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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

LATANOPROSTENE BUNOD (VYZULTA)

(Bausch Health, Canada Inc.)

Indication: For the reduction of intraocular pressure (IOP) 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.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

CDR	CADTH Common Drug Review
ICUR	incremental cost-utility ratio
IOP	intraocular pressure
OAG	open-angle glaucoma
OHT	ocular hypertension
LBN	latanoprostene bunod
NMA	network meta-analysis
PGA	prostaglandin analogue
QALY	quality-adjusted life-year

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Latanoprostene bunod (Vyzulta)
Study Question	What is the cost-effectiveness of latanoprostene bunod compared with current prostaglandin analogues (PGA) in the treatment of patients with ocular hypertension (OHT) and open-angle glaucoma (OAG) in Canada?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adult patients with OHT and OAG
Treatment	Latanoprostene bunod, 0.024% w/v
Outcome	QALYs
Comparator(s)	PGAs: bimatoprost 0.01%, bimatoprost 0.03%, generic latanoprost 0.005%, and travoprost 0.004%
Perspective	Canadian public health care payer
Time Horizon	Lifetime (approximately 40 years)
Results for Base Case	• The ICUR for latanoprostene bunod was $44,505 per QALY gained compared with travoprost. • The probability that latanoprostene bunod was the most likely cost-effective intervention compared with the other PGAs was 22.4% and 23.3% at a willingness-to-pay threshold of $50,000 and $100,000 per QALY, respectively.
Key Limitations	CADTH identified several key limitations with the submitted analysis: • The submitted model was not stable at the base case up to 20,000 iterations over multiple runs of the probabilistic analysis, increasing the uncertainty associated with the reported cost-effectiveness estimates. • The relative treatment effects of latanoprostene bunod compared with other PGAs are uncertain. Estimates from the manufacturer-commissioned network meta-analysis were based on mixed patient populations without appropriate assessment of the impact on clinical heterogeneity, and there was insufficient statistical analysis to evaluate inconsistency. • The efficacy of latanoprostene bunod was pooled from clinical trials in which baseline patient characteristics may be imbalanced and efficacy end points were defined at different follow-up times. • The treatment costs of PGAs and other glaucoma medications were underestimated due to lack of consideration for recommended product shelf-life. • There were inappropriate assumptions relating to the frequency of follow-up and costs associated with medical visits, according to the clinical expert consulted by CADTH. • The approach to treatment switching for patients who failed to respond to PGA therapy did not align with clinical practice as patients who did not respond to first-line PGA therapy switched to treatments within the same treatment class, and treatment costs for switching included the cost of the existing PGA to which patients had not responded.
CADTH Estimate(s)	CADTH reanalysis corrected modelling errors, incorporated appropriate parameter uncertainty, re-estimated the pooled efficacy associated with latanoprostene bunod, adjusted treatment costs to account for recommended product shelf-life, revised the costs associated with follow-up and monitoring, and revised treatment-switching costs to account for prior PGA use. Based on these revisions, CADTH found that: • The ICUR for latanoprostene bunod was $142,801 per QALY gained when compared with generic latanoprost. All other PGAs studied were dominated by latanoprostene bunod (associated with greater expected costs and fewer expected QALYs) or subjected to extended dominance. • A price reduction of at least 33% is required for latanoprostene bunod to achieve an ICUR below $50,000 per QALY gained compared with generic latanoprost.

ICUR = incremental cost-utility ratio; OAG = open-angle glaucoma; OHT = ocular hypertension; PGA = prostaglandin analogue; QALY = quality-adjusted life-year; w/v = weight per volume.

Drug	Latanoprostene bunod (Vyzulta), 0.24 mg/mL (0.024% w/v)
Indication	For the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension
Reimbursement Request	As per indication
Dosage Form(s)	Sterile topical ophthalmic solution
NOC Date	December 27, 2018
Manufacturer	Bausch Health, Canada Inc.

Executive Summary

Background

Latanoprostene bunod (LBN) 0.024% ophthalmic solution (Vyzulta) is indicated for the reduction of intraocular pressure (IOP) in patients with ocular hypertension (OHT) or open-angle glaucoma (OAG).[1] It is available as a sterile topical ophthalmic solution containing 0.24 mg/mL LBN supplied in an eye-drop dispenser with a 5 mL fill volume.[1] The recommended dosage is one drop in the affected eye(s) once daily.[1] At the manufacturer-submitted price of $26.25 per dispenser, LBN costs approximately $0.30 per day, assuming treatment of both eyes.[2]

The manufacturer submitted a cost-utility analysis comparing LBN with currently available prostaglandin analogues (PGAs) for the treatment of patients with OHT and OAG (bimatoprost 0.01%, bimatoprost 0.03%, generic latanoprost 0.005%, and travoprost 0.004%). All patients were assumed to have both eyes treated. The analysis was conducted from the Canadian publicly funded health care payer perspective over a lifetime time horizon (approximately 40 years), with future costs and benefits discounted at 1.5%. The model structure included a decision tree to reflect patients in the first year of initiating treatment and movement through alternative therapies, if they did not respond to their initial treatment, until an optimal treatment was found.[2] At the end of the decision tree, patients entered the Markov state-transition model, which predicted long-term progression of disease through six health states: OHT, mild OAG, moderate OAG, advanced OAG, blindness, and death.[2] The manufacturer assumed that first-year changes in IOP affected the risk of progression in the transitions from OHT to mild OAG, while overall responder status affected the risk of progressions from mild OAG to advanced OAG. The comparative efficacy of first-line LBN compared with other PGAs was obtained from an unpublished network meta-analysis (NMA) conducted by the manufacturer,[3] while the efficacies of second-line monotherapy and bi-therapy were obtained from a published mixed-treatment comparison by Orme et al.[4] Health-state utility values were derived from the published literature. Resource use and health system costs were derived from Canadian data sources.

The manufacturer reported that LBN dominated bimatoprost 0.01% in the probabilistic base-case analysis (LBN was less costly and produced more quality-adjusted life-years [QALYs]). LBN was less costly than bimatoprost 0.03% but less effective (associated with fewer QALYs). Conversely, LBN was more costly and more effective than generic latanoprost and

travoprost, such that if a decision-maker is willing to pay $50,000 per QALY, LBN is the optimal treatment, although only with a 22.4% probability of being the most likely cost-effective intervention.

Summary of Identified Limitations and Key Results

The CADTH Common Drug Review (CDR) identified a number of key limitations relating to the manufacturer's model. First, there was uncertainty in the comparative clinical efficacy of LBN versus other PGAs owing to the poor methodological quality of the manufacturer's submitted NMA. Namely, the indirect treatment comparison was based on a mixture of studies that included a wide variety of patient populations and employed different methods to measure IOP. No assessment was made to evaluate the potential impact of clinical heterogeneity on treatment effect estimates. In addition, insufficient statistical analysis was performed to evaluate inconsistency within the network. Due to these concerns, little can be elucidated from the NMA about the comparative effectiveness of LBN versus other PGAs. The manufacturer's model further defined the efficacy for LBN (i.e., reduction in mean diurnal IOP at three months) based on pooling the key efficacy end points from three clinical studies: two phase III, multi-centre, randomized trials (i.e., the APOLLO and LUNAR trials) and a phase II dose-finding study (i.e., the VOYAGER study). The design, baseline characteristics, and time at which the main IOP efficacy measurement was taken differed between VOYAGER and APOLLO and LUNAR. Therefore, it may be inappropriate to pool the results of the VOYAGER study with the findings from the phase III trials.

The manufacturer underestimated the treatment costs associated with pharmacotherapy of glaucoma. The clinical expert consulted by CADTH noted an average shelf-life of four weeks for the majority of glaucoma eye drops once a bottle was opened; patients are advised to renew their medication when shelf-life is exceeded due to concerns regarding microbial contamination and medication stability.[5] However, the manufacturer assumed that refills occurred only after eye-drop dispensers were emptied, and did not consider the impact of real-world refills according to recommended product shelf-life. This resulted in lowered estimates of treatment costs. The clinical expert further noted that the frequency and costs of follow-ups modelled by the manufacturer, according to the stage of glaucoma, do not reflect existing clinical practices.

The manufacturer further assumed that patients who did not respond to first-line monotherapy with their initial PGA would transition to second-line monotherapy with another PGA; drug costs associated with that treatment switch were calculated as the average of all PGA comparators, including the treatment that was discontinued due to treatment failure. The same assumption was also made for patients who did not fully respond to second-line bi-therapy and were switched to another PGA as third-line therapy. However, treatment switching is not typically performed within the same class of medication, according to the clinical expert consulted by CADTH; rather, patients who fail to respond to treatment with a PGA are more likely to be switched to another class of medications, such as beta blockers.

Finally, CADTH noted that the manufacturer's probabilistic base case was not reproducible over multiple model runs up to 20,000 iterations. The model lacked stability due to errors in coding and the application of incorrect methods to define the probabilistic distributions of model inputs.

