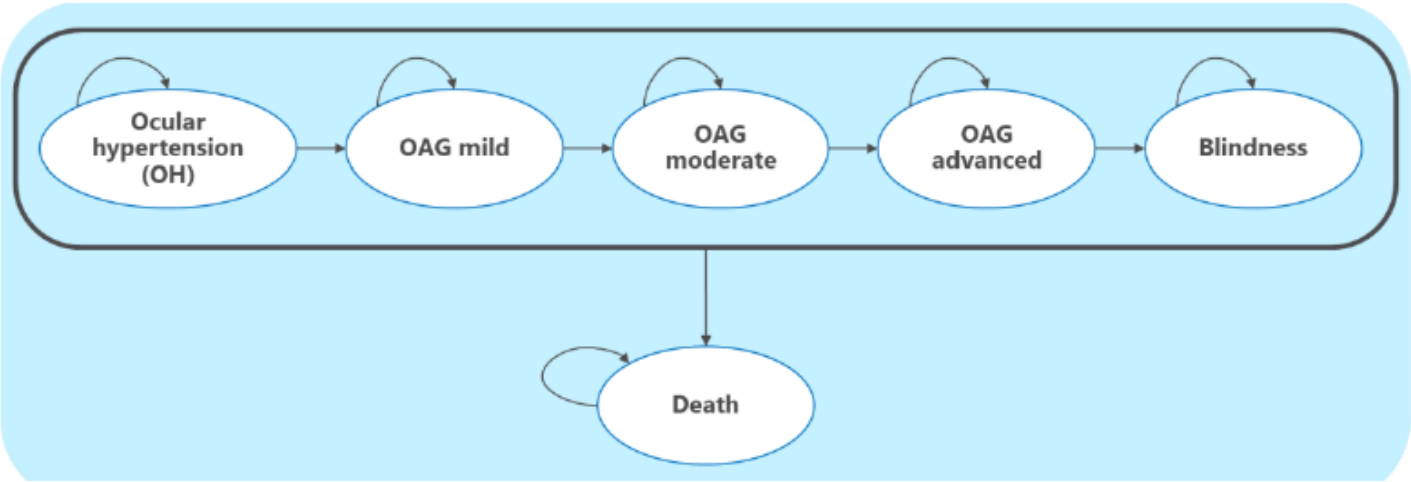
IOP = intraocular pressure.

Source: Manufacturer's pharmacoeconomic submission.[3]

The model used a decision tree and a cohort multi-state Markov model developed in Microsoft Excel (Figure 2).[3] At the start of the model, patients with ocular hypertension (OH) or open-angle glaucoma (OAG) entered a decision tree and received one of the available PGAs as the first-line monotherapy. Based on the results of a published network meta-analysis,[4] these patients may fully respond, partially respond, not respond, or not tolerate the PGA. Responders continued an existing treatment. Partial responders received additional therapies until laser therapy was required. Nonresponders and those who were intolerant to the first-line therapy switched to the second-line monotherapy. Additional treatments were added for partial responders and nonresponders. The safety and efficacy of the second- and third-line therapies were based on a published indirect comparison study.[5] The model allowed a maximum of three consecutive lines of treatment in the decision tree before laser trabeculoplasty was performed. Response to therapy was assessed using the IOP. For the first-line treatments, it was assumed that an IOP decrease of at least 25% from the baseline represented treatment response. If the IOP decrease was between 15% and 25%, this was considered a partial response. Any decrease lower than 15% represented nonresponse. For treatments prescribed after the first-line monotherapy, a decrease in IOP of 20% was considered a response.[3]

At the terminal node of the decision tree, patients entered the Markov model (Figure 2) and cycled through the model at discrete 1-year intervals over a lifetime time horizon.[3] The model assumed that changes in IOP affected only the risk of progression from OH to mild OAG and did not affect transition probabilities in the more severe health states (e.g., from the mild OAG to blindness health states). The mortality risk depended on the sex ratio and the age of the patients. The submitted model incorporated the effect of adherence on IOP response. Nonadherent patients were assumed to have a lower IOP decrease than adherent patients.[3]

Figure 2: Markov Model Structure



OAG = open-angle glaucoma; OH = ocular hypertension.

