



CDEC FINAL RECOMMENDATION

NEBIVOLOL

(Bystolic – Forest Laboratories Canada Inc.)

Indication: Mild to Moderate Essential Hypertension

Recommendation:

The Canadian Drug Expert Committee (CDEC) recommends that nebivolol not be listed at the submitted price.

Reasons for the Recommendation:

1. The evidence for nebivolol does not support greater efficacy or safety than less costly alternative treatments for mild to moderate essential hypertension.
2. At the submitted price (\$1.20 per day), nebivolol is more expensive than other beta-blockers reimbursed for the treatment of essential hypertension (\$71 to \$403 more per year).

Of Note:

Based on a review of the clinical evidence, the Committee felt that a reduced price would increase the likelihood of a recommendation to “list” or “list with clinical criteria and/or conditions.”

Background:

Nebivolol has a Health Canada indication for the treatment of mild to moderate essential hypertension. It may be used alone or concomitantly with thiazide diuretics. Nebivolol is available as tablets of 2.5 mg, 5 mg, 10 mg, and 20 mg. The recommended starting dose is 5 mg once daily, which can be increased at two-week intervals up to 20 mg once daily for patients requiring further reduction in blood pressure.

Summary of CDEC Considerations:

CDEC considered the following information prepared by the Common Drug Review (CDR): a systematic review of randomized controlled trials (RCTs) of nebivolol, a critique of the manufacturer’s pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

Common Drug Review

Patient Input Information

The following is a summary of information provided by one patient group that responded to the CDR call for patient input.

- High blood pressure is the number one risk factor for stroke and a major risk factor for heart disease. With proper diagnosis and treatment, the risk of stroke and heart attack can be considerably reduced.
- Low adherence to prescribed medications is a growing concern, and has been implicated as one of the major contributors to uncontrolled high blood pressure and risk of cardiovascular disease.

Clinical Trials

The systematic review included four double-blind, placebo-controlled RCTs and five beta-blocker-controlled RCTs of adults with mild to moderate essential hypertension. Three of the placebo-controlled trials compared the clinical efficacy and harms of nebivolol 1.25 mg to 40 mg once daily (q.d.) to placebo (NEB-202, N = 301; NEB-302, N = 913; NEB-305, N = 811).

NEB-CAN-3 (N = 240) was a 12-arm trial (3 × 4 factorial design) comparing nebivolol monotherapy

(1 mg, 5 mg, and 10 mg), hydrochlorothiazide monotherapy (12.5 mg and 25 mg), combination therapy with nebivolol and hydrochlorothiazide, and placebo.

Three beta-blocker-controlled trials compared nebivolol 5 mg once daily with metoprolol (Uhlir et al. 1991, 100 mg b.i.d., N = 155; Celik et al. 2006, 100 mg q.d., N = 80; Kampus et al. 2011, 50 mg to 100 mg q.d., N = 80), and two trials compared nebivolol 5 mg once daily with atenolol (Grassi et al. 2003, 100 mg q.d., N = 225; Boydak et al. 2005, 50 mg to 100 mg q.d., N = 131).

Outcomes

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

- Change in mean trough sitting diastolic blood pressure (SiDBP) from baseline to end point – defined as diastolic blood pressure measured at trough drug level (24 ± 2 hours after the previous dose)
- Change in mean peak SiDBP from baseline to end point – defined as diastolic blood pressure measured at peak drug level (two to three hours following dose)
- Change in mean trough/peak sitting systolic blood pressure (SiSBP) from baseline to end point
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

Change in mean trough SiDBP from baseline to study end point was the primary outcome in all four placebo-controlled trials. The primary outcomes in the beta-blocker-controlled trials included change in sitting blood pressure (Uhlir et al. 1991 and Grassi et al. 2003), sexual function (Boydak et al. 2005), platelet activation (Celik et al. 2006), and endothelial function (Kampus et al. 2011).

Results

Based on the dosing recommended in the product monograph, CDEC focused their discussion on the results for nebivolol 5 mg to 20 mg per day.