There remains uncertainty relating to the likely cost-effectiveness of LBN given the lack of robust information on the relative treatment effects. The relative treatment efficacy used in the model was based on the manufacturer's NMA, for which CADTH could not address the

previously noted limitations. CADTH attempted to address the remaining limitations by: correcting errors to appropriately reflect parameter uncertainty; removing the VOYAGER study when pooling outcome data from primary studies; modifying the treatment costs of glaucoma medications to account for recommended product shelf-life; revising resource use and costs associated with medical follow-ups to reflect routine clinical practice; and adjusting treatment-switching costs to account for prior PGA use. Based on these revisions, in the CADTH base case, LBN was the optimal therapy at a willingness-to-pay threshold greater than or equal to $142,801 per QALY gained; if a decision-maker was willing to pay less than $142,801 per QALY gained, generic latanoprost was the optimal therapy. All other treatments were dominated or extendedly dominated.

Conclusions

In patients with OHT and OAG, CADTH found that LBN was associated with an additional benefit of 0.015 QALYs at an additional cost of $2,160 compared with generic latanoprost, resulting in an incremental cost-utility ratio of $142,801 per QALY gained. All other evaluated PGAs were dominated or subject to extended dominance. At a reduction of at least 33% of the submitted price, the incremental cost-utility ratio of LBN would fall below $50,000 per QALY compared with generic latanoprost.

It should be noted that there remains significant uncertainty regarding the comparative efficacy of LBN versus other PGA therapies, which introduces uncertainty regarding the true cost-effectiveness of LBN compared with alternative PGA therapies. The drug cost of LBN ($0.300 per drop) is greater than that of generic latanoprost ($0.219 per drop).

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a cost-utility analysis that compared latanoprostene bunod (LBN) 0.024% ophthalmic solution with other prostaglandin analogues (PGAs) reimbursed in Canada, including bimatoprost 0.01%, bimatoprost 0.03%, generic latanoprost 0.005%, and travoprost 0.004%.[2] The modelled population comprised adult patients with ocular hypertension (OHT) and open-angle glaucoma (OAG), reflecting the baseline characteristics in the LUNAR[6] and APOLLO[6] clinical trials (mean age, 64 years; 59.5% female; mean baseline intraocular pressure [IOP], 26.6 mm Hg). Patients were distributed across various levels of disease severity based on the baseline distribution observed in a Canadian cross-sectional study.[7] Namely, 27.9% of patients were assumed to be diagnosed with OHT, while the remainder (72.1%) had OAG; of the patients with OAG, 52.05% were assumed to have mild OAG, 27.05% had moderate OAG, and 20.89% had severe OAG. Patients were assumed to have both eyes treated throughout the model. The model adopted a lifetime time horizon (approximately 40 years), with all costs and outcomes discounted at an annual rate of 1.5%. The analysis was conducted from the perspective of the Canadian publicly funded health care system.

The manufacturer submitted a hybrid model structure consisting of a one-year decision tree and a long-term Markov state-transition model. Patients all entered the decision tree and were assumed to receive one of the available PGAs. After first-line monotherapy with a PGA, patients may achieve a full response to therapy (IOP reduction ≥ 25% from baseline), a partial response to therapy (IOP reduction > 15% and < 25% from baseline), or no response to therapy (IOP reduction ≤ 15% from baseline). Treatment response for first-line treatments was estimated based on the manufacturer's network meta-analysis (NMA) and defined as a reduction in IOP at three months versus baseline for all comparators.[3] Patients who experienced a full response remained on existing treatment, while additional therapy (e.g., bi-therapy or switch to another PGA) was prescribed for partial responders or non-responders. For treatment prescribed after first-line monotherapy, a reduction in IOP of at least 20% was considered a full treatment response; the efficacy of subsequent treatments was based on a published NMA.[4] The decision tree permitted up to two treatment changes before laser trabeculoplasty was performed.

At the end of the first year, all patients entered the multi-state Markov cohort model, which was used to predict long-term disease progression. Six health states were defined: OHT, mild OAG, moderate OAG, advanced OAG, blindness, and death. Patients could enter the model in any of the five alive health states depending on their IOP response and the line of treatment in which response was achieved during the first year of treatment, and transitioned through the model at one-year cycles. It was assumed that changes in IOP from the decision tree affected the risk of progression from OHT to mild OAG,[8] while transition probabilities from mild OAG to advanced OAG were based on overall responder status. Transitions from mild OAG to more severe glaucoma states were informed by natural history data sourced from the Swedish-based Early Manifest Glaucoma Trial;[9,10] these transitions remained constant over time. At any point, patients could transition to death, as informed by general population mortality estimates. The manufacturer assumed no mortality effect from

treatment; all treatment benefits were captured by an improvement in health-related quality of life.

Utility values for the Markov health states were sourced from a European study[11] that reported utility derived from the Health Utility Index Mark 3 (HUI-3); utility values relating to blindness were obtained from a study by Brown et al.[12] Costs included those for treatment (i.e., drug and laser), health-state specific follow-up and monitoring costs (e.g., medical consultations, diagnostic procedures), as well as the costs associated with blindness. Cost estimates were obtained from provincial formularies and databases, manufacturers, and Canadian literature sources; all costs were reported in 2018 Canadian dollars. Adverse events were not included in the model.

Manufacturer's Base Case

Results of the manufacturer's probabilistic base-case analysis were based on 5,000 Monte Carlo simulations.

LBN was found to be associated with an expected cost of $12,553 and 13.89 quality-adjusted life-years (QALYs) over the time horizon. LBN was more costly, but produced more QALYs than generic latanoprost or travoprost, resulting in a sequential incremental cost-utility ratio (ICUR) of $44,505 per QALY gained compared with travoprost (Table 2). The analysis was associated with a high degree of decision uncertainty because compared with currently available PGAs, LBN had a 22.4% probability of being considered the most likely cost-effective intervention at a $50,000 per QALY threshold (Figure 3).

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

	Total Costs ($)	Total QALYs	Δ Cost vs. Latanoprost ($)	Δ QALYs vs. Latanoprost	ICUR ($/QALY) vs. Latanoprost	Sequential ICUR ($/QALY)
Non-Dominated Options						
Generic latanoprost	12,227	13.882	–	–	–	–
Travoprost, 0.004%	12,246	13.887	19	0.006	3,454	3,454
Latanoprostene bunod	12,553	13.894	326	0.012	26,127	44,505
Bimatoprost 0.03%	13,828	13.897	1,602	0.015	106,557	502,228
Dominated Options						
Bimatoprost 0.01%	14,684	13.893	$2,458	0.011	Dominated by latanoprostene bunod and bimatoprost 0.03%	

Δ = incremental; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; vs. = versus.

Note: Total costs and QALYs are discounted probabilistic values based on 5,000 Monte Carlo iterations. Sequential ICURs should be interpreted with caution, as findings could not be reproduced over multiple runs of the probabilistic base case, up to 20,000 iterations.

Source: Adapted from the manufacturer's submission.[2] All costs are presented in 2018 Canadian dollars.

Summary of Manufacturer's Sensitivity Analyses

The manufacturer undertook scenario analyses by varying the following parameters: a shorter time horizon (10, 20, and 30 years), treatment of one eye, and an alternative definition of blindness. All scenario analyses were run probabilistically using 5,000 Monte Carlo simulations. Results of the sequential scenario analyses revealed that in almost all cases, results remained robust. Reducing the time horizon to 10 years had the largest impact on the results, resulting in a sequential ICUR of $99,784 per QALY gained for LBN versus latanoprost.

The uncertainty around the majority of input parameters in the manufacturer's model was assumed to be greater than or less than 25% of the parameter point estimate (e.g., mean value). Therefore, the uncertainty observed in the results of the probabilistic base-case and scenario analyses may not fully reflect the uncertainty around model parameters.