Source: Manufacturer's pharmacoeconomic submission.[3]

Table 12: Data Sources

Data Input	Description of Data Source	Comment
Efficacy	• Baseline and 3-month IOP: phase III Monoprost trial (T2345)[6]	• Acceptable. Baseline characteristics of participants reported in the trial were slightly different from those reported in a Canadian cross-sectional study:[7] mean age (63.9 versus 61.2 years), the proportion of females (54% versus 49%), and baseline IOP (24.1 versus 21.3 mm Hg).
	• Comparative safety and efficacy of Monoprost and other first-line PGAs: a network meta-analysis and ITC[4]; and • Comparative safety and efficacy of PGAs used in the following lines of therapy: MTC and meta-regression of the efficacy and safety of prostaglandin analogues and comparators for primary OAG and OH.[5]	• Acceptable, given the lack of direct-comparison evidence on the safety and efficacy of Monoprost and other PGAs, except for preserved latanoprost. However, the ITC and MTC have several important limitations, including limited descriptions of the risk-of-bias assessment of included studies and insufficient justification for the planned statistical analysis. A full assessment of the methodological quality of the ITC reporting comparative efficacy was provided in the CDR Clinical Review Report.
	• **Decision tree:** • Transition probability for first-line treatments: phase III trial (T2345), a network meta-analysis, and microsimulations • Transition probability for subsequent treatment lines: weighting the proportion of responders and nonresponders obtained from microsimulations by the rate of patient switching after having experienced hyperemia • Transition probabilities for laser therapy: Bovell et al.[14]	• As there is no empirical data on the distribution of responders in OH and OAG patients, the microsimulation methods used to derive the proportion of responders, partial responders, and nonresponders are appropriate. The same approach was used to calculate the proportion of patients with IOP lower than an absolute target in a published study.[17]
	• **Markov model:** • Transitioning from OH to mild OAG: a previous Dutch CEA study[8]	• The Dutch cost-effectiveness study did not provide the details of methods used to estimate or synthesize these transition probabilities from 11 cited references published between 1977 and 2003. There was also wide variation in interventions being evaluated in these cited references, including (but not limited to) topical timolol, timolol, betaxolol, and placebo. CDR was unable to assess the direct impact of this

Data Input	Description of Data Source	Comment
		limitation because of the paucity of data. However, CDR assessed the uncertainty of this equation by refitting the IOP against transition probabilities from OH to mild OAG with a third-degree polynomial equation (transition probabilities = –0.0000027105 × IOP^3 + 0.0003087576 × IOP^2 – 0.0063674411 × IOP + 0.0351285220). This equation has a slightly better fit than a second-degree polynomial that used in the model (R^2 = 0.99967).
	• Transitioning from mild to moderate OAG and moderate to advanced OAG: Canadian Glaucoma Study[15]	• Acceptable
	• Transitioning from advanced OAG to blindness: Van Gestel et al.[16]	• The CDR clinical expert suggested that 2% annual probability of progressing to blindness was too high. A 1% annual probability of blindness was used in CDR's reanalysis. This lower probability was guided by a cohort study including 305,000 patients.[11]
Natural history	• Distribution of OH and OAG: a Canadian cross-sectional study (Buys et al.)[7]	• The proportion of patients with OAG used in the model (70%) was greatly different from the proportion of patients with a history of OAG at the trial baseline (1%). However, the proportion of OH used in the model may be generalized to Canadian population, as it was consistent with a distribution of patients enrolled in a Canadian cross-sectional study.[7]
	• Proportion of nonadherent patients: expert opinion	• Highly uncertain. Given the paucity of comparative adherence rates between preservative-free and preserved PGAs, the use of expert opinion is appropriate. However, expert opinion was from outside of Canada (Europe), the manufacturer excluded one-third of the expert opinion elicited for this parameter, and no rationale for the expert's opinion was provided. Published literature has reported adherence rates for PGAs varying between 43% and 66%.
	• Effect of adherence to IOP response: Nordmann et al.[18]	• The cited paper used to inform the assumption of adherence and IOP response provided insufficient details

Data Input	Description of Data Source	Comment
		regarding methods used to derive the association between adherence rate and IOP response. This reduces the credibility of the assumption. Based on feedback from the clinical expert consulted by CDR, CDR assessed the impact of this assumption by using the following alternative IOP response: 0 mm Hg and 3 mm Hg.
Utilities	• Specific utility value for each OAG health state: Wolfram et al.[9] and Brown et al.[19] • Utility decrement due to hyperemia	• Utility values were based on the European studies. The estimated values may not be generalizable to the Canadian population. However, they were considered acceptable in the absence of Canadian utility data. • The utility decrement for hyperemia is a key input parameter. It was obtained from expert opinion, but the manufacturer did not describe how it was derived. The application of this value over the duration of the lifetime horizon may overestimate the impact on patients' quality of life. The manufacturer assessed the impact of no decrease in utility in a scenario analysis.
Resource use	• The resource use data are taken from Ontario Health System data sources, based on expert clinical advice.	• The clinical expert consulted by CDR indicated the frequency of follow-up visits, the cost of laser therapy, and the type of health care practitioners involved may be overestimated. The impact on the cost-effectiveness findings is expected to be minimal, as follow-up visits and laser treatments apply to all PGAs. CDR assessed the impact of resource use and associated costs of the laser therapy in a scenario analysis.
Adverse events	• Hyperemia rate following treatment with Monoprost: phase III Monoprost trial (T2345) • Hyperemia rates associated with PGA comparators: a network meta-analysis study[4] • Hyperemia rates for subsequent treatment lines: Orme et al.[5]	• The rate of hyperemia was uncertain (see CDR Clinical Report appraisal of ITC). The rates for subsequent treatment may be acceptable; however, CDR was concerned with the assumed proportion of patients with hyperemia still on treatment, given the impact of this parameter on the model results.
Mortality	Statistics Canada life tables incorporating sex ratio[3]	Appropriate. The clinical expert consulted by CDR agreed that PGAs do not affect mortality.
Costs		

