CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

PERINDOPRIL ARGININE/AMLODIPINE
(Viacoram — Servier Canada Inc.)
Indication: Mild to Moderate Essential Hypertension

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that perindopril arginine/amlodipine fixed-dose combination (FDC) be reimbursed for the treatment of mild to moderate essential hypertension in patients for whom combination therapy is appropriate, if the following conditions are met:

Conditions:
- Reimburse in a similar manner to other angiotensin receptor blocker (ARB)/calcium channel blocker (CCB) or angiotensin converting enzyme (ACE)/CCB FDC products.
- Drug plan cost of treatment with perindopril arginine/amlodipine should not exceed the drug plan cost of treatment with the least costly option of ARB/CCB or ACE/CCB FDC products.

Reasons for the Recommendation:
1. Two randomized controlled trials (RCTs) — one phase II trial (CL2-005; N = 1,581) and one phase III trial (PATH; N = 837) demonstrated that perindopril arginine/amlodipine FDC resulted in statistically significantly greater reductions in systolic blood pressure (SBP) and diastolic blood pressure (DBP) compared with perindopril arginine and amlodipine individually. One phase III RCT (CL3-018; N = 1,774) demonstrated that an up-titration treatment strategy with perindopril arginine/amlodipine FDC resulted in statistically significantly greater reductions in SBP and DBP compared with an up-titration strategy with valsartan/amlodipine.
2. There is no evidence to suggest that there are any additional benefits compared with ARB/CCB or ACE/CCB FDC products to justify a price premium for perindopril arginine/amlodipine FDC.
3. At the manufacturer-submitted price, the CADTH Common Drug Review calculated that perindopril arginine/amlodipine ($347 to $420 per patient annually) is more costly than perindopril erbumine ($238 to $413 per patient annually) and amlodipine ($50 to $131 annually) used as monotherapy, and is generally less costly than the free-dose combination (i.e., individual agents used in combination) of perindopril erbumine and amlodipine ($289 to

$544 per patient annually) based on publicly available prices. In general, in situations where combination therapy is indicated, perindopril arginine/amlodipine is less costly than other fixed-dose or free-dose combination products, with the exception of ACE/diuretic or ARB/diuretic combinations, and the ARB/CCB combination (telmisartan/amlodipine).

Of Note:

1. CDEC noted that the 2016 Canadian Hypertension Education Program guidelines defined patients for whom combination therapy is appropriate as those with SBP ≥ 20 mm Hg or DBP ≥ 10 mm Hg above target.

Background:

Perindopril arginine/amlodipine FDC is indicated for the treatment of mild to moderate essential hypertension in patients for whom combination therapy is appropriate. It is indicated for initial therapy in patients with mild to moderate essential hypertension. It is not indicated for switching therapy from the individual drugs currently on the market (perindopril as erbumine or arginine salt, amlodipine). It is available in three doses in Canada: 3.5 mg/2.5 mg, 7 mg/5 mg, and 14 mg/10 mg.

Summary of CDEC Considerations

CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs and pivotal studies of perindopril arginine/amlodipine, and a critique of the manufacturer's pharmacoeconomic evaluation.

Patient Input Information:

No patient input was received for this submission.

Clinical Trials

The evidence for this review was primarily drawn from three RCTs. CL2-005 (N = 1,581) was a phase II trial in which participants from Europe were randomized to receive one of six treatments: perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC; perindopril arginine 3.5 mg (not approved in Canada); amlodipine 2.5 mg; perindopril arginine 5 mg; amlodipine 5 mg; or placebo. PATH (N = 837) was a phase III trial in which participants from the US were randomized to receive one of three treatments: perindopril arginine 14 mg/amlodipine besylate 10 mg FDC; perindopril erbumine 16 mg; or, amlodipine besylate 10 mg. CL3-018 (N = 1,774) was a phase III trial in which participants from 18 countries, including Canada, were randomized to receive treatment according to one of two antihypertensive strategies: one initiated with perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC, the other was initiated with valsartan 80 mg. The up-titration steps in the perindopril arginine/amlodipine FDC strategy were perindopril arginine 7 mg/amlodipine 5 mg FDC, perindopril arginine 14 mg/amlodipine 10 mg FDC, and perindopril arginine 14 mg/amlodipine 10 mg FDC plus indapamide 1.5 mg sustained release.

All three trials included participants aged ≥ 18 years who had hypertension. Approximately 80% of participants in CL2-005 and CL3-018 had grade II hypertension — defined as SBP 160 mm

Hg to 179 mm Hg and DBP 100 mm Hg to 109 mm Hg. In PATH, [redacted] of participants had grade I hypertension — SBP 140 mm Hg to 159 mm Hg and DBP 90 mm Hg to 99 mm Hg, while [redacted] had grade III hypertension — SBP ≥ 180 mm Hg or DBP ≥ 110 mm Hg. Each study excluded individuals with comorbidities such as cerebrovascular diseases, heart disease, liver disease, and/or renal impairment. CL2-005 and CL3-018 also excluded participants with a body mass index of > 30 kg/m^2, while CL2-005 additionally excluded participants with type 1 or 2 diabetes.