Limitations of the Manufacturer's Submission

CADTH identified the following limitations with the manufacturer's model:

- **Lack of stability:** CADTH noted that, up to 20,000 iterations, probabilistic results varied notably between different model runs. CADTH evaluated the potential causes of instability and noted that a number of factors may have contributed to this instability. First, the relative efficacy of PGA comparators as first-line therapy (i.e., hazard ratios based on inputs derived from the manufacturer's NMA) was incorrectly linked to the deterministic absolute IOP reduction value for LBN. Thus, in conducting probabilistic analysis, the relativity in treatment effects was not preserved. Another cause of model instability was the use of an arbitrary coefficient of variation (i.e., ± 25%) for the majority of cost and probability parameters in the manufacturer's model. As a result, the uncertainty observed in the probabilistic results may not fully reflect the true uncertainty around model parameters. The arbitrary assumption in defining probability distributions is inappropriate as parameters with low sensitivity but higher uncertainty should affect the model's output more than more sensitive parameters that are estimated more precisely. Lastly, despite the manufacturer's attempts to conduct internal model validation,[2] the submitted model suffered from a considerable amount of error in coding and calculations. This included minor errors relating to cost calculations (e.g., using three-month costs to represent one-month costs) and incorrect rates-to-probabilities conversion. The CADTH reanalysis included applying the hazard ratios for the PGA comparators to the probabilistically drawn efficacy input for LBN to preserve relativity throughout all probabilistic runs, use of published estimates of uncertainty to define parameter distribution, and correcting model errors.
- **Uncertainty with comparative clinical information:** The clinical trial evidence on LBN included placebo-control and active-control (i.e., timolol maleate 0.5%) trials. However, given that the manufacturer's economic model compared LBN with other available PGAs, relative treatment efficacy was informed by an unpublished NMA conducted by the manufacturer. Specifically, relative reduction in mean diurnal IOP at three months was incorporated into the manufacturer's economic model for the comparator PGAs based on estimates derived from the NMA. However, these estimates of relative efficacy may not be reliable owing to limitations with the methodological quality of the manufacturer's NMA. There was substantial clinical heterogeneity as included studies recruited patients with different subtypes of glaucoma and used different methods for measuring IOP. There was also a lack of transparency in the reporting of the methods, and insufficient statistical analysis was conducted to evaluate the potential inconsistency within the network. Together, these concerns limit the understanding of the true comparative efficacy of LBN versus other PGAs.
- **Inappropriate pooling of efficacy data from the primary studies:** The main efficacy input to the manufacturer's model was the decrease in IOP at three months from baseline. For LBN, this was calculated as the weighted average of the mean diurnal IOP reduction sourced from the phase III LUNAR[13] and APOLLO[6] multi-centre randomized trials and the phase II VOYAGER[14] dose-ranging study. Despite few differences in study eligibility criteria between these three trials, their designs, the baseline characteristics of

their recruited patients, and the times at which the efficacy measurement was taken differed. VOYAGER had, on average, more female patients (i.e., 67% in VOYAGER versus 58% in LUNAR and APOLLO) and more patients who were treatment-naive at baseline (i.e., 43% in VOYAGER versus 29% in APOLLO and LUNAR). In addition, the primary efficacy end point in the VOYAGER study was measured at 28 days compared with a three-month follow-up in the two phase III trials. Given the potential imbalance in patients' baseline characteristics and concerns with pooling observations at different follow-up times, combining the results of the VOYAGER study with those of APOLLO and LUNAR was considered inappropriate. In the CADTH reanalysis, data from VOYAGER were removed.

- **Lack of consideration for product's shelf-life in the estimation of treatment costs:** Treatment costs were calculated for LBN and comparators as the product of the per-drop price and the expected treatment duration (based on recommended dosing). It was assumed that patients would use the full treatment dispenser prior to refilling their prescription. However, this assumption fails to consider product shelf-life following bottle opening, and the resultant product wastage that is likely to occur due to the need to renew medications when shelf-life is exceeded. The clinical expert consulted by CADTH noted that the average shelf-life for glaucoma medications after an eye-drop dispenser bottle is opened is approximately four weeks due to concerns regarding microbial contamination of the dispenser[15] (i.e., risk of infection) and medication stability.[16] This is further documented in published literature.[5] Given that the number of drops expected to be used during a four-week period for most glaucoma medications is well below the maximum drop yield per bottle (assuming a drop yield of 35 drops per millilitre), patients would be advised to renew their medications before their eye-drop dispensers were empty, according to the clinical expert consulted by CADTH, resulting in considerable product wastage. Given that the manufacturer did not account for the likely wastage associated with the use of LBN and other comparators included in the model, the yearly and three-month treatment costs were significantly underestimated. In the CADTH reanalysis, treatment costs for all comparators were adjusted based on the assumption that eye-drop dispensers would be renewed every four weeks and that at least 13 bottles would be needed per year regardless of medication or maximum drop yield per bottle.
- **Calculation of costs associated with follow-up and monitoring:** The manufacturer assumed that all visits to an ophthalmologist would include a measurement of IOP by tonometry, an assessment of visual field by automated perimetry, and a structural assessment by optical coherence tomography, in addition to the fee for the specialist's visit, according to the Ontario Schedule of Benefits for Physician Services (hereafter referred to as "the Schedule").[17] The first visit was billed as a consultation, whereas all subsequent follow-up visits were billed as partial assessments. The manufacturer's model further assumed that patients had three medical visits per year in the first two years, regardless of disease severity; thereafter, the annual frequency of follow-up visits varied according to disease severity (i.e., one per year for mild OAG, two per year for moderate OAG, and three per year for severe OAG). According to the clinical expert consulted by CADTH, there were a number of assumptions about resource use and associated fee schedules that did not reflect clinical practice. These included the use of tonometry (not eligible for payment under the Schedule at the same time as a consultation), not reflecting the allowable annual limit for certain tests, and underestimating the number of physician visits expected in the first two years and for mild OAG. To improve face validity on resource use, the CADTH reanalysis removed tonometry and included corneal pachymetry (code G813 in the Schedule) during the initial consultation, restricted the maximum number of allowable optical coherence

tomography (OCT) services to twice per year, and set the number of follow-up visits to two in the first two years and in subsequent years for those with mild OAG.

- **Assumptions pertaining to treatment switching:** The manufacturer assumed that non-responders to first-line monotherapy, or those who did not fully respond to second-line bi-therapy, would be switched to monotherapy with another PGA medication. However, according to the clinical expert consulted by CADTH, this does not reflect current clinical practice. Patients who do not respond to first-line monotherapy with a PGA are not likely to be switched to second-line monotherapy or bi-therapy with another PGA. Rather than treatment switching within the same class of medication; patients who fail to respond to a first-line PGA are more likely to be treated with another class of medication, such as beta blockers, in subsequent lines of therapy. Due to the model structure, CADTH was unable to test the impact of this limitation in the model.

  Another concern with how switching was modelled by the manufacturer related to how drug costs were calculated following treatment switching. Namely, once a patient had switched from their existing PGA, drug costs associated with treatment switching were assumed to be the average of all PGAs, including the treatment that had been discontinued due to treatment failure. This effectively biases results in favour of comparators that are less expensive (i.e., latanoprost, travoprost), as their post-switch treatment costs should be higher than the cost of switching from a higher-cost PGA to a lower-cost PGA. In CADTH reanalysis, the average cost of switching represented the average cost of the other PGAs.

Other limitations identified included:

- **Uncertainty with methods used to derive progression from OHT to mild OAG:** The model submitted by the manufacturer assumed that transitioning from OHT to mild OAG depended on the change in IOP. Transition probabilities were based on a previous Dutch cost-effectiveness study by Peeters et al.[8] that described the relationship between IOP and yearly incidence of primary OAG in OHT patients. A polynomial model was fitted to these data, with a third-order polynomial equation chosen in order to generate a distribution of transition probabilities of progressing from OHT to OAG based on first-year IOP change. However, this cost-effectiveness study did not provide the details of the methods used to synthesize these transition probabilities that came from 11 cited references published between 1977 and 2003. There was also wide variation in the interventions evaluated in the cited studies, including (but not limited to) timolol, betaxolol, and placebo. Therefore, the methods used to derive progression from OHT to mild OAG lacked transparency, and may not be applicable to the Canadian setting. CADTH was unable to assess the direct impact of this limitation due to the paucity of data.
- **Uncertainty in the use of LBN as a subsequent PGA:** The manufacturer's base case assessed the cost-effectiveness of LBN as first-line therapy. The effectiveness of LBN was assumed to be equal to that of other PGAs in subsequent lines of treatment. While this assumption may be appropriate, it is associated with some uncertainty, given that LBN has not been compared with other PGAs in subsequent lines of therapy. CADTH was unable to test the impact of this limitation in the model due to the paucity of data.

CADTH Common Drug Review Reanalyses

As noted in the limitations, CADTH identified several important shortcomings relating to the manufacturer's economic evaluation. Before undertaking any reanalyses, CADTH corrected

programming and other model errors (i.e., revised errors in formulas; defined parameter uncertainty to reflect the expected sampling error; and ensured relative efficacy was preserved between comparators [to address the key limitation, lack of stability]). This improved the model stability and allowed for robust estimates to be produced in the probabilistic analysis.

CADTH subsequently conducted the following reanalyses:

1. Re-estimation of the average baseline IOP and average decrease of IOP at three months (change from baseline) for LBN using the weighted values from the LUNAR and APOLLO trials.
2. Adjustment of treatment costs for all comparators included in the model to account for the recommended shelf-life for glaucoma medications.
3. Adjustment of the annual frequency of follow-up and annual costs associated with medical visits to better align with Canadian clinical practice.
4. Revisions in the costs related to PGA switching to reflect the average costs of the other PGAs and to exclude the cost of the discontinued PGA.

The CADTH base case was informed by all of the previously described reanalyses (1 to 4).