Data Input	Description of Data Source	Comment
Drug	• Monoprost: Laboratoires Théa • Other branded and generic PGAs and subsequent lines of therapy: Ontario Drug Benefit Formulary/Comparative Drug Index	The unit costs are appropriate.
Administration	None	None
Event	• Laser treatment: Ontario Ministry of Health and Long-Term Care – Schedule of benefits • OH monitoring: Ontario Ministry of Health and Long-Term Care – Schedule of benefits • Gonioscopy: physician fee schedules in Alberta, British Columbia, Manitoba, New Brunswick, Nova Scotia, Quebec, and Saskatchewan (Cruess et al.)[20]	• The clinical expert consulted by CDR indicated that the laser treatment costs were overestimated. The manufacturer used incorrect fee codes for laser and follow-up visits. However, this concern is less likely to affect the cost-effectiveness findings, as the required follow-up visits and laser treatments would apply to all PGAs.
AEs	Not included	
Health state	• Costs associated with mild, moderate, and advanced OAG: a Canadian study (Iskedjian et al.)[10] • Cost of blindness: a Canadian study	• Although this study is dated, it is the only Canadian costing study of glaucoma that is available to date. • Appropriate

AE = adverse event; CEA = cost-effectiveness analysis; CDR = CADTH Common Drug Review; IOP = intraocular pressure; ITC = indirect treatment comparison; MTC = mixed treatment comparison; OAG = open-angle glaucoma; OH = ocular hypertension; PGA = prostaglandin analogue.

Table 13: Manufacturer's Key Assumptions

Assumption	Comment
No more than 3 lines of medications before entering the Markov model	Uncertain. The clinical expert consulted by CDR indicated that, once controlled on treatment, patients are likely to remain on treatment; however, there is uncertainty over the treatment mix (i.e., use of multiple PGAs).
Treatment effect maintained over time for all treatments	The clinical expert consulted by CDR considered that this assumption is appropriate.
Second-line monotherapy, combination therapy, and third-line treatments included in the model were a mixture of preferred treatments. Second- and third-line monotherapy PGAs include Monoprost.	Based on the model, it appears the manufacturer assumed the efficacy and safety of Monoprost as second- and third-line therapies to be the same as the other PGAs. The assumption of using PGAs as the third-line therapy was not supported by opinion elicited from experts consulted by the manufacturer or the clinical expert consulted by CDR. Patients who require a third-line (or even second-line) therapy would expect to try other classes of treatment, such as beta blockers, alpha-2 selective adrenergic agonists, and carbonic anhydrase inhibitors.
Preservative-free PGAs were assumed to have higher adherence rates	Although the use of expert opinion may be appropriate given the paucity of data comparing adherence between preservative-free and preserved PGAs, the manufacturer excluded one-third of the expert opinion elicited