Outcomes

The following outcomes were defined a priori in the CDR systematic review protocol:

- change in blood pressure (SBP and DBP)
- hypertension-related morbidity, including:
  - cardiovascular disease: myocardial infarction, heart failure, left ventricular hypertrophy, angina
  - cerebrovascular disease: stroke, transient ischemic attack
  - other target-organ damage: hypertensive retinopathy, chronic kidney disease
- change in health-related quality of life (HRQoL)
- adherence
- mortality, adverse events (AEs), serious AEs, withdrawals due to AEs, and notable harms (hypotension, peripheral edema, cough, hyperkalemia, acute kidney injury).

In CL2-005, the primary efficacy outcome was the change in supine DBP from baseline to the last post-baseline value over the six-week treatment period. In PATH, the primary efficacy outcome was the change in seated trough (approximately 24 hours after the last dose) DBP from baseline at day 42 of the trial. In CL3-018, the primary efficacy outcome was the change in supine SBP from baseline to the last post-baseline value at the third month.

Efficacy

In CL2-005, at the last post-baseline assessment over the eight-week treatment period, the mean decreases in supine DBP (primary efficacy outcome) and SBP were statistically significantly greater with perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC than with the following treatments (estimate [95% confidence interval [CI]] for DBP/estimate [95% CI] for SBP):

- Placebo: –4.1 (–5.6 to –2.6)/–7.2 (–9.6 to –4.8)
- Perindopril arginine 3.5 mg: –3.6 (–5.1 to –2.2)/–5.0 (–7.4 to –2.7)
- Amlodipine 2.5 mg: –3.0 (–4.5 to –1.5)/–5.2 (–7.5 to –2.9).

The mean decreases in supine DBP and SBP were statistically non-inferior with perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC group than with the following treatments (estimate [95% CI] for DBP/estimate [95% CI] for SBP):

- Perindopril arginine 5 mg: –2.6 (–4.1 to –1.1)/–2.8 (–5.1 to –0.5)
- Amlodipine 5 mg: –0.8 (–2.3 to 0.7)/ –0.3 (–2.6 to 2.1).

Further, there was a statistically significantly greater percentage of participants who achieved blood pressure (BP) normalization (SBP < 140 mm Hg and DBP < 90 mm Hg) or were considered responders (SBP < 140 mm Hg and DBP <90 mm Hg and/or SBP decrease ≥ 20 mm Hg from baseline and/or DBP decrease ≥ 10 mm Hg from baseline) in the perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC group (43.5% achieved normalization; [redacted] were

responders) than in the placebo (26.6% achieved normalization, *P* < 0.001; [redacted] were responders, [redacted]) group. There was a greater percentage of participants who achieved BP normalization or were considered responders in the perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC group than in the perindopril arginine 5 mg (33.3% achieved normalization; [redacted] were responders) and the amlodipine 5 mg (37.9% achieved normalization; [redacted] were responders) groups.

In PATH, at day 42, the mean decreases in seated DBP (primary efficacy outcome) and SBP were statistically significantly greater with perindopril arginine 14 mg/amlodipine 10 mg FDC than with the following treatments (least squares [LS] mean difference [95% CI] for DBP/LS mean difference [95% CI] for SBP):

- Perindopril erbumine 16 mg: –6.3 (–7.7 to –4.9)/–10.1 (–12.6 to –7.6)
- Amlodipine 10 mg: –2.5 (–3.9 to –1.1)/–3.9 (–6.4 to –1.5).

Further, there was a statistically significantly greater percentage of responder participants (BP < 140/90 mm Hg, or < 130/80 mm Hg if a participant had diabetes) in the perindopril arginine 14 mg/amlodipine 10 mg FDC group (51.6%) than in the perindopril erbumine 16 mg (27.1%) and amlodipine 10 mg (37.5%) groups (*P* < .001 for both comparisons).

In CL3-018, at the last post-baseline assessment over the first three-month treatment period, the mean decreases in supine DBP and SBP (primary efficacy outcome) were statistically significantly greater in participants randomized to the perindopril arginine/amlodipine FDC group versus those assigned to the valsartan/amlodipine group: estimate (95% CI) for DBP of –1.5 (–2.2 to –0.7) and for SBP of –2.0 (–3.2 to –0.9). The results were similar over the entire six-month treatment period, as well as at each study visit. There was a statistically significantly greater percentage of participants who achieved BP control (SBP < 140 mm Hg and DBP < 90 mm Hg) or who were considered responders (BP control and/or reduction in SBP ≥ 20 mm Hg and/or reduction in DBP ≥ 10 mm Hg) in the perindopril arginine/amlodipine FDC group (56.4% achieved control; [redacted] were responders) than in the valsartan/amlodipine group (49.0% achieved control, *P* = 0.002; [redacted] were responders, [redacted]). The results were similar over the entire six-month treatment period, as well as at each study visit.