Based on sequential probabilistic analysis of the CADTH Common Drug Review (CDR) base case (Table 3 and Table 12), CADTH found that LBN was associated with an additional benefit of 0.015 QALYs at an additional cost of $2,160 when compared with generic latanoprost, resulting in an ICUR of $142,801 per QALY gained. The overall QALY difference was small, and can be interpreted as LBN producing, on average, an extra five days of perfect health over a patient's lifetime compared with generic latanoprost. Sequential analysis further revealed that LBN was the optimal therapy at a willingness-to-pay threshold greater than or equal to $142,801; if a decision-maker's willingness-to-pay threshold was less than $142,801, latanoprost was the optimal therapy. All other treatments were either dominated or subject to extended dominance. The probability that LBN was the most likely cost-effective intervention compared with the other PGAs was 8.2% and 8.3% at a willingness-to-pay threshold of $50,000 and $100,000 per QALY, respectively.

Table 3: CADTH Common Drug Review Reanalyses

	Scenario	Treatments	Total QALYs	Total Costs ($)	Sequential ICUR ($ per QALY)
	Base case submitted by manufacturer[a]	Generic latanoprost	13.882	12,227	–
		Travoprost 0.004%	13.887	12,246	3,454
		Latanoprostene bunod	13.894	12,553	44,505
		Bimatoprost 0.03%	13.897	13,828	502,228
		Bimatoprost 0.01%	13.893	14,684	Dominated
	Corrected base case submitted by manufacturer	Generic latanoprost	13.739	12,929	–
		Travoprost 0.004%	13.740	12,974	Extendedly dominated
		Latanoprostene bunod	13.753	13,254	22,676
		Bimatoprost 0.03%	13.750	14,499	Dominated
		Bimatoprost 0.01%	13.745	15,317	Dominated
1		Generic latanoprost	13.811	12,997	–
		Travoprost 0.004%	13.812	13,039	Extendedly dominated

	Scenario	Treatments	Total QALYs	Total Costs ($)	Sequential ICUR ($ per QALY)
	Revised pooled efficacy for latanoprostene bunod (excluding VOYAGER study)	Latanoprostene bunod	13.824	13,317	23,411
		Bimatoprost 0.03%	13.823	14,551	Dominated
		Bimatoprost 0.01%	13.818	15,355	Dominated
2	**Adjusted treatment costs accounting for product shelf-life**	Generic latanoprost	13.779	15,358	–
		Travoprost 0.004%	13.780	16,289	Extendedly dominated
		Latanoprostene bunod	13.793	17,955	177,444
		Bimatoprost 0.03%	13.791	19,914	Dominated
		Bimatoprost 0.01%	13.786	26,490	Dominated
3	**Adjusted annual rate of medical visits and associated costs reflecting routine clinical practice**	Generic latanoprost	13.858	13,244	–
		Travoprost 0.004%	13.861	13,293	21,756
		Latanoprostene bunod	13.873	13,573	22,680
		Bimatoprost 0.03%	13.872	14,817	Dominated
		Bimatoprost 0.01%	13.866	15,629	Dominated
4	**Corrected costs associated with PGA switching**	Generic latanoprost	13.758	13,145	–
		Travoprost 0.004%	13.760	13,190	Extendedly dominated
		Latanoprostene bunod	13.773	13,242	6,686
		Bimatoprost 0.03%	13.771	14,550	Dominated
		Bimatoprost 0.01%	13.764	15,287	Dominated
1 to 4	**CADTH base case**	Generic latanoprost	13.773	16,484	–
		Travoprost 0.004%	13.773	17,338	Extendedly dominated
		Latanoprostene bunod	13.788	18,644	142,801
		Bimatoprost 0.03%	13.785	20,484	Dominated
		Bimatoprost 0.01%	13.778	26,507	Dominated

ICUR = incremental cost-utility ratio; PGA = prostaglandin analogue; QALY = quality-adjusted life-year.

Note: Unless otherwise specified, total costs and QALYs are discounted probabilistic values, based on 20,000 Monte Carlo iterations. All costs are presented in 2018 Canadian dollars.

[a] Based on a probabilistic analysis using 5,000 Monte Carlo iterations. Findings were not reproducible over multiple model runs up to 20,000 Monte Carlo iterations, and should be interpreted with caution.

CDR undertook a price-reduction analysis based on the manufacturer-submitted and CDR base-case analyses, assuming proportional price reductions for LBN (Table 4). Findings revealed that a reduction of at least 33% in the submitted price is required for LBN to achieve an ICUR of $50,000 per QALY gained compared with generic latanoprost.

Table 4: CADTH Reanalysis Price-Reduction Scenarios

ICURs of LBNs Versus PGA Comparators		
Price	**Base-Case Analysis Submitted by Manufacturer**	**Reanalysis by CADTH**
Submitted	If λ < $3,454, latanoprost is optimal. If $3,454 < λ < $44,505, travoprost is optimal. If $44,505 < λ < $502,228, latanoprostene bunod is optimal. If λ > $502,228, bimatoprost 0.03% is optimal.	If λ < $142,801, latanoprost is optimal. If λ > $142,801, latanoprostene bunod is optimal.
20% reduction	If λ < $1,246,606, latanoprostene bunod is optimal. If λ > $1,246,606, bimatoprost 0.03% is optimal.	If λ < $85,489, latanoprost is optimal. If λ > $85,489, latanoprostene bunod is optimal.
30% reduction	If λ < $714,482, latanoprostene bunod is optimal. If λ > $714,482, bimatoprost 0.03% is optimal.	If λ < $59,013, latanoprost is optimal. If λ > $59,013, latanoprostene bunod is optimal.
33% reduction	If λ < $727,540, latanoprostene bunod is optimal. If λ > $727,540, bimatoprost 0.03% is optimal.	If λ < $41,881, latanoprost is optimal. If λ > $41,881, latanoprostene bunod is optimal.
40% reduction	If λ < $686,885, latanoprostene bunod is optimal. If λ > $686,885, bimatoprost 0.03% is optimal.	If λ < $22,014, latanoprost is optimal. If λ > $22,014, latanoprostene bunod is optimal.
50% reduction	If λ < $1,325,089, latanoprostene bunod is optimal. If λ > $1,325,089, bimatoprost 0.03% is optimal.	Latanoprostene bunod dominant.
60% reduction	If λ < $1,097,728, latanoprostene bunod is optimal. If λ > $1,097,728, bimatoprost 0.03% is optimal.	Latanoprostene bunod dominant.
70% reduction	If λ < $1,041,624, latanoprostene bunod is optimal. If λ > $1,041,624, bimatoprost 0.03% is optimal.	Latanoprostene bunod dominant.

λ = willingness-to-pay; ICUR = incremental cost-utility ratio; LBN = latanoprostene bunod; PGA = prostaglandin analogue.

Note: All price-reduction scenarios were based on a probabilistic analysis using 20,000 Monte Carlo iterations, with the exception of the manufacturer's base-case analysis at the submitted price.

CADTH also considered an analysis assuming equal treatment efficacy among first-line PGAs. This assessment was conducted based on the cost of each treatment per drop. The result suggests a price reduction of approximately 27% would be required to be equivalent to the least-costly PGA (latanoprost) on a per-drop basis. However, CADTH acknowledges the uncertainty regarding the number of drops per bottle and notes that consequently, the results of this analysis should be interpreted with caution.

Table 5: CADTH Common Drug Review Scenario Analysis: Price per Drop

Drug	Cost per Bottle ($)	Drops per Bottle	Cost per Drop ($)	Price Reduction Required for Latanoprostene Bunod to Be Cost Equivalent per Drop
Latanoprostene bunod	**26.2500**	**175**	**0.1500**	**–**
Bimatoprost 0.01%	59.3000	175	0.3389	NA
Bimatoprost 0.03%	27.5808	105	0.2627	NA
Travoprost (generics)	10.0660	87.5	0.1150	23%
Latanoprost (generics)	9.5830	87.5	0.1095	27%

NA = not applicable.

Note: All prices are from the Ontario Drug Benefit Formulary/Comparative Drug Index (accessed February 2019) and do not include dispensing fees. This analysis assumes drop sizes were the same across treatments (35 drops/mL).

Issues for Consideration

Adherence with glaucoma medications is generally very poor, and difficulty with medication adherence in patients with OHT and OAG is arguably the largest contributor to vision loss from glaucoma. While poor adherence is not unique to LBN or any other glaucoma

medication, the comparative cost-effectiveness of treatments for OHT and OAG may be considerably different where there are differences in adherence rates between treatments.

Patient Input

Patient input gathered by the Canadian Council of the Blind, the Canadian National Institute for the Blind, and the Foundation Fighting Blindness was obtained from Canadian patients living with glaucoma and their caregivers. The majority of patients from which input was sought had prior experience with drug therapy (eye drops or oral medications); some patients had also received laser eye surgery or another surgical intervention, including minimally invasive glaucoma surgery. Patients noted that the severity of glaucoma varies considerably among those living with this condition, and ranges from no vision loss to complete blindness. Glaucoma exerts a significant impact on all aspect of life, including quality of life, psychosocial functioning, and the ability to undertake activities of daily living. Given the progressive and irreversible nature of disease, these domains are increasingly affected as the severity of visual impairment increases over time. In particular, patients may experience increased anxiety, depression, and fear associated with worsening disease, as well as increased mobility issues, such as difficulty performing household chores and engaging in recreational fitness; these limitations ultimately threaten patients' psychological well-being and functional independence. The HUI-3 scale, which was the health outcome measure used in the economic analysis, includes these dimensions. As such, with increasing disease severity, the associated utility weight was lower in the manufacturer's model.