Assumption	Comment
	for this parameter, and no rationale for the expert's opinion was provided. Furthermore, the difference in adherence rates was not supported by the results of the pivotal trial, suggesting that mean compliance based on amount of drug instilled was similar between Monoprost and BAK-preserved latanoprost (ranging from 98.4% to 99.7%).[21] CDR assessed this assumption by assuming equal adherence rates between Monoprost and other preserved PGAs.
The impact of low adherence (defined as ≤ 80% treatment) on treatment effect was associated with an increase in IOP of 2 mm Hg compared with the IOP value measured in adherent patients.	It is unclear how the relationship between adherent status and IOP was derived. The cited paper used to inform the assumption of adherence and IOP response provided insufficient details regarding methods used to derive the association between adherence rate and IOP response. This reduces the credibility of the assumption and results in substantial uncertainty in the relationship between adherent status and IOP. CDR assessed the impact of this assumption by using the following alternative IOP values: 0 mm Hg and 3 mm Hg.
Severity of glaucoma (mild, moderate, or advanced) did not affect probabilities of being a responder or experiencing an AE.	The CDR clinical expert agreed that this assumption is acceptable.
Treatment switching occurred as a result of one AE (hyperemia).	The justification of the exclusion of other AEs was provided and deemed to be appropriate.
Responders were defined by the following IOP-reduction thresholds: • At least 25% of IOP decrease for the first-line treatment • At least 20% of IOP decrease for the following treatment lines For partial responders, the following IOP-reduction thresholds were applied: • 15% to 25% for the first-line treatment • 15% to 20% for the following treatment lines Nonresponders were defined as having an IOP reduction less than 15%.	The CDR clinical expert agreed that these assumptions are acceptable.
Disease progression moving through the mild, moderate, and advanced OAG health states was assumed to follow a linear progression and to be constant over time.	The CDR clinical expert agreed that the assumption is acceptable.
20% of patients experiencing hyperemia would switch treatment due to the hyperemia.	Uncertain. The CDR clinical expert indicated this assumption is notably higher than expected in Canadian clinical practice.
5% of patients with hyperemia experience a reduced quality of life but would stay on treatment.	Potentially appropriate. Although it is difficult to determine, given the lack of clarity in the manufacturer's report, it appeared to assume that, in patients who did not initially switch because of hyperemia, 5% would experience a reduction in quality of life due to the hyperemia, while the remaining 95% would not experience a notable decrease in quality of life.
Generic PGA therapies had the same effectiveness and	Appropriate.

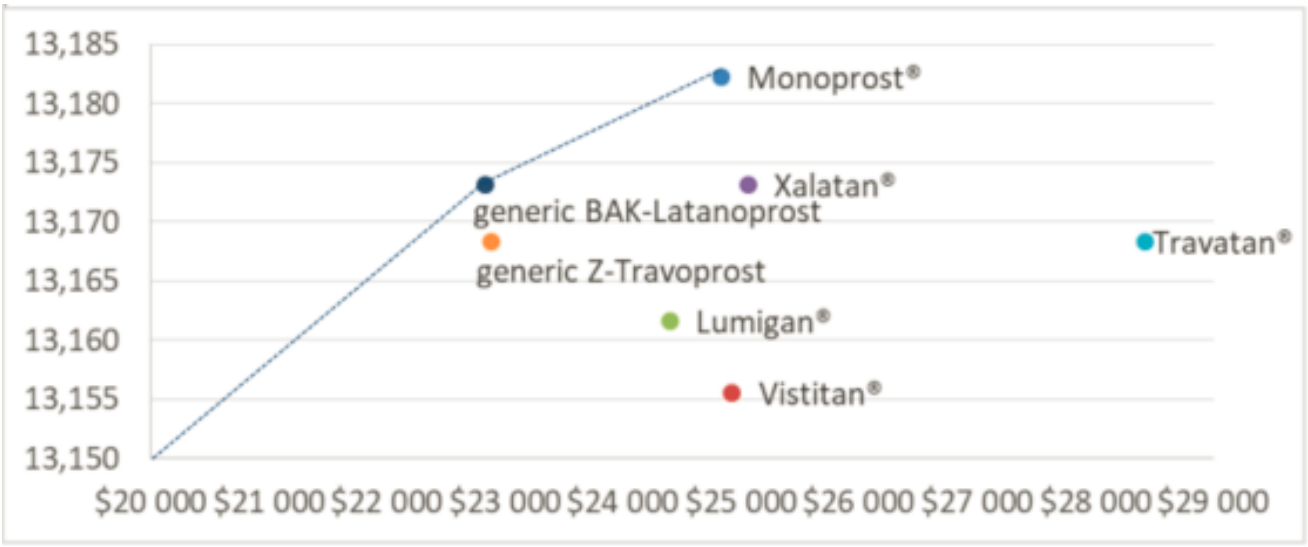
Assumption	Comment
safety outcomes as their branded counterparts.	
Patients experienced OH or OAG in both of their eyes, and, as a result, used two drops of their topical therapy at each administration.	This assumption likely overestimates the costs of drugs and glaucoma management, as patients may experience OH or OAG in one eye. However, the assumption should not affect the cost-effectiveness findings, as it was applied to all PGAs.

AE = adverse event; BAK = benzalkonium chloride; CEA = cost-effectiveness analysis; CDR = CADTH Common Drug Review; IOP = intraocular pressure; OAG = open-angle glaucoma; OH = ocular hypertension; PGA = prostaglandin analogue.

