CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

Latanoprost (Monoprost — Laboratoires Théa)
Indication: Glaucoma and Ocular Hypertension

RECOMMENDATION:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that preservative-free latanoprost 50 µg/mL ophthalmic solution (Monoprost) be reimbursed for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension, if the following condition is met:

Condition:
- The drug plan cost of treatment with Monoprost should not exceed the drug plan cost of treatment with the least costly prostaglandin analogue (PGA).

Service Line:	CADTH Drug Reimbursement Recommendation
Version:	1.0
Publication Date:	April 2018
Report Length:	7 Pages

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

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LATANOPROST (MONOPROST — Laboratoires Théa)

Indication: Glaucoma and Ocular Hypertension

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that preservative-free latanoprost 50 µg/mL ophthalmic solution (Monoprost) be reimbursed for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension, if the following condition is met:

Condition

- The drug plan cost of treatment with Monoprost should not exceed the drug plan cost of treatment with the least costly prostaglandin analogue (PGA).

Reasons for the Recommendation

1. There is no evidence that Monoprost is more efficacious than other PGA formulations. Specifically, results from two phase III, investigator-masked, randomized controlled trials (RCTs) (pivotal study LT2345-PIII-12/08, N = 404; supportive study LT2345-001, N = 334) showed similar efficacy in lowering IOP between Monoprost and benzalkonium chloride (BAK)-preserved latanoprost (Xalatan) during a period of 84 days. The 95% confidence interval (CI) for the difference between treatment groups in mean change in IOP from baseline to days 15, 42, and 84 met the pre-specified non-inferiority margin of 1.5 mm Hg in the pivotal study and was within the equivalence margin of 1.5 mm Hg in the supportive study.
2. CDEC concluded that the potential tolerability benefits of Monoprost over Xalatan had not been demonstrated. This conclusion was based on methodological limitations (the lack of validated instruments to assess tolerability outcomes, the absence of patient masking, and the lack of control for multiple statistical testing) and uncertainty in the clinical meaningfulness of the observed differences in tolerability outcomes (conjunctival hyperemia and symptoms of ocular discomfort) between treatment groups in the pivotal study. In addition, there were no observed differences in tolerability between Monoprost and Xalatan in the supportive study.
3. At the submitted price of $20.54 per pack of 30 single-use containers, the base case of the manufacturer's cost-utility analysis reported an incremental cost-utility ratio (ICUR) of $217,790 per quality-adjusted life-year (QALY) compared with generic BAK-preserved latanoprost. Monoprost was not cost-effective compared with other PGAs, based on the CADTH Common Drug Review (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. A price reduction of approximately 65% is required for Monoprost to be priced equivalently to BAK-preserved latanoprost on a per drop basis.

Of Note

- CDEC noted that, although Monoprost is the first Health Canada–approved preservative-free PGA, there are other publicly reimbursed BAK-free treatment options available for patients with open-angle glaucoma or ocular hypertension who are unable to tolerate BAK-preserved options.
- CDEC noted that the studies included in this review assessed Monoprost as first-line monotherapy; consequently, there was no evidence for CDEC to consider recommending Monoprost for other lines of treatment.

Discussion Points

- CDEC noted that preservatives in topical ophthalmic solutions have been associated with ocular surface disease. The implication is that Monoprost could offer improved patient tolerability, adherence, and overall ocular health. In addition to the tolerability results of the pivotal and supportive study for Monoprost, CDEC considered the evidence from a phase IV study and an adjusted indirect treatment comparison reviewed by CDR. These studies, however, had methodological limitations similar to those of the pivotal and supportive study. Therefore, the committee considered the evidence reviewed to be insufficient to suggest that Monoprost has better tolerability than BAK-preserved latanoprost.