Patients also noted that the cost of medication, as well as the costs associated with travel and accommodation required for specialist visits, pose a significant barrier to their care. A substantial burden on caregivers (i.e., emotional and physical support, time commitment) was also implied where patients experience a loss of independence and become reliant on their loved ones for assistance with daily activities and accompaniment to visits with health care providers. Caregiver burden and indirect costs, including out-of-pocket costs associated with travel and accommodation, were not considered in the manufacturer's model.

No patients specifically reported having previous experience with LBN. As such, the relative impact of LBN versus existing PGA treatments on the patient-important outcomes noted previously remains unknown.

Conclusions

In patients with OHT and OAG, CADTH found that LBN was associated with an additional benefit of 0.015 QALYs at an additional cost of $2,160 when compared with generic latanoprost, resulting in an ICUR of $142,801 per QALY gained. All other evaluated PGAs were dominated or subject to extended dominance. At a reduction of at least 33% of the submitted price, the ICUR of LBN would fall below $50,000 per QALY compared with generic latanoprost.

It should be noted that there remains significant uncertainty regarding the comparative efficacy of LBN compared with other PGA therapies, which introduces uncertainty regarding the true cost-effectiveness of LBN compared with alternative PGA therapies. The drug cost of LBN ($0.300 per drop) is greater than that of generic latanoprost ($0.219 per drop).

Appendix 1: Cost Comparison

The comparators presented in Table 6 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

Table 6: Cost Comparison Table for Prostaglandin Analogues for Ocular Hypertension and Open-Angle Glaucoma

Drug/Comparator	Dosage Form	Size	Price per Bottle	Price ($/mL)	Recommended Dosage[a]	Cost per Day ($)
Latanoprostene bunod 0.024% (Vyzulta)	**Ophthalmic solution**	**5 mL**	**26.2500[b]**	**5.2500**	**One drop daily**	**0.30**
Prostaglandin Analogues						
Latanoprost 50 mcg/mL (Monoprost)	Ophthalmic solution, single-use containers	30 containers, 0.2 mL	20.5338	3.4223[c]	One drop daily	0.68
Bimatoprost 0.03% (Vistitan)	Ophthalmic solution	3 mL 5 mL	27.5808 45.9680	9.1936	One drop daily	0.53
Bimatoprost 0.01% (Lumigan RC)	Ophthalmic solution	5 mL 7.5 mL	59.3000 88.9500	11.8600	One drop daily	0.68
Latanoprost 0.005% (generics)	Ophthalmic solution	2.5 mL	9.5830	3.8332	One drop daily	0.22
Travoprost 0.003% (Izba)	Ophthalmic solution	5 mL	20.1300	4.0260[d]	One drop daily	0.23
Travoprost Z 0.004% (generics)	Ophthalmic solution	2.5 mL 5 mL	10.0660 20.1320	4.0264	One drop daily	0.23

Note: All prices are from the Ontario Drug Benefit Formulary/Comparative Drug Index (accessed February 2019) unless otherwise indicated, and do not include dispensing fees. Cost per day calculation assumes drop sizes were the same across treatments (35 drops/mL). Daily cost assumes treatment of both eyes.

[a] Recommended dosage is for each affected eye.

[b] Manufacturer-submitted price.[2]

[c] IQVIA Delta PA wholesale acquisition cost (February 2019).[18]

Table 7: Other Eye Drops for Ocular Hypertension and Open-Angle Glaucoma

Comparator	Dosage Form	Size	Price per Bottle	Price ($/mL)	Recommended Dosage[a]	Cost per Day ($)
Alpha2 Adrenergic Agonists						
Apraclonidine 0.5% (Iopidine)	Ophthalmic solution	5 mL	24.1800[b]	4.8360	One drop two to three times daily	0.55 to 0.83
Brimonidine P 0.15% (generic)	Ophthalmic solution	5 mL 10 mL 15 mL	9.3700 18.7400 28.1100	1.8740	One drop three times daily	0.32
Brimonidine 0.2% (generic)	Ophthalmic solution	5 mL 10 mL 15 mL	5.7750 11.5500 17.3250	1.1550	One drop twice daily	0.13
Beta Blockers						
Betaxolol 0.25% (Betoptic S)	Ophthalmic solution	10 mL	25.5800	2.5580	One drop twice daily	0.29
Levobunolol 0.5% (Betagan)	Ophthalmic solution	10 mL	36.0000	3.6000	One drop twice daily	0.41
Timolol 0.25% (generic)	Ophthalmic solution	5 mL 10 mL	4.8390 9.6780	0.9678	One drop twice daily	0.11
Timolol 0.5% (generic)	Ophthalmic solution	5 mL 10 mL	6.0725 12.1450	1.2145	One drop twice daily	0.14
Carbonic Anhydrase Inhibitors						
Brinzolamide 1% (Azopt)	Ophthalmic solution	5 mL	17.7800	3.5560	One drop two to three times daily	0.41 to 0.61
Dorzolamide 2% (generic)	Ophthalmic solution	5 mL	15.3500	3.0700	One drop three times daily	0.53
Miotics						
Pilocarpine 2% (Isopto Carpine)	Ophthalmic solution	15 mL	4.0110	0.2674[b]	Two drops three to four times daily	0.09 to 0.12
Pilocarpine 4% (Isopto Carpine)	Ophthalmic solution	15 mL	4.5510	0.3034[b]	Two drops three to four times daily	0.10 to 0.14
Dual Therapies						
Brimonidine/timolol 0.2%/0.5% (Combigan)	Ophthalmic solution	10 mL	44.5300	4.4530	One drop twice daily	0.51
Brinzolamide/brimonidine 1.0%/0.2% (Simbrinza)	Ophthalmic solution	10 mL	46.8100	4.6810	One drop twice daily	0.54
Brinzolamide/timolol 1%/0.5% (Azarga)	Ophthalmic solution	5 mL	23.3500	4.6700	One drop twice daily	0.53
Dorzolamide/timolol 2%/0.5% (generics)	Ophthalmic solution	10 mL	20.9510	2.0951	One drop twice daily	0.24
Latanoprost/timolol 50mcg/5mg /mL (generics)	Ophthalmic solution	2.5 mL	11.0700	4.4280	One drop daily	0.25
Travoprost/timolol 0.004%/0.05% (DuoTrav PQ)	Ophthalmic solution	5 mL	58.9500	11.7900	One drop daily	0.67

Note: All prices are from the Ontario Drug Benefit Formulary (accessed February 2019) unless otherwise indicated, and do not include dispensing fees. Cost per day calculation assumes drop sizes were the same across treatments (35 drops/mL). Daily cost assumes treatment of both eyes.

[a] Recommended dosage is for each affected eye.

[b] Saskatchewan Online Formulary Database (February 2019).[19]

[c] IQVIA Delta PA wholesale acquisition cost (February 2019).[18]

Appendix 2: Additional Information

Table 8: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?			X
Comments Reviewer to provide comments if checking “no”	A number of programming errors were found in the model, including: • errors in the formulas used to calculate subsequent drug and health care costs in the decision tree; • references to deterministic input values rather than probabilistic values in multiple calculation worksheets (e.g., Markov traces, efficacy inputs), which prevented parameters from being varied when conducting the probabilistic analysis; • inappropriate use and application of standard statistical formulas (e.g., pooled standard deviation, probability-to-rate conversion); and, • inappropriate selection of distributions for model inputs. It was also challenging to validate estimates from the clinical trials and network meta-analysis as it was unclear which study samples informed point estimates used in the pharmacoeconomic model. Furthermore, an arbitrary coefficient of variation (± 25%) was used to define parameter uncertainty for the majority of input parameters rather than using published sources, where available.		
Was the material included (content) sufficient?		X	
Comments Reviewer to provide comments if checking “poor”	None		
Was the submission well organized and was information easy to locate?		X	
Comments Reviewer to provide comments if checking “poor”	None		

Table 9: Author Information

Authors of the Pharmacoeconomic Evaluation Submitted to CADTH Common Drug Review

☐ 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 3: Summary of Other Health Technology Assessment Reviews of Drug

No other Health Technology Assessment agencies have reviewed latanoprostene bunod for ocular hypertension or open-angle glaucoma. Latanoprostene bunod is currently undergoing review at the Institut national d'excellence en santé et en services sociaux (INESSS) in Quebec.[20]