Manufacturer's Results

The manufacturer's base-case analysis and sequential analysis are reported earlier in the report (Table 2 and Table 3). The manufacturer's efficiency frontier is reported in Figure 3.

Figure 3: Manufacturer's Efficiency Frontier



BAK = benzalkonium chloride; Z = sofZia.

Source: Manufacturer's pharmacoeconomic submission.[3]

Manufacturer's Sensitivity Analyses

The results of the scenario analyses suggested that the proportion of patients who experienced long-term hyperemia, disutility due to hyperemia, and IOP level at baseline for nonadherent patients were the three main drivers of the cost-effectiveness results. If there was no disutility due to hyperemia, the incremental cost-utility ratio (ICUR) of Monoprost compared with generic benzalkonium chloride (BAK)-preserved latanoprost increased substantially, from $217,790 to $365,978 per one quality-adjusted life-year (QALY) gained. Moreover, if there was no adherence difference between preserved and preservative-free treatments, the ICURs were found to increase from the manufacturer's base case; the ICUR of Monoprost compared with generic BAK-preserved latanoprost rose to $245,061 per QALY gained.

The results of probabilistic sensitivity analysis with 5,000 iterations showed that, compared with generic BAK-preserved latanoprost, in 10% of the simulations, Monoprost was under the threshold of $50,000 per QALY gained; the percentage increased to 20% with a threshold of $100,000 per QALY gained. The cost-effectiveness acceptability curve revealed that, at the lower level of willingness-to-pay (WTP) values, the generic BAK-preserved latanoprost had the highest probability of being cost-effective. Monoprost had the highest probabilities of being the most cost-effective therapy at a WTP of $190,000 per QALY. The probability increased with the greater WTP values and reached 35% at a WTP value of $250,000 per QALY.

CADTH Common Drug Review Reanalyses

CDR undertook a series of scenario analyses to test the impact of various parameters, including IOP and hyperemia rates, on the CDR base-case results. In the scenario analyses, CDR used fewer iterations (10,000) to undertake the scenario analyses because of the long model run time.

Comparative efficacy of Monoprost compared with other PGAs licensed in Canada. The comparative efficacy of Monoprost is associated with uncertainty. CDR performed a scenario analysis in which it assumed no difference in mean IOP at three months across PGA therapies. The results showed a slight change in ICURs (Table 14). The lack of model stability leads to some uncertainty in this result.

Table 14: CDR Scenario Analysis: Assume Comparable Effects on Intraocular Pressure at Three Months Across Prostaglandin Analogues

	Total Costs ($)	Total QALYs	Incremental Cost per QALY Gained Versus BAK-Preserved Latanoprost	Sequential ICUR ($/QALY)
Nondominated options				
Generic/branded BAK-preserved latanoprost	$22,786	13.1985	–	–
Monoprost	$24,812	13.2059	$273,691	$273,691
Dominated options				
Generic/branded travoprost	$22,831	13.1927	Dominated by BAK-preserved latanoprost	
Bimatoprost 0.01%	$24,368	13.1868	Dominated by BAK-preserved latanoprost	
Bimatoprost 0.03%	$24,900	13.1813	Dominated by BAK-preserved latanoprost	

BAK = benzalkonium chloride; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Note: All costs are presented in 2016 Canadian dollars.

Comparative safety of Monoprost compared with other PGAs licensed in Canada. CDR performed a scenario analysis by assuming no difference in hyperemia rates across PGA therapies. The results show that Monoprost was no longer a dominant strategy if the comparable safety across PGA therapies were assumed (Table 15). The impact of the lack of model stability leads to some in uncertainty in this result.

Table 15: CDR Scenario Analysis: Assume Equivalent Hyperemia Rates Across Prostaglandin Analogues

	Total Costs ($)	Total QALYs	Incremental Cost per QALY Gained Versus Generic BAK-Preserved Latanoprost	Sequential ICUR ($/QALY)
Nondominated options				
Generic/branded BAK-preserved latanoprost	$22,722	13.2191	-	-
Dominated options				
Generic/branded travoprost	$22,783	13.2191	Dominated by BAK-preserved latanoprost	
Bimatoprost 0.01%	$24,427	13.2181	Dominated by BAK-preserved latanoprost	
Monoprost	$24,741	13.2173	Dominated by BAK-preserved latanoprost	
Bimatoprost 0.03%	$25,063	13.2189	Dominated by BAK-preserved latanoprost	

BAK = benzalkonium chloride; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Note: All costs are presented in 2016 Canadian dollars.