Background

Monoprost has a Health Canada–approved indication for the reduction of IOP in patients with open-angle glaucoma or ocular hypertension. Monoprost is a preservative-free formulation of latanoprost, a PGA. It is available as a 50 µg/mL topical ophthalmic solution in single-dose units, and the Health Canada–approved dose is one drop in the affected eye(s) once daily.

Summary of CDEC Considerations

The committee considered the following information prepared by CDR: a systematic review of RCTs of Monoprost and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from a clinical expert with experience in treating patients with open-angle glaucoma and ocular hypertension.

Patient Input

No patient input was received for this submission.

Clinical Trials

The systematic review included two investigator-blinded RCTs of patients with ocular hypertension or open-angle glaucoma. Patients enrolled in both studies had primary open-angle glaucoma or ocular hypertension and were on latanoprost 0.005% monotherapy for at least nine months in the LT2345-PIII-12/08 study (N = 404) and at least four weeks in the LT2345-001 study (N = 334). Following a washout period, patients in both trials self-administered one drop of Monoprost or Xalatan (benzalkonium chloride–preserved latanoprost 0.005%) daily in the evening in the eligible eye or eyes. Patients were followed up for 84 days.

Because of the single-masked nature of the studies, there was some risk of bias in patient-reported outcomes such as ocular symptoms and adverse events. Measurements of treatment compliance were based on patient recall, and drug accountability was affected by the fact that it was easier to count returned single-dose Monoprost units than multi-dose bottles of Xalatan, which were not weighed.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the committee discussed the following:

- IOP: Change in IOP from baseline to days 15, 42, and 84 was measured using Goldmann applanation tonometry, which is considered the gold standard for measuring IOP.
- Conjunctival hyperemia: Change in conjunctival hyperemia from baseline to days 15, 42, and 84 was assessed using the McMonnies photographic scale. Conjunctival hyperemia is redness in the eye membrane covering the front of the eye and lining the inner surface of the eyelids; it results from vasodilation of the conjunctival vessels. The McMonnies photographic scale consists of photographs of the inferior conjunctiva representing six levels of hyperemia (1 to 6, with higher numbers indicating more severe hyperemia). Investigators determined which level most closely corresponded to the patient's degree of hyperemia. No minimal clinically important difference was identified.
- Ocular symptoms: At each post-baseline visit in both trials, patients were asked whether they had felt the ocular symptoms of pruritus, burning/stinging, blurred vision, sticky eye sensation, eye dryness sensation, or foreign body sensation upon instillation of the study medication since the previous visit. Patients graded each symptom on a four-point ordinal scale ranging from 0 or "none" to 3 or "very disturbing." In the LT2345-PIII-12/08 study, a total symptom score was calculated by dividing the sum of the individual symptom scores by the number of symptoms experienced. No minimal clinically important difference was identified for the total symptom score. Patients in the LT2345-PIII-12/08 study also graded eye dryness sensation, foreign body sensation, irritation/burning/stinging, itching, photophobia, or tearing experienced at least one hour before or after instillations.
- Compliance with study medication: In the LT2345-PIII-12/08 study, compliance was based on patients' recall during questioning and, in the LT2345-001 study, it was based on the count of returned drug containers.

The primary outcome in the LT2345-PIII-12/08 study was the change in IOP at 9:00 a.m. from baseline to day 84 in the study eye. Non-inferiority of Monoprost compared with Xalatan was assessed for this end point using a margin of 1.5 mm Hg. The primary outcome in the LT2345-001 study was study eye IOP at 8:00 a.m., 10:00 a.m., and 4:00 p.m. on each of days 15, 42, and 84. Equivalence in IOP change from baseline of Monoprost compared with Xalatan was assessed using a margin of 1.5 mm Hg for all nine comparisons and a margin of 1.0 mm Hg for five of nine comparisons.