Appendix 4: Reviewer Worksheets

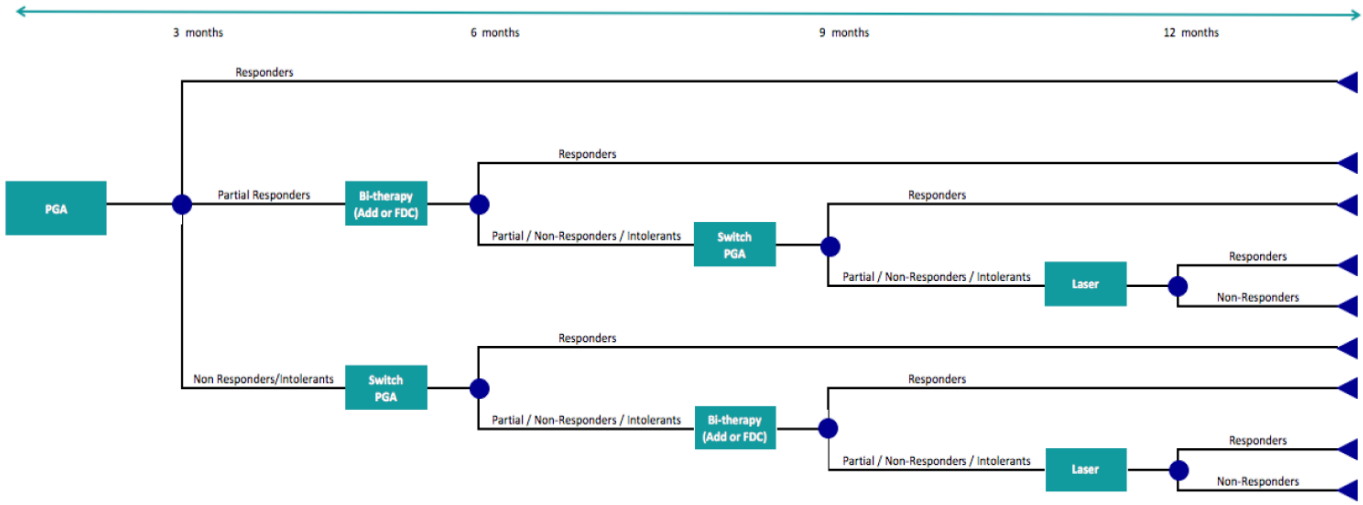
Manufacturer's Model Structure

The manufacturer submitted a hybrid decision tree and cohort-based Markov state-transition model developed in Microsoft Excel. The decision tree was used to estimate therapeutic adjustments based on intraocular pressure (IOP) response during the first year of treatment, while the Markov model predicted the lifetime progression of disease using a series of health states relating to disease severity. The modelled patient cohort was aligned with the population from the LUNAR,[13] APOLLO,[6] and VOYAGER[14] clinical studies (mean age, 64.0 years; 59.5% female; mean IOP at baseline, 26.6 mm Hg), while the baseline distribution of disease severity was based on a Canadian cross-sectional study.[7]

At the start of the decision tree (Figure 1), patients with ocular hypertension (OHT) and open-angle glaucoma (OAG) were assumed to receive one of the available prostaglandin analogues (PGA) as first-line monotherapy. Based on the results of a manufacturer-commissioned, unpublished network meta-analysis (NMA),[3] these patients could fully respond, partially respond, or not respond to the first-line PGA. Responders remained on existing treatment. Partial responders received additional bi-therapy and, for partial or non-responders to bi-therapy, PGA were switched as third-line therapy. Non-responders were switched to second-line monotherapy with another PGA; bi-therapy was added to partial or non-responders in the third line. The efficacy of subsequent treatments was based on a published NMA.[4] The model assumed that follow-up consultations to assess treatment response would be performed every three months during the first year; therefore, a maximum of three consecutive lines of treatment were possible in the decision tree before laser trabeculoplasty was performed for partial responders or non-responders. Response to therapy was assessed based on percentage reduction in IOP. Specifically, for the first-line treatments, it was assumed that an IOP decrease of at least 25% from baseline represented full response to therapy. Partial response to therapy was assumed where the IOP decrease was between 15% and 25% from baseline; any decrease in IOP of 15% or less was considered non-response. Although patients who experienced intolerance to therapy were considered as non-responders in this model, intolerance was not explicitly modelled. For subsequent lines of treatment, a decrease in IOP of at least 20% was considered a full response.

At the terminal node of the decision tree, patients entered the Markov model (Figure 2) and cycled through a number of health states at one-year intervals over approximately 40 years; health states were defined based on the degree of glaucomatous damage and included OHT, mild OAG, moderate OAG, advanced OAG, blindness, and death. Patients could enter the model in any of the OHT or OAG health states depending on their baseline disease severity and response to treatment at the end of the first treatment year (i.e., decision tree). The model assumed that changes in IOP from the decision tree affected the risk of progression from OHT to mild OAG,[8] but did not affect transition probabilities in the more severe health states; transitions from mild OAG to more severe glaucoma states were based on two studies from the Early Manifest Glaucoma Trial.[9,10] Mortality risk was age- and sex-dependent; patients could transition to this absorbing death state at any point.

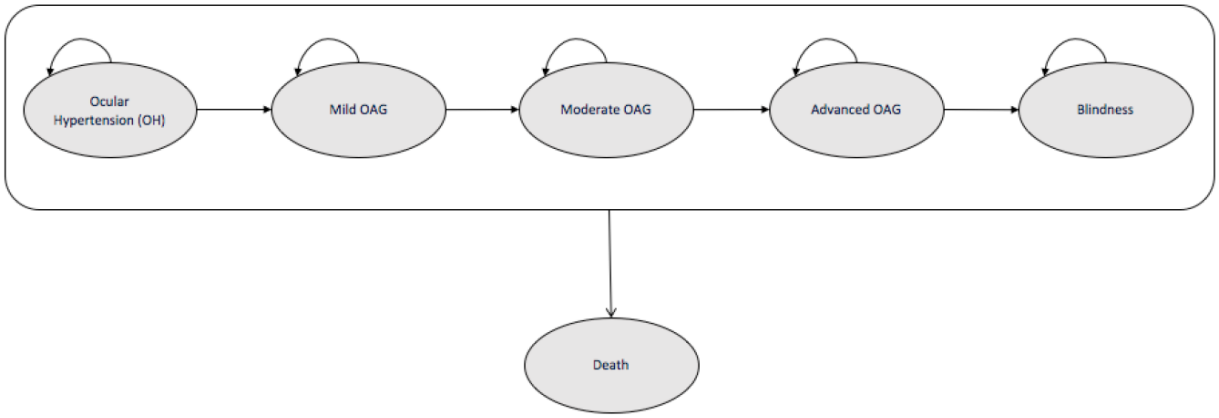
Figure 1: Decision Tree Structure Representing Response to Prostaglandin Analogues



FDC = fixed-dose combination; PGA = prostaglandin analogue.

Source: Manufacturer's pharmacoeconomic submission.[2]

Figure 2: Markov Model Structure



OAG = open-angle glaucoma.

Source: Manufacturer's pharmacoeconomic submission.[2]

Table 10: Data Sources

Data Input	Description of Data Source	Comment*
Efficacy, Safety, and Withdrawals		
Efficacy • Reduction in mean diurnal IOP (mm Hg) at 3 months • Proportion of responders (measured as percentage reduction in IOP decrease from baseline)	The clinical efficacy of latanoprostene bunod (measured as the decrease in mean diurnal IOP at 3 months versus baseline) was sourced from two phase III RCTs (APOLLO[6] and LUNAR[13]) and a phase II dose-ranging study (VOYAGER).[14] The comparative efficacy of latanoprostene bunod and other first-line PGAs was obtained from an unpublished NMA commissioned by the manufacturer.[3] The comparative efficacy of PGAs used in subsequent lines of treatment was obtained from a MTC and meta-regression of the efficacy of PGAs and comparators for OAG and OHT published by Orme et al.[4] The distribution of responders (≥ 25% IOP reduction), partial responders (> 15% and < 25% IOP reduction), and non-responders (< 15% IOP reduction) for first-line treatments was derived using microsimulation methods. The same computer simulation technique was used to derive the proportion of responders (≥ 20% IOP reduction) and partial/non-responders (< 20% IOP reduction) for subsequent-line treatments.	Acceptable, given the lack of direct comparative evidence on the efficacy of latanoprostene bunod and other PGAs. However, the manufacturer's NMA has several important limitations, including the reliance on studies with a wide variety of patient populations, a lack of assessment of the potential impact of clinical heterogeneity on estimates of treatment effect, and no analysis relating to comparative safety or tolerability. There was also a lack of transparency in the methods used for indirect treatment comparison and insufficient statistical analysis for inconsistency. A full assessment of the methodological quality of the manufacturer's NMA is provided in the CDR Clinical Review Report. As there is no empirical data on the distribution of responders in OHT and OAG patients, the microsimulation methods used by the manufacturer to derive the proportions of responders, partial responders, and non-responders may be appropriate. This approach was used previously by Orme et al.[4,21] to calculate the proportion of patients with IOP below an absolute target.
AEs	Not included.	Acceptable. The clinical expert consulted by CADTH expressed concerns that certain adverse events associated with latanoprostene bunod (i.e., conjunctival hyperemia) may be particularly problematic if this product is used in routine practice; however, it seems unlikely that adverse events associated with latanoprostene bunod compared with other PGAs would disproportionally affect treatment costs or health-related quality of life for patients with OHT or OAG.
Natural History		
Baseline characteristics	Baseline patient demographics (mean age and proportion of females) were based on pooled data relating to patients included in the APOLLO,[6] LUNAR,[13] and VOYAGER[14] studies. The initial distribution of disease severity was based on the full patient population in the Canadian cross-sectional study by Buys et al.[7]: 27.9% of patients had OHT, while the	Mostly acceptable. Baseline characteristics of participants reported in the manufacturer's model were slightly different from what was reported in the Canadian cross-sectional study by Buys et al.[7] The mean age (64.0 vs. 61.2 years), the proportion of females (59.49% vs. 49.6%), and baseline IOP (26.6 mm Hg vs. 21.3 mm Hg) differed slightly between trial participants and the patient population in the Canadian cross-sectional study. The clinical expert consulted by CADTH noted that the initial distribution of disease severity is appropriate for the Canadian setting.

