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CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

LATANOPROSTENE BUNOD (VYZULTA — BAUSCH HEALTH, CANADA INC.)
Indication: For the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

RECOMMENDATION

The CADTH Canadian Drug Expert Committee (CDEC) recommends that latanoprostene bunod 0.24 mg/ml ophthalmic solution (Vyzulta) be reimbursed for the reduction of intraocular ocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT) only if the following conditions are met:

Conditions for Reimbursement

Initiation criteria

1. Patient must be ≥ 18 years
2. Patient must have a documented diagnosis of open-angle glaucoma or ocular hypertension in one or both eyes

Pricing condition

- The cost of treatment with LBN ophthalmic 0.024% solution should not exceed the drug plan cost of treatment with the least costly alternative prostaglandin analogue (PGA) or least costly beta-blocker reimbursed for the treatment of open-angle glaucoma or ocular hypertension.

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Reasons for the Recommendation

1. Two Phase III, double-blind, double-dummy, randomized controlled trials (APOLLO, N=420; LUNAR, N=420) compared once-daily LBN ophthalmic 0.024% solution to timolol maleate (0.5%), in patients with OHT or OAG. While the mean IOP was lower in LBN-treated patients compared to timolol treated patients (treatment difference of –1.03 to –1.37 mmHg in APOLLO and −0.44 to −1.34 mmHg in LUNAR), LBN treatment was associated with a higher frequency of ocular adverse events (AEs) compared to timolol (13.4% versus 11.9% of patients in APOLLO and 23.8% versus 13.3% of patients in LUNAR).
2. CDEC did not find any studies comparing LBN to other PGAs. The results of an indirect drug comparison (IDC) comparing LBN 0.024% ophthalmic solution to alpha-2 adrenergic agonists, beta-blockers, carbonic anhydrase inhibitors, PGAs, and placebo, found that LBN was likely better than placebo in terms of efficacy on lowering IOP. However, the IDC did not provide high quality evidence on the comparative efficacy with other medications.
3. At the manufacturer-submitted price of $26.25 per 5mL bottle, the daily cost of LBN treatment for both eyes ($0.30 per day) is higher than that of most beta-blockers ($0.11 - $0.41 per day) and some PGAs ($0.22 - $0.68 per day).

Discussion Points

- The committee discussed whether timolol was a suitable comparator given the current guidance from the Canadian Ophthalmological Society and similar organizations. PGAs are considered first-line therapy for OAG and recommended over beta-blockers as PGAs are considered to be as or more effective, well-tolerated and administered once daily. The committee noted that the manufacturer did not provide any information on the cost effectiveness of latanoprostene bunod compared with beta-blockers.

- Although in both APOLLO and LUNAR RCTs, LBN met the criteria for non-inferiority to timolol maleate, the committee noted that only APOLLO found LBN to have greater efficacy, but this was only of modest clinical relevance. There were also higher rates of ocular AEs reported for LBN over timolol, particularly in the LUNAR study. There were no appreciable differences in serious AEs or withdrawal due to AEs. Both studies were identical in design (in the efficacy phase) and had similar baseline patient characteristics. It is unclear how inconsistencies arose in efficacy and AEs outcomes.

- The committee discussed the lack of data comparing LBN to other PGAs. Only one phase II dose-finding study reported LBN produced statistically significant reductions in IOP compared to latanoprost; however this study did not meet the inclusion criteria for the CDR systematic review due to the study design, and the conclusions of this study were not supported by the results of the manufacturer-provided IDC of phase III trials.
- The committee noted the insufficient evidence to support the claim that nitric oxide, released from the LBN molecule, results in increased outflow for the IOP lowering effect. The role of nitric oxide in lowering IOP remains unclear currently. Hence, the resulting purported superiority of LBN to other available PGAs remains unsubstantiated. Therefore, LBN does address any unmet patient need that cannot be fulfilled with other available PGAs
- The committee noted that the observed high rates of hyperemia may preclude the anticipated widespread use of LBN by ophthalmologists as a first-line therapy.

Background

Vyzulta has a Health Canada indication for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. Vyzulta is a prostaglandin $F_{2\alpha}$ analogue. It is available as sterile topical ophthalmic solution preserved with benzalkonium chloride (0.02%) and the Health Canada–approved dose is one drop in the conjunctival sac of the affected eye(s) once daily in the evening.