Efficacy

In the two RCTs, mean IOP efficacy from baseline to days 15, 42, and 84 was similar between Monoprost and Xalatan. Non-inferiority in efficacy was established for Monoprost compared with Xalatan in the LT2345-PIII-12/08 study. The 95% CI for the difference between treatment groups in mean change in IOP from baseline to day 84 at 9:00 a.m. was within the pre-specified 1.5 mm Hg non-inferiority margin (mean 0.42; 95% CI, 0.00 to 0.84 mm Hg). In the LT2345-001 study, mean change in study eye IOP from baseline between Monoprost and Xalatan met the 1.5 mm Hg equivalence criterion but not the 1.0 mm Hg criterion that needed to be met by the majority of the measurements. That is, the 95% CI for the difference between treatment groups in mean change of IOP from baseline to each of days 15, 42, and 84 at all three times of day fell within a 1.5 mm Hg margin, and the first pre-specified criterion for equivalence was met. However, only four of the nine 95% CIs met the 1.0 mm Hg margin, so the second criterion for equivalence was not met in the main analysis.

Tolerability

Outcomes other than the primary efficacy outcomes were not controlled for type I error and should be treated as exploratory in nature. The trials were not powered to assess outcomes other than the primary efficacy outcomes.

In the LT2345-PIII-12/08 study, severe hyperemia (score of 5 or 6 on the McMonnies photographic scale) was not observed in any of the patients after baseline. Although score distributions differed between the Monoprost and Xalatan groups at days 42 and 84, the percentages of patients with moderate hyperemia (score of 3 or 4) were only 4.9% and 5.3% in the Monoprost group and 8.6% and 7.6% in the Xalatan group. In the LT2345-001 study, the mean hyperemia score did not differ between the treatment groups.

For each ocular symptom evaluated upon instillation of study medication in both trials, the symptom was rated as “disturbing” or “very disturbing” (as opposed to “none” or “present not disturbing”) by less than 4% of patients in each treatment group at each time point. In the LT2345-PIII-12/08 study, ocular symptoms between instillations were “disturbing” or “very disturbing” in less than 6% of patients in each treatment group at each time point. As well, in the Xalatan group, score distributions tended to be more severe for burning/stinging upon instillation at all time points. However, absolute differences in percentage between groups were less than 3% for patients with “disturbing” or “very disturbing” burning/stinging.

Based on patient recall in the LT2345-PIII-12/08 study, the study medication protocol was completely followed in fewer patients in the Monoprost group than in the Xalatan group according to questioning at day 42 (78% versus 93%) and day 84 (82% versus 91%). All of the six patients reporting less than 70% compliance (based on the number of instillations) were in the Monoprost group.

Harms

In both trials, no serious ocular adverse events were reported. Ocular adverse events were fewer with Monoprost than with Xalatan in the LT2345-PIII-12/08 study (9% versus 12% of patients) and in the LT2345-001 study (14% versus 23% of patients). The most frequent ocular adverse events were pain at the instillation site, conjunctival hyperemia, and punctate keratitis. Conjunctival hyperemia, allergic conjunctivitis, blepharitis, drug intolerance, punctate keratitis, and pain at the instillation site were more frequent in the patients taking Xalatan, although the proportions of patients with each adverse event were low (5% or less). There was potential for bias in the reporting of adverse events, as patients were not blinded to the study medication they were receiving.

Indirect Treatment Comparisons

An additional search for indirect treatment comparisons and network meta-analyses found one indirect comparison meta-analysis of RCTs of Monoprost with other PGAs. The objective of the meta-analysis was to evaluate the efficacy in lowering IOP and the safety of Monoprost monotherapy compared with monotherapy using other PGAs for the treatment of open-angle glaucoma and ocular