Efficacy

- In three placebo-controlled trials, all doses of nebivolol monotherapy demonstrated statistically significant improvements in trough SiDBP relative to placebo. The least-square mean difference (95% confidence interval [CI]) from baseline to end of study between nebivolol and placebo was reported, as follows:
 - nebivolol 5 mg compared with placebo: $-4.9 \text{ mmHg} (-8.1 \text{ to } -1.6)$ in NEB-202; $-5.5 \text{ mmHg} (-7.7 \text{ to } -3.4)$ in NEB-302, and $-3.2 \text{ mmHg} (-5.2 \text{ to } -1.1)$ in NEB-305
 - nebivolol 10 mg compared with placebo: $-6.1 \text{ mmHg} (-9.3 \text{ to } -2.8)$ in NEB-202; $-6.3 \text{ mmHg} (-8.4 \text{ to } -4.2)$ in NEB-302, and $-3.9 \text{ mmHg} (-5.9 \text{ to } -1.8)$ in NEB-305
 - nebivolol 20 mg compared with placebo: $-6.0 \text{ mmHg} (-9.3 \text{ to } -2.8)$ in NEB-202; $-6.9 \text{ mmHg} (-9.0 \text{ to } -4.7)$ in NEB-302, and $-4.5 \text{ mmHg} (-6.6 \text{ to } -2.5)$ in NEB-305.
- The least-square mean difference in change of trough SiSBP from baseline to end of study between nebivolol and placebo ranged from -2.6 mmHg (95% CI, -8.4 to 3.3) to -8.1 mmHg (95% CI, -11.6 to -4.5) for nebivolol 5 mg, from -3.1 mmHg (95% CI, -6.6 to 0.4) to -9.2 mmHg (95% CI, -12.8 to -5.7) for nebivolol 10 mg, and from -6.3 mmHg (95% CI, -9.8 to -2.8) to -8.6 mmHg (95% CI, -12.2 to -5.1) for nebivolol 20 mg.
- In the study NEB-CAN-3, combination therapy with nebivolol and hydrochlorothiazide showed greater SiDBP and SiSBP reductions from baseline compared with placebo and hydrochlorothiazide monotherapy; however, incremental reductions in trough SiDBP and SiSBP were inconsistently observed with combination therapy versus the corresponding nebivolol monotherapy doses, the magnitude of the incremental reductions was generally small, and there was a lack of statistical comparisons.
- One beta-blocker-controlled trial (Boydak et al. 2005) reported a statistically significant difference in SiDBP favouring nebivolol (5 mg to 10 mg) over atenolol (50 mg to 100 mg q.d.); -11.1 mmHg versus -8.5 mmHg , $P = 0.003$. None of the other trials reported statistically significant differences in SiDBP between nebivolol and active comparators.

Harms (Safety and Tolerability)

- Compared with placebo, more patients treated with nebivolol experienced at least one adverse event. A pooled analysis of NEB-202, NEB-302, and NEB-305 provided by the manufacturer indicated higher rates of headache (7.1% versus 5.9%) and fatigue (3.6% versus 1.5%) with nebivolol.
- Serious adverse events were rare in the placebo-controlled trials.
- In the placebo-controlled trials, withdrawals due to adverse events ranged from 0% to 2.0% for 5 mg nebivolol, 0% to 4.2% for 10 mg nebivolol, 2.0% to 4.2% for 20 mg nebivolol, and 0% to 5.3% for placebo.
- There were limited data regarding adverse events, serious adverse events, and withdrawals due to adverse events reported for the beta-blocker-controlled trials.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis comparing treatment costs (including drug costs and physician visit costs) for nebivolol to other pharmacotherapies for essential hypertension approved in Canada: angiotensin receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEIs), beta-blockers, and calcium channel blockers. Evidence to support a cost-minimization analysis was based on head-to-head studies comparing nebivolol with an ACEI (lisinopril), an ARB (losartan), a calcium channel blocker (amlodipine), and multiple beta-blockers. At a cost of \$483.90 annually (2.5 mg to 20.0 mg daily; \$1.20 per day),

nebivolol is more expensive than all comparators, including beta-blockers, ARBs, ACEIs, and calcium channel blockers (\$30 to \$403 more per year).

Other Discussion Points:

CDEC noted the following:

- There were inadequate data to assess the adverse effect profile of nebivolol relative to comparators.

Research Gaps:

CDEC noted that there is insufficient evidence regarding the following:

- Data comparing nebivolol with other antihypertensive agents on cardiovascular events, end-organ damage, or mortality.

CDEC Members:

Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi,

Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt,

Dr. Peter Jamieson, Dr. Julia Lowe, Dr. Kerry Mansell, Dr. Irvin Mayers,

Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

June 19, 2013 Meeting

Regrets:

None

Conflicts of Interest:

None

About This Document:

CDEC provides formulary listing recommendations or advice to CDR participating drug plans.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the CDR Confidentiality Guidelines.

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