Data Input	Description of Data Source	Comment*
	remaining 72.1% had OAG; of the patients with OAG, 52.05% had mild OAG, 27.05% had moderate OAG, and 20.89% had severe OAG.	
OH to mild OAG transitions (within Markov model)	Transitioning from OH to mild OAG depended on change in IOP and was based on a previous Dutch cost-effectiveness analysis study by Peeters et al.[8] A polynomial model was fitted to these data and a third-degree polynomial equation was retained in order to generate a distribution of transition probabilities of progressing from OHT to OAG per mm Hg IOP.	The cost-effectiveness study by Peeters et al. did not provide the details of methods used to estimate or synthesize these transition probabilities from the 11 cited references (long-term OHT studies) published between 1977 and 2003. There were also wide variations in the interventions being evaluated in these long-term OHT studies, including (but not limited to) timolol, betaxolol, and placebo. CDR was unable to assess the direct impact of this limitation due to the paucity of data. However, the use of the third-degree polynomial equation to generate the distribution of transition probabilities from OHT to OAG is acceptable.
Mild to moderate OAG and moderate to advanced OAG transitions (within Markov model)	Transitioning from mild OAG to more severe glaucoma health states was based on natural history data derived from the Swedish-based Early Manifest Glaucoma Trial, as described by Hejil et al.[9] and Leske et al.[10]	Acceptable. Patient demographics were comparable between the Early Manifest Glaucoma Trial and the patient cohort modelled by the manufacturer (mean age, 68.1 vs. 64.0 years; 66.0% vs. 59.5% females; baseline IOP, 26.6 mm Hg vs. 20.7 mm Hg). The annual probability of progression for non-treated patients is higher than the value derived from the Canadian Glaucoma Study (approximately 12% vs. 7%).[22] The clinical expert consulted by CADTH noted that progression in the absence of treatment is challenging to define; yet given the robustness of the Early Manifest Glaucoma Trial, these estimates are likely to be reasonable for the Canadian setting.
Advanced OAG to blindness transitions (within Markov model)	Progressing to blindness (unilateral and bilateral) from advanced OAG was derived from a study by Peters et al.[23]	The clinical expert consulted by CADTH suggested that a 2.4% annual rate of progression to unilateral blindness may be higher than what is observed in routine clinical practice; however, it may be acceptable to use this estimate in the absence of other estimates.
Mortality	Mortality rates were based on the general Canadian population data.[24]	Appropriate given that disease and treatment do not affect mortality.
Utilities		
Health-state utilities	Specific utility values for each health state were sourced from a European study by Wolfram et al.[11] that reported utility derived from the Health Utility Index Mark 3. Utility values relating to blindness were obtained from a study by Brown et al.[12]	Utility values were based on the European studies. The estimated values may not be generalizable to the Canadian population, but may be acceptable in the absence of Canadian utility data.
Resource Use and Costs		
Treatment (drugs)	The drug cost for latanoprostene bunod was provided by the manufacturer.[2] Drug acquisition costs for all other comparators were obtained from the Ontario Drug Benefit Formulary/ Comparative Drug Index.[25]	The unit costs of medications are appropriate, and lowest-cost alternatives were selected for all comparators. However, the clinical expert consulted by CADTH noted that the average shelf-life for glaucoma eye drops after opening is approximately four weeks. Medication renewal after four weeks of use is advised due to

Data Input	Description of Data Source	Comment*
		concerns regarding contamination of the bottle (infection) and medication stability. Given that the manufacturer did not account for the likely wastage that results from the need to renew glaucoma eye drops before the bottle is empty, costs associated with latanoprostene bunod and other comparators were underestimated in the model. Dispensing fees and mark-ups were not applied for any medications in the submitted model, which is acceptable.
Administration	None.	Appropriate.
Follow-up and monitoring	Physician fees for medical visits were obtained from the Ontario Health Insurance Plan's (OHIP) Schedule of Benefits for Physician Services.[17] Medical visits were defined as consisting (at minimum) of one measurement of IOP by tonometry; one assessment of visual field by automated perimetry; and OCT. The frequency of follow-up visits according to stage of glaucoma was estimated using the COS guidelines[26] and the Canadian Glaucoma Study,[22] published by Chauhan et al.	The clinical expert consulted by CADTH noted that tonometry (OHIP code G435) cannot be billed together with a consultation (OHIP code A235); instead, physicians in Ontario may bill pachymetry (code G813), with the caveat that this fee code can only be applied once during a patient's lifetime by one physician. The clinical expert also noted that, where there are multiple follow-ups per patient per year, Ontario physicians may bill structural assessment by OCT up to two times per year, and that most physicians will bill a special assessment (code A233; higher unit cost than partial assessment) at least once per year (maximum allowed) instead of a partial assessment. The clinical expert consulted by CADTH suggested that most physicians are not likely to perform testing more than two times per year due to restrictions on physician billing (e.g., maximum of two OCT assessments per year). The frequency of follow-up visits did not align with the practice of the clinical expert consulted by CADTH as it was overestimated by the manufacturer in the first two years of treatment and underestimated for mild OAG.
AEs	Not included.	Appropriate. According to the clinical expert consulted by CADTH, no costs are associated with the management of adverse events in patients with OHT or OAG.
Health state	Costs associated with bilateral blindness were sourced from a Canadian study by Cruess et al.[27] The ratio of unilateral versus bilateral blindness was sourced from a costing study by Koberlein et al.[28] Costs associated with other health states (mild, moderate, or advanced OAG) were calculated based on the annual number of physician visits and diagnostic procedures performed.	Acceptable. The micro-costing approach used by the manufacturer to determine costs according to stage of glaucoma did not align with the expectations of the clinical expert consulted by CADTH. See main report.

CDR = CADTH Common Drug Review; COS = Canadian Ophthalmological Society; IOP = intraocular pressure; MTC = mixed-treatment comparison; OAG = open-angle glaucoma; NMA = network meta-analysis; OCT = optical coherence tomography; OHIP = Ontario Health Insurance Plan; OHT = ocular hypertension; RCT = randomized controlled trial; PGA = prostaglandin analogue; vs. = versus.

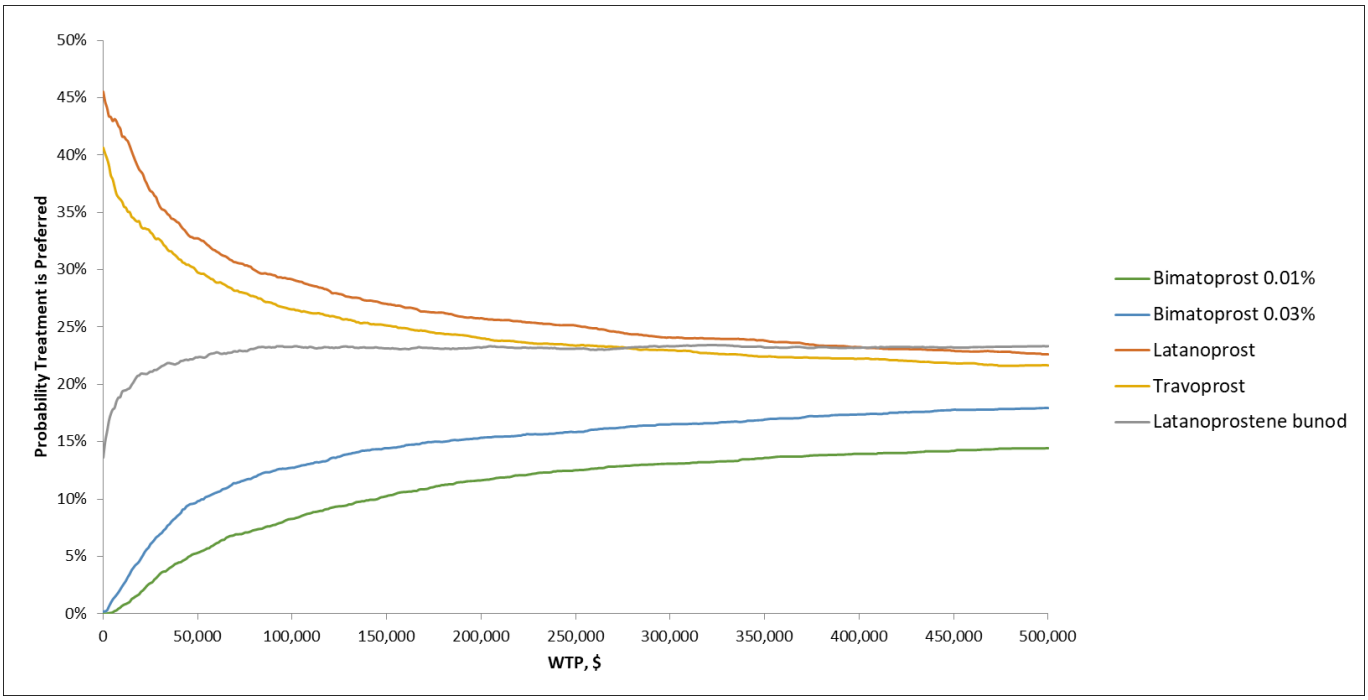
Table 11: Manufacturer's Key Assumptions