Effects of adherence on IOP decrease. CDR varied a decrease in IOP among nonadherent patients, from 0 mm Hg to 3 mm Hg (Table 16 and Table 17). The results showed that the Monoprost was more cost-effective compared with generic/branded BAK-preserved latanoprost with the greater decrease in IOP, as a result of treatment nonadherence.

Table 16: CDR Scenario Analysis: Assume No Intraocular Pressure Increase in Patients Who Do Not Adhere to Treatment

	Total Costs ($)	Total QALYs	Incremental Cost per QALY Gained Versus BAK-preserved latanoprost	Sequential ICUR ($/QALY)
Nondominated options				
Generic/branded BAK-preserved latanoprost	$22,803	13.5012	–	–
Monoprost	$24,847	13.5075	$325,264	$325,264
Dominated options				
Generic/branded travoprost	$22,851	13.4968	Dominated by BAK-preserved latanoprost	
Bimatoprost 0.01%	$24,394	13.4921	Dominated by BAK-preserved latanoprost	
Bimatoprost 0.03%	$24,932	13.4873	Dominated by BAK-preserved latanoprost	

BAK = benzalkonium chloride; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Note: All costs are presented in 2016 Canadian dollars.

Table 17: CDR Scenario Analysis: Assume 3 mm Hg Increase in Intraocular Pressure in Patients Who Do Not Adhere to Treatment

	Total Costs ($)	Total QALYs	Incremental Cost per QALY Gained Versus BAK-preserved latanoprost	Sequential ICUR ($/QALY)
Nondominated options				
Generic/branded BAK-preserved latanoprost	$22,814	13.2061	–	–
Monoprost	$24,848	13.2140	$260,087	$260,087
Dominated options				
Generic/branded travoprost	$22,858	13.2010	Dominated by BAK-preserved latanoprost	
Bimatoprost 0.01%	$24,398	13.1946	Dominated by BAK-preserved latanoprost	
Bimatoprost 0.03%	$24,928	13.1886	Dominated by BAK-preserved latanoprost	

BAK = benzalkonium chloride; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Note: All costs are presented in 2016 Canadian dollars.

Slower progression from advanced OAG to blindness. CDR reduced the transition probability from advanced OAG to blindness from 2% to 1%. The reduction caused a slight reduction in the ICUR of Monoprost. The impact of the lack of model stability leads to some in uncertainty in this result.

Table 18: CDR Scenario Analysis: Assume a lower progression From Open-Angle Glaucoma to Blindness (1%)

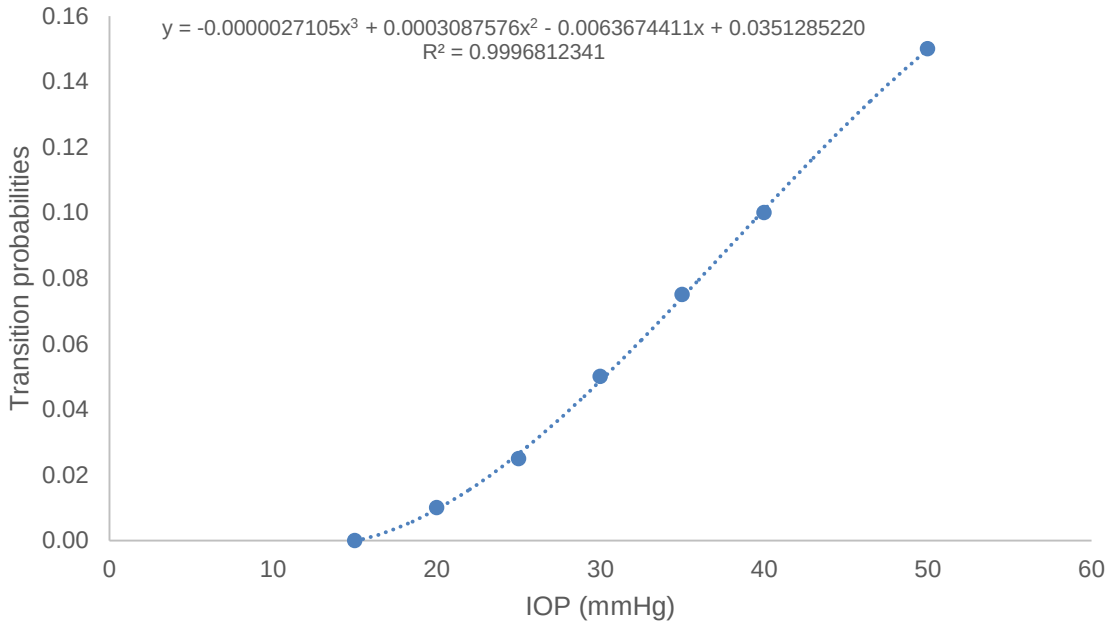
	Total Costs ($)	Total QALYs	Incremental Cost per QALY Gained Versus BAK-Preserved Latanoprost	Sequential ICUR ($/QALY)
Nondominated options				
Generic/branded BAK-preserved latanoprost	$17,143	13.3443	-	-
Monoprost	$19,227	13.3529	$244,069	$244,069
Dominated options				
Generic/branded travoprost	$17,190	13.3391	Dominated by BAK-preserved latanoprost	
Bimatoprost 0.01%	$18,762	13.3325	Dominated by BAK-preserved latanoprost	
Bimatoprost 0.03%	$19,313	13.3272	Dominated by BAK-preserved latanoprost	