None of the trials evaluated the effects of the study treatments on hypertension-related morbidity, HRQoL, or adherence as efficacy outcomes.

Harms (Safety and Tolerability)

Across all three studies, at least 15% of study participants in each trial experienced a treatment-emergent adverse event (TEAE). A greater percentage of participants in PATH (six-week treatment period) experienced a TEAE than in CL2-005 (eight weeks) and CL3-018 (six months). The most common TEAE across the CL2-005 and PATH was peripheral edema, which appeared to occur more frequently at the higher dose of the perindopril arginine/amlodipine FDC, and, in general, more frequently with amlodipine alone (5 mg in CL2-005 and 10 mg in PATH) than other treatments, including perindopril arginine/amlodipine FDC. Other common TEAEs in CL2-005 and PATH were headaches, which occurred at a similar rate across the treatment groups, and cough, which, in PATH, appeared to occur more frequently in the perindopril arginine 14 mg/amlodipine 10 mg FDC (3.2%) and perindopril erbumine 16 mg (2.9%) groups than in the amlodipine 10 mg (0.7%) group. In CL2-005, participants receiving perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC appeared to experience a similar rate of

hyperkalemia versus the amlodipine 2.5 mg group (2.4% versus 2.2%), but more so than the remaining treatment groups. In CL3-018, at each step of the titration strategy, there were no apparent differences in the percentage of participants who experienced a TEAE between the two treatment groups, although a greater percentage of participants experienced a TEAE at steps three and four (approximately 25%) than at the first two steps (approximately 18%). Results from the open-label, long-term extension phase of CL3-018 indicated a higher rate of TEAEs over the entire 14-month study period than the initial 6-month double-blind phase. Across all three trials, there were very few reports of serious AEs (less than 1% in CL2-005 and PATH; less than 1.5% in CL3-018 in each group at every step) and deaths (one in CL2-005; two in CL3-018).

Cost and Cost-Effectiveness

At the manufacturer-submitted prices, the daily cost of perindopril arginine/amlodipine (3.5 mg/2.5 mg, 7 mg/5 mg, and 14 mg/10 mg tablets) is $0.95 to $1.15 per patient, or $347 to $420 annually.

The manufacturer submitted a cost comparison of perindopril arginine/amlodipine for the treatment of patients with mild to moderate hypertension, primarily compared with the individual components used as monotherapy (perindopril erbumine [Coversyl], amlodipine), the individual components used as a free-dose combination (perindopril erbumine plus amlodipine), and the other FDC that contains perindopril (perindopril erbumine/indapamide [Coversyl Plus]). Similar efficacy and safety of perindopril/amlodipine with these primary comparators was assumed based on manufacturer-sponsored RCTs.

CDR noted the following limitations with the manufacturer's analysis:

- For other hypertensive drugs not included as active comparators within the clinical trials, but are relevant comparators to perindopril arginine/amlodipine, no direct or indirect evidence was provided to support a claim of similar efficacy. In the absence of this information, only costs could be considered, which may not be sufficient to justify a price premium.
- The manufacturer calculated the average annual costs of treatments based on weighted averages of the different dosing strategies. There is uncertainty as to whether this will be representative of the usage of perindopril arginine/amlodipine in clinical practice. The cost differential reported by the manufacturer will only be realized should perindopril arginine/amlodipine be used in clinical practice and replace existing comparators in the proportions assumed by the manufacturer.

At the manufacturer-submitted price, perindopril arginine/amlodipine ($347 to $420 per patient annually) is more costly than perindopril erbumine ($238 to $413 per patient annually) and amlodipine (by $50 to $131 per patient annually) used as monotherapy. It is within the range of the FDC perindopril/indapamide ($309 to $417 per patient annually), and is generally less costly than the free-dose combination of perindopril erbumine and amlodipine ($289 to $544 per patient annually) based on publicly available prices.

For the secondary comparators, the total cost of perindopril arginine/amlodipine is generally more costly than the cost of ACEs, ARBs, and CCBs when used as monotherapy ($25 to $543 per patient annually). Perindopril arginine/amlodipine is less costly than the other available ACE/CCB combination (verapamil/trandolapril; $629 to $698 annually); but is more costly than the ARB/CCB combination (telmisartan/amlodipine; $256 annually). It is generally less costly

than free-dose combinations of CCBs plus ACEs ($160 to $887 per patient annually), CCBs plus ARBs ($208 to $953 per patient annually), and CCBs plus beta blockers ($131 to $872 per patient annually); however, the cost differential varies widely based on the combinations used. Perindopril arginine/amlodipine is more costly than FDCs with diuretics (ACEs/diuretics, $76 to $392 per patient annually; ARBs/diuretics, $103 to $420 per patient annually).

CDEC Members:
Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

September 21, 2016 Meeting

Regrets:
Three CDEC members did not attend.

Conflicts of Interest:
None

About This Document:
CDEC provides formulary reimbursement 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 requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

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