Summary of Evidence Considered by CDEC Considerations

The committee considered the following information prepared by the Common Drug Review: a systematic review of phase III and IV randomized control trials of Vyzulta and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from a clinical expert(s) with experience in treating patients with open-angle glaucoma or ocular hypertension, and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

Three different patient organizations worked together to provide one submission: the Canadian Council of the Blind (CCB), the Canadian National Institute for the Blind (CNIB), and the Foundation Fighting Blindness (FFB). Patient perspectives were obtained from an online survey in response to the call for patient experiences for the Minimally Invasive Glaucoma Surgery (MIGS) Health Technology Assessment. The following is a summary of key input from the perspective of the patient groups:

- While the psychological, physical, and financial burdens of the disease ranges between patients, all domains can be profoundly affected as the severity of visual impairment increases over time. Psychologically, patients experience everything from anxiety to depression. The physical challenges and loss of independence associated with sight impairment cannot be overstated. While the effects on daily living vary with the degree of visual impairment, patients noted difficulties with the ability to function independently.
- The cost of the medication, the transportation to and from specialist appointments, and the length of time to reach these specialists can be problematic. In addition, the constant need for eye drops or the time and recovery associated with other treatment paradigms (primarily surgical) can also present as barriers for these patients. In terms of disease management, many patients noted the burden associated with multiple administrations daily of eye drops and the increased potential for issues with adherence. This can occur in either early stages where the disease is largely asymptomatic or in later stages where treatment is more complex and employing multiple therapies.
- This combined submission focused on a survey relating to the CADTH MIGS Health Technology Assessment which did not include specific questions regarding Vyzulta; however, it was evident that patients are always open to new to additional treatment options.

Clinical Trials

The systematic review included two phase III, double-blind randomized controlled trials of patients with open-angle glaucoma or ocular hypertension. APOLLO (N = 420) and LUNAR (N = 420) randomized patients in a 2:1 ratio for treatment with LBN 0.024% ophthalmic solution (once daily in the evening) and timolol maleate 0.5% (twice daily) for three months. Non-inferiority was determined in both APOLLO and LUNAR if the upper limit of the confidence intervals (CIs) did not exceed 1.5 mmHg at any of the nine time points and did not exceed 1.00 mmHg for at least five out of the nine time points of the time points. In APOLLO the criteria for superiority of LBN ophthalmic 0.024% solution arm compared with timolol maleate 0.5% was met as the upper limit of the 95% CI did not exceed 0 mmHg at any of the nine time points. In LUNAR, the criteria for superiority were not met due to the treatment difference at the first time point (Week 2 at 8 AM).

Limitations with the reviewed studies included: the use of timolol maleate 0.5% (not recommended as first-line therapy) as the active comparator; concurrent use of medications known to affect IOP; inability to assess the extent of missing data; no health-related or vision-related quality of life outcomes assessed. The proportion of patients that discontinued the trial were similar between treatment arms in both APOLLO and LUNAR. In APOLLO, 7.0% to 7.5% of patients discontinued the efficacy phase. Similarly, in LUNAR, 5.9% to 6.8% of patients discontinued the efficacy phase.

Outcomes

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

- Intraocular pressure (IOP): IOP in patients' study eye measured at nine time points (8 AM, 12 PM, and 4 PM at Week 2, Week 6, and Month 3); proportion of patients with IOP less than or equal to 18 mmHg consistently at all nine time points in the first three months; proportion of patients with IOP reduction greater than or equal to 25% consistently at all nine time points in the first three months, measured using Goldmann applanation tonometry, which is considered the gold standard for measuring intraocular pressure.

The primary outcome in both trials was was the intraocular pressure in patients' study eye measured at the following nine time points: 8 AM, 12 PM, and 4 PM at Week 2, Week 6, and Month 3.

Efficacy

Results from the two RCTs indicated that LBN 0.024% ophthalmic solution appeared to be better than timolol maleate 0.5% with unknown or perhaps only modest clinical implications.

In both APOLLO and LUNAR, the least square (LS) mean IOP in patients' study eye was numerically lower in the LBN 0.024% ophthalmic solution arm compared with the timolol maleate 0.5% arm at all nine time points. In APOLLO, the difference between trial arms was statistically significant across all nine time points. In LUNAR, the difference between trial arms was statistically significant across eight out of nine time points, with the first time point (Week 2 at 8 AM) showing a difference that was not statistically significant. In APOLLO, the treatment difference between arms ranged from –1.03 mmHg (95% CI: –0.37mmHg to –1.6 8mmHg) to –1.37 mmHg (95% CI: –0.69 mmHg to –2.05 mmHg). In LUNAR, the treatment difference between arms ranged from −0.44 mmHg (95% CI, 0.26 mmHg to −1.13 mmHg) to −1.34 mmHg (95% CI: −0.72 mmHg to −1.95 mmHg).

In both APOLLO and LUNAR the proportion of patients with IOP less than or equal to 18 mmHg at all nine time points was numerically greater in the LBN 0.024% ophthalmic solution arm compared with the timolol maleate 0.5% arm in the first three months. In APOLLO, 22.9% compared with 11.3%, and in LUNAR 17.7% compared with 11.1% of patients in the LBN 0.024% ophthalmic solution arm compared with the timolol maleate 0.5% arm, respectively, had IOP less than or equal to 18 mmHg at all nine time points. The difference of proportions was statically significant in APOLLO (11.6%, 95% CI, 4.3% to 18.9%, p = 0.005) but not in LUNAR (6.6%, 95% CI, −0.4 to 13.5, p = 0.084).