BAK = benzalkonium chloride; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Note: All costs are presented in 2016 Canadian dollars.

The alterative equation for the estimation of transition probabilities of OH progression to mild OAG. An alternative plot and equations used to estimate the progression probabilities from OH to OAG are shown in Figure 4.

Figure 4: Third-Degree Polynomial Equation Derived From Transition Probabilities and IOP Data From a Previous Cost-Effectiveness Analysis



IOP = intraocular pressure.

Replacing a second-degree with a third-degree polynomial equation decreased the ICURs of Monoprost compared with generic BAK-preserved latanoprost (Table 19). The impact of the lack of model stability leads to some in uncertainty in this result.

Table 19: CDR Scenario Analysis: Alternative Equation Used to Estimate Transition Probabilities of Ocular Hypertension Progression to Mild Open-Angle Glaucoma

	Total Costs ($)	Total QALYs	Incremental Cost per QALY Gained Versus BAK-Preserved Latanoprost[a]	Sequential ICUR ($/QALY)[a]
Nondominated options				
Generic/branded BAK-preserved latanoprost	$22,790	13.2201	–	–
Monoprost	$24,821	13.2287	$238,536	$238,536
Dominated options				
Generic/branded travoprost	$22,844	13.2148	Dominated by BAK-preserved latanoprost	
Bimatoprost 0.03%	$24,389	13.2093	Dominated by BAK-preserved latanoprost	
Bimatoprost 0.01%	$24,878	13.2031	Dominated by BAK-preserved latanoprost	

BAK = benzalkonium chloride; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Note: All costs are presented in 2016 Canadian dollars.

[a] 7,500 iterations.

The cost of ophthalmologist and laser therapy. As noted in the Limitations section, the clinical expert consulted by CDR indicated that the cost of an ophthalmologist and cost of laser therapy were overestimated; therefore, CDR reduced these costs by 25%. Variation in the cost of laser therapy leads to a slight increase in the ICUR for Monoprost (Table 20). The impact of the lack of model stability leads to in uncertainty of this result.

Table 20: CDR Scenario Analysis: Assume a 25% Reduction in the Cost of Ophthalmologist and Laser Therapy

	Total Costs ($)	Total QALYs	Incremental Cost per QALY Gained Versus BAK-Preserved Latanoprost	Sequential ICUR ($/QALY)
Nondominated options				
Generic/branded BAK-preserved latanoprost	$22,515	13.1868	–	–
Monoprost	$24,546	13.1937	$290,918	$290,918
Dominated options				
Generic/branded travoprost	$22,554	13.1818	Dominated by BAK-preserved latanoprost	
Bimatoprost 0.01%	$24,096	13.1852	Dominated by BAK-preserved latanoprost	
Bimatoprost 0.03%	$24,632	13.1704	Dominated by BAK-preserved latanoprost	

BAK = benzalkonium chloride; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Note: All costs are presented in 2016 Canadian dollars.