Assumption	Comment
All patients were assumed to have both eyes treated.	This assumption likely overestimates the costs of medications and glaucoma management as it is possible for patients to experience OHT or OAG in only one eye. However, this assumption should not affect the cost-effectiveness findings as it was applied to all comparators included in the model.
No more than three lines of medication were considered before entering the Markov model.	Uncertain. The clinical expert consulted by CADTH suggested uncertainty over treatment switching for non-responders and partial responders. Most patients in routine practice would be expected to receive at least three classes of medication (and potentially four) before undergoing laser treatment.
Treatment response was based on percentage reduction in IOP. For first-line treatments, it was assumed that an IOP decrease of at least 25% from baseline represented full treatment response, regardless of disease severity. If the IOP decrease was between 15% and 25%, this was considered a partial response, regardless of disease severity. Any decrease lower than 15% represented non-response. For treatments prescribed after the first-line monotherapy (i.e., second-line monotherapy or bi-therapy), an IOP decrease of at least 20% from baseline was considered full treatment response.	The clinical expert consulted by CADTH considered that these assumptions were reasonable and noted that the threshold for full response is slightly more aggressive than the conventionally used threshold for treatment response in clinical practice (i.e., a decrease of at least 20% from baseline). The expert further noted that a more aggressive IOP reduction may be desired for patients with advanced OAG. Additionally, it is reasonable to accept a lower threshold for treatments prescribed after first-line monotherapy as IOP would likely already have been reduced for these patients compared with their IOP at treatment initiation (i.e., at first-line therapy).
Patients not responding to first-line treatment, or who are not full responders to bi-therapy, were switched to a different PGA.	Patients who do not respond to first-line monotherapy with a PGA are not likely to be switched to second-line monotherapy with another PGA, according to the clinical expert consulted by CADTH. Treatment switching is not generally performed within the same medication class; therefore, patients who fail to respond to a first-line PGA are more likely to receive second-line treatment with another class of medication (usually beta blockers) rather than another product within the same class.
Patients responding to therapy are assumed to have remained on existing treatment.	Appropriate, according to the clinical expert consulted by CADTH.
Treatment effect maintained over time for all treatments.	Appropriate. The clinical expert consulted by CADTH noted that while the use of beta blockers in the management of OHT and OAG may frequently lead to tachyphylaxis (i.e., rapidly decreasing response or desensitization to a drug after initial administration), this is generally not a concern with PGAs, which are likely to maintain efficacy over time.
The model assumed that changes in IOP affected progression from OHT up to severe OAG.	Acceptable.
Disease progression through health states was assumed to follow a linear progression and to be constant over time.	Acceptable, according to the clinical expert consulted by CADTH. However, uncertainty remains with regards to how the natural history of the disease may progress. The clinical expert noted an alternate study is available: the Canadian Glaucoma Study.[22]
Adherence and intolerance were not considered.	The clinical expert consulted by CADTH felt that while adherence was a significant problem for medications used in the management of OHT and OAG, this issue is not unique to latanoprostene bunod, but is likely to apply equally to all comparators included in the manufacturer's model.

IOP = intraocular pressure; OAG = open-angle glaucoma; OHT = ocular hypertension; PGA = prostaglandin analogue.

Manufacturer's Results

Figure 3: Cost-Effectiveness Acceptability Curve of the Manufacturer's Probabilistic Base Case



WTP = willingness-to-pay.

Source: Manufacturer's pharmacoeconomic submission.[2]

CADTH Common Drug Review Reanalyses

Table 12: CADTH Common Drug Review Probabilistic Base Case

	Total Costs ($)	Total QALYs	Δ Cost vs. Latanoprost ($)	Δ QALYs vs. Latanoprost	ICUR ($/QALY) vs. Latanoprost	Sequential ICUR ($/QALY)
Non-Dominated Options						
Latanoprost	16,484	13.773	–	–	–	–
Latanoprostene bunod	18,644	13.788	2,160	0.015	142,801	142,801
Dominated Options						
Travoprost	17,338	13.773	854	0.000	Subject to extended dominance through latanoprost and latanoprostene bunod	
Bimatoprost 0.03%	20,484	13.785	4,000	0.012	Dominated by latanoprostene bunod	
Bimatoprost 0.01%	26,507	13.778	10,023	0.005	Dominated by latanoprostene bunod	

Δ = incremental; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; vs. = versus.

Note: Total costs and QALYs are discounted probabilistic values based on 20,000 Monte Carlo iterations. All costs are presented in 2018 Canadian dollars.

CADTH conducted a number of scenario analyses using alternative assumptions relating to the CADTH base case. These included:

(1) testing alternative assumptions relating to product shelf-life recommendations (i.e., six weeks for all comparators, recommended shelf-life from individual product monographs, and assuming no shelf-life restrictions)

(2) testing slower disease progression based on estimates sourced from the Canadian Glaucoma Study

(3) testing treatment of one eye only and assuming unilateral blindness.

Table 13 presents the results of all scenario analyses.

Table 13: CADTH Common Drug Review Scenario Analyses[a]

	Scenario	Treatments	Total QALYs	Total Costs ($)	Sequential ICUR ($ per QALY)
Scenario 1: Alternative Product-Shelf-Life Assumptions					
1a	**Product shelf-life of 6 weeks for all glaucoma medications**	Generic latanoprost	13.808	14,881	–
		Travoprost 0.004%	13.809	15,480	Extendedly dominated
		Latanoprostene bunod	13.823	16,344	94,601
		Bimatoprost 0.03%	13.821	17,613	Dominated
		Bimatoprost 0.01%	13.814	21,729	Dominated
1b	**Recommended shelf-life based on product monographs**	Generic latanoprost	13.832	15,763	–
		Travoprost 0.004%	13.836	16,347	Extendedly dominated
		Latanoprostene bunod	13.849	16,358	35,223
		Bimatoprost 0.03%	13.845	20,251	Dominated
		Bimatoprost 0.01%	13.841	26,200	Dominated
1c		Generic latanoprost	13.791	13,704	–

	Scenario	Treatments	Total QALYs	Total Costs ($)	Sequential ICUR ($ per QALY)
	All medications used until end of treatment (i.e., no product shelf-life recommendations)	Travoprost 0.004%	13.792	13,736	Extendedly dominated
		Latanoprostene bunod	13.806	13,876	11,292
		Bimatoprost 0.03%	13.803	15,048	Dominated
		Bimatoprost 0.01%	13.799	15,815	Dominated
Scenario 2: Slower Disease Progression					
2	**Annual rate of disease progression and progression risk by mm Hg of IOP reduction (hazard ratio) from Canadian Glaucoma Study**	Generic latanoprost	14.466	14,223	–
		Travoprost 0.004%	14.467	15,102	Extendedly dominated
		Latanoprostene bunod	14.477	16,407	200,082
		Bimatoprost 0.03%	14.476	18,257	Dominated
		Bimatoprost 0.01%	14.473	24,272	Dominated
Scenario 3: Unilateral Treatment and Blindness Definition					
3	**One eye treated and unilateral blindness**	Generic latanoprost	13.800	22,880	–
		Travoprost 0.004%	13.800	23,689	Extendedly dominated
		Latanoprostene bunod	13.815	24,877	125,821
		Bimatoprost 0.03%	13.813	26,635	Dominated
		Bimatoprost 0.01%	13.807	32,336	Dominated

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

Note: All costs are presented in 2018 Canadian dollars.

[a] Total costs and QALYs are discounted probabilistic values based on 20,000 Monte Carlo iterations.

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