The proportion of patients with IOP reduction greater than or equal to 25% consistently at all nine time points in the first three months was another key secondary endpoint assessed in both trials. According to the clinical expert consulted for this review, the 25% criterion was deemed to be a clinically meaningful and somewhat conservative threshold. The difference of proportions for this

outcome were statically significant in both APOLLO (15.3%, 95% CI, 6.6% to 24.0%, p = 0.001) and LUNAR (12.5%, 95% CI, 4.0% to 21.1%, p = 0.007), indicating that LBN 0.024% ophthalmic solution is better than timolol maleate 0.5%.

Outcomes related to health-related quality of life and vision-related quality of life were identified as important to patients but were not assessed in either of the trials, and moreover, there is insufficient evidence supporting the correlation between the effect of glaucoma treatment on patient-reported outcomes. Visual acuity assessed via best-corrected visual acuity (BCVA) and the appearance of the optic nerve showed no numerical difference in both trials, however these outcomes were not assessed statistically thereby reducing the ability to further interpret the findings. Outcomes related to visual field loss and symptoms of glaucoma were not assessed in either of the trials.

Harms (Safety)

In both trials, the safety profiles in terms of eye-related complications were in favor of timolol maleate 0.5% compared with LBN 0.024% ophthalmic solution as ocular adverse events (in the study eye) occurred more frequently in the LBN 0.024% ophthalmic solution arm compared with the timolol maleate 0.5% arm. In APOLLO and LUNAR, the most common ocular adverse event (in the study eye) was related to conjunctival hyperemia and eye irritation.

Indirect Treatment Comparisons (If applicable)

One manufacturer supplied indirect treatment comparison of LBN with other treatments (alpha-2 adrenergic agonists, beta-blockers, carbonic anhydrase inhibitors, and PGAs) was identified. The results of the indirect treatment comparison indicate that treatment with LBN 0.024% ophthalmic solution is likely favourable over placebo, however, little can be elucidated on the comparative efficacy to other products. Overall the results of this analysis must be interpreted with caution due to limitations pertaining to issues with transparency in the systematic review methods and analysis and no control for heterogeneity in any manner that would be useful limiting the utility and the robustness of the results.

Cost and Cost-Effectiveness

LBN is available as a topical ophthalmic solution (0.24 mg/mL) at a recommended dose of one drop in the affected eye(s) once daily. At the manufacturer-submitted price of $26.25 per 5 mL bottle, LBN costs approximately $0.30 per day assuming treatment of both eyes.

The manufacturer submitted a cost-utility analysis comparing LBN with currently available PGAs (bimatoprost 0.01%, bimatoprost 0.03%, generic latanoprost 0.005%, and travoprost 0.004%) in the treatment of patients with OHT and OAG. The analysis was conducted over a lifetime time horizon (approximately 40 years) from the perspective of the Canadian publicly funded health care payer. Patient characteristics were based on the pivotal trials of LBN with all patients assumed to have both eyes treated. A decision tree was used to determine the movement of patients initiating treatment and switching to alternative therapies, if they did not respond to their initial treatment, until an optimal treatment was found within the first year. At the end of the decision tree, patients entered a Markov model which predicted long-term progression of disease through five disease states: OHT, mild OAG, moderate OAG, advanced OAG, and blindness; at any point, patients could also transition to an absorbing death state. 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 impacted the risk of progressions from mild OAG to advanced OAG.

In the manufacturer's probabilistic base case analysis, LBN was more costly but produced more QALYs than generic latanoprost or travoprost, resulting in a sequential ICUR of $44,505 per QALY gained compared to travoprost. The analysis was associated with a high degree of uncertainty as LBN had a 22.4% probability of being considered the most likely cost-effective intervention compared with currently available PGAs at a $50,000 per QALY willingness-to-pay threshold.

CADTH identified the following key limitations:

The submitted model was not stable up to 20,000 Monte Carlo iterations.

Relative treatment effects of LBN compared to other PGAs are uncertain given that the IDC provided by the manufacturer included mixed patient populations without appropriate assessment of the impact on clinical heterogeneity and lacked statistical analysis to evaluate inconsistency.

Efficacy of LBN was pooled from clinical trials with imbalanced baseline patient characteristics and different follow-up times.

Treatment costs of PGAs and other glaucoma medications were underestimated given the lack of consideration for recommended product shelf-life.

Assumptions relating to the frequency of follow-up and costs associated with medical visits may not reflect clinical routine practice.

The approach to treatment switching for patients who failed to respond to PGA therapy does not align with clinical practice.

CADTH re-analysis accounted for the identified limitations. The ICUR for LBN was $142,801 per QALY gained when compared to generic latanoprost. All other PGAs considered in the analysis were dominated by LBN (i.e., associated with greater expected costs and fewer expected QALYs) or subjected to extended dominance. A price reduction of at least 33% is required for LBN to achieve an ICUR below $50,000 per QALY gained compared with generic latanoprost.

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

April 9, 2019 Meeting

Regrets

One CDEC member did not attend.

Conflicts of Interest

None

July 17, 2019 Meeting

Regrets

None

Conflicts of Interest

None