References

1. [Pr]Monoprost® (latanoprost ophthalmic solution): 50 mg/mL (sterile, preservative-free, single dose container) [product monograph]. Clermont-Ferrand (FR): Laboratoires THÉA; 2017 Oct 19. Imported by Labtician Ophthalmics Inc.
2. CDR submission: Monoprost (latanoprost), 50 ug/mL ophthalmic solution. Company: Laboratoires Théa [**CONFIDENTIAL** manufacturer's submission]. Clermont-Ferrand (FR): Laboratoires Théa; 2017 Oct.
3. Pharmacoeconomic evaluation. In: CDR submission: Monoprost (latanoprost), 50 ug/mL ophthalmic solution. Company: Laboratoires Théa. [**CONFIDENTIAL** manufacturer's submission]. Clermont-Ferrand (FR): Laboratoires Théa; 2017 Oct.
4. Cucherat M, Stalmans I, Rouland JF. Relative efficacy and safety of preservative-free latanoprost (T2345) for the treatment of open-angle glaucoma and ocular hypertension: an adjusted Indirect comparison meta-analysis of randomized clinical trials. J Glaucoma. 2014 Jan;23(1):e69-e75.
5. Orme M, Collins S, Dakin H, Kelly S, Loftus J. Mixed treatment comparison and meta-regression of the efficacy and safety of prostaglandin analogues and comparators for primary open-angle glaucoma and ocular hypertension. Curr Med Res Opin. 2010 Mar;26(3):511-28.
6. Rouland JF, Traverso CE, Stalmans I, Fekih LE, Delval L, Renault D, et al. Efficacy and safety of preservative-free latanoprost eyedrops, compared with BAK-preserved latanoprost in patients with ocular hypertension or glaucoma. Br J Ophthalmol. 2013 Feb;97(2):196-200.
7. Buys YM, Harasymowycz P, Gaspo R, Kwok K, Hutnik CM, Blondeau P, et al. Comparison of newly diagnosed ocular hypertension and open-angle glaucoma: ocular variables, risk factors, and disease severity. J Ophthalmol. 2012;2012:757106.
8. Peeters A, Schouten JS, Severens JL, Hendrikse F, Prins MH, Webers CA. Latanoprost versus timolol as first choice therapy in patients with ocular hypertension. A cost-effectiveness analysis. Acta Ophthalmol. 2012 Mar;90(2):146-54.
9. Wolfram C, Lorenz K, Breitscheidel L, Verboven Y, Pfeiffer N. Health- and vision-related quality of life in patients with ocular hypertension or primary open-angle glaucoma. Ophthalmologica. 2013;229(4):227-34.
10. Iskedjian M, Walker J, Vicente C, Trope GE, Buys Y, Einarson TR, et al. Cost of glaucoma in Canada: analyses based on visual field and physician's assessment. J Glaucoma. 2003 Dec;12(6):456-62.
11. Peters D, Bengtsson B, Heijl A. Lifetime risk of blindness in open-angle glaucoma. Am J Ophthalmol. 2013 Oct;156(4):724-30.
12. latanoprost 50microgram/mL preservative-free single-dose eye-drops (Monopost®) [Internet]. Glasgow: Scottish Medicines Consortium; 2013 Jun 7. (SMC product update; no. 879/13).
13. Transparency Committee. Monoprost 50 mg/mL eye drops solution in single-dose container [Internet]. Saint-Denis (FR): Haute Autorité de Santé; 2013 May 29.
14. Bovell AM, Damji KF, Hodge WG, Rock WJ, Buhrmann RR, Pan YI. Long term effects on the lowering of intraocular pressure: selective laser or argon laser trabeculoplasty? Can J Ophthalmol. 2011 Oct;46(5):408-13.
15. Chauhan BC, Mikelberg FS, Balaszi AG, LeBlanc RP, Lesk MR, Trope GE, et al. Canadian Glaucoma Study: 2. risk factors for the progression of open-angle glaucoma. Arch Ophthalmol. 2008 Aug;126(8):1030-6.
16. van Gestel A, Webers CA, Beckers HJ, Peeters A, Severens JL, Schouten JS. Ocular hypertension and the risk of blindness. J Glaucoma. 2015 Jan;24(1):9-11.
17. Orme M, Collins S, Loftus J. Long-term medical management of primary open-angle glaucoma and ocular hypertension in the UK: optimizing cost-effectiveness and clinic resources by minimizing therapy switches. J Glaucoma. 2012 Sep;21(7):433-49.
18. Nordmann JP, Baudouin C, Renard JP, Denis P, Lafuma A, Laurendeau C, et al. Measurement of treatment compliance using a medical device for glaucoma patients associated with intraocular pressure control: a survey. Clin Ophthalmol [Internet]. 2010 Jul 30 [cited 2018 Jan 18];4:731-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2915860
19. Brown MM, Brown GC, Sharma S, Kistler J, Brown H. Utility values associated with blindness in an adult population. Br J Ophthalmol [Internet]. 2001 Mar [cited 2018 Jan 26];85(3):327-31. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1723892
20. Cruess AF, Gordon KD, Bellan L, Mitchell S, Pezzullo ML. The cost of vision loss in Canada. 2. Results. Can J Ophthalmol. 2011 Aug;46(4):315-8.
21. Clinical Study Report: LT2345-PIII-12/08. Efficacy and Safety assessment of T2345 unpreserved eyedrops versus Xalatan® in ocular hypertensive or glaucomatous patients. [**CONFIDENTIAL** internal manufacturer's report]. Clermont-Ferrand (FR): Laboratoires THÉA; 2011 Apr 4.