hypertension. Indirect comparisons were available between Monoprost and sofZia-preserved travoprost 0.004%, bimatoprost 0.03%, and bimatoprost 0.01% for the outcome of hyperemia. Indirect comparisons for the efficacy outcomes were available only for the bimatoprost therapies. The mean differences in IOP after three months of treatment between Monoprost and the two bimatoprost comparators were 0.49 mm Hg and 0.19 mm Hg in favour of bimatoprost 0.03% and bimatoprost 0.01%, respectively. The mean difference in IOP reduction after three months of treatment between Monoprost and bimatoprost 0.03% was 0.94 mm Hg in favour of bimatoprost 0.03%, although the difference was not statistically significant. Monoprost was not favoured in any of the efficacy comparisons, but the mean differences in IOP were not clinically important. Results for hyperemia indicated statistically significantly lower proportions of patients with hyperemia with Monoprost therapy compared with sofZia-preserved travoprost and bimatoprost 0.03% and 0.01%, with mean odds ratios ranging from 0.18 to 0.37. There were significant limitations that contributed to uncertainty in the estimates. These included lack of information on quality assessment of individual studies, methods used to derive individual study estimates, differences in instruments used to measure IOP, varying definitions of hyperemia, potential bias in hyperemia assessments, and concerns with the accuracy of data extraction from the individual studies. Pooling of hyperemia estimates was likely inappropriate, as the outcome was not well defined.

Cost and Cost-Effectiveness

The manufacturer's submitted price was $20.54 per pack of 30 single-use containers, corresponding to a price of $0.68 per day.

The manufacturer submitted a cost-utility analysis based on a decision tree and a Markov model, comparing Monoprost with other PGAs (bimatoprost 0.01%, bimatoprost 0.03%, travoprost Z, BAK-preserved latanoprost) for the treatment of patients with ocular hypertension or open-angle glaucoma. The analysis was carried out from the Canadian public-payer perspective during a 41-year (lifetime) time horizon. Patient characteristics were based on the pivotal trial of Monoprost, and all patients were assumed to be treated bilaterally. A decision tree was used to reflect patients moving through alternative therapies, based on treatment response, during a period of one year. 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: ocular hypertension, mild open-angle glaucoma, moderate open-angle glaucoma, advanced open-angle glaucoma, blindness, and death. Changes in IOP were assumed to affect the risk of progression from ocular hypertension to mild open-angle glaucoma but did not affect transition probabilities in the more severe health states (e.g., from the mild open-angle glaucoma to blindness health states). The comparative safety and efficacy of first-line Monoprost compared with other available PGAs were obtained from a published indirect treatment comparison, while the efficacy and safety of the second-line monotherapy and biotherapy were assumed from a separate indirect treatment comparison.

In the manufacturer's probabilistic base-case analysis, when considering all treatments, Monoprost was the optimal therapy at a willingness-to-pay threshold greater or equal to $217,790 per QALY. If the willingness-to-pay is less than $217,791 per QALY, generic BAK-preserved latanoprost is the optimal therapy. All other PGAs were dominated by generic BAK-preserved latanoprost.

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

- There is uncertainty in the efficacy and safety of Monoprost compared with other PGAs, given the poor methodological quality of the studies included in the published indirect treatment comparison.
- The manufacturer incorrectly used the full price of branded travoprost, BAK-preserved latanoprost, and latanoprost-timolol (second-line), rather than the price paid by the public payer, which is lower.
- The manufacturer assumed that adherence would be greater with preservative-free treatments, which was not justified based on data from studies of preservative-free treatments.
- The manufacturer's model lacked stability at 5,000 iterations.

CDR conducted a base case using revised comparator costs and equal adherence rates (67.5%), correcting minor model errors, and increasing the number of iterations to 20,000. This led to Monoprost being 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 is less than $268,842 per QALY, generic BAK-

preserved latanoprost is the optimal therapy. All other PGAs were dominated. 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.

However, as noted in the limitations, 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. Therefore, the ICURs presented should be interpreted with caution. Given this uncertainty, CDR noted that a price reduction of approximately 65% is required for Monoprost to be priced equivalently to BAK-preserved latanoprost on a per drop basis.

CDEC Members

Dr. James Silvius (Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

March 21, 2018 Meeting

Regrets

None

Conflicts of Interest

None