



Common Drug Review

Pharmacoeconomic Review Report

October 2016

Drug	Perindopril arginine/amlodipine (as amlodipine besylate) (Viacoram) (fixed-dose combination)
Indication	<p>Viacoram is indicated for the treatment of mild to moderate essential hypertension in patients for whom combination therapy is appropriate.</p> <p>Viacoram 3.5 mg/2.5 mg is indicated for initial therapy in patients with mild to moderate essential hypertension.</p> <p>Viacoram is not indicated for switching therapy from the individual drugs currently on the market (perindopril as erbumine or arginine salt, amlodipine)</p>
Reimbursement request	As per indication.
Dosage form(s)	<ul style="list-style-type: none">• 3.5 mg perindopril arginine/2.5 mg amlodipine (as amlodipine besylate) oral tablet• 7 mg perindopril arginine/5 mg amlodipine (as amlodipine besylate) oral tablet• 14 mg perindopril arginine/10 mg amlodipine (as amlodipine besylate) oral tablet
NOC date	January 28, 2016
Manufacturer	Servier Canada Inc.

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ABBREVIATIONS

ACE	angiotensin-converting enzyme
ARB	angiotensin receptor blocker
BB	beta blocker
CCB	calcium channel blocker
CDR	CADTH Common Drug Review
DBP	diastolic blood pressure
FDC	fixed-dose combination
ODB	Ontario Drug Benefit
RAMQ	Régie de l'assurance maladie du Québec
SBP	systolic blood pressure

SUMMARY

Background

Perindopril arginine/amlodipine (Viacoram) is a fixed-dose combination (FDC) of perindopril arginine (an angiotensin-converting enzyme [ACE] inhibitor) and amlodipine (a calcium channel blocker [CCB]) indicated for the treatment of mild-to-moderate essential hypertension in patients for whom combination therapy is appropriate.¹ Perindopril arginine/amlodipine is available as 3.5 mg/2.5 mg (\$0.95), 7 mg/5 mg (\$1.05), and 14 mg/10 mg (\$1.15) tablets, with a recommended starting dose of 3.5 mg/2.5 mg once daily. In uncontrolled patients, the dose may be increased to 7 mg/5mg after four weeks; in patients who remain uncontrolled, the dose may be further increased to 14 mg/10 mg after an additional four weeks. At manufacturer-submitted prices, the daily cost of perindopril arginine/amlodipine is \$0.95 to \$1.15 per patient, or \$346.75 to \$419.75 annually.²

Summary of the Economic Analysis Submitted by the Manufacturer

The manufacturer submitted a cost comparison of perindopril arginine/amlodipine for the treatment of patients with mild-to-moderate hypertension that compared: 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 FDC that includes perindopril (perindopril erbumine/indapamide [Coversyl Plus]).² The manufacturer also included secondary comparisons with other typical first-line antihypertensive drugs — ACE inhibitors, angiotensin II receptor blockers (ARBs), CCBs, free-dose combinations (CCBs plus ACE inhibitors, CCBs plus ARBs, CCBs plus beta blockers) — and with FDCs (amlodipine plus telmisartan, trandolapril plus verapamil, ACE inhibitors plus diuretics, and ARBs plus diuretics).² The analysis was conducted from the perspective of a publicly funded health care payer, based on a time horizon of one year. The manufacturer assumed that all aspects of patient management were equivalent across treatments; therefore, only drug costs were considered. Drug costs were obtained from the Ontario Drug Benefit (ODB) Formulary or the Régie de l'assurance maladie du Québec (RAMQ) Liste des médicaments.^{3,4} The prices included dispensing fees (\$8.83) and a markup (8%).²

The assumption of similar efficacy and safety of perindopril/amlodipine with the primary comparators was based on manufacturer-sponsored randomized controlled trials (RCTs): CL2-005 and PATH reported superior efficacy of perindopril arginine/amlodipine in reducing systolic blood pressure (SBP) and diastolic blood pressure (DBP) compared with perindopril or amlodipine; CL3-018 was a titration study that reported superior reduction in both SBP and DBP at three months with a perindopril arginine/amlodipine strategy compared with a valsartan/amlodipine strategy.² No direct evidence was provided to support the equal efficacy of perindopril arginine/amlodipine with monotherapies or combination therapies not included within the trials.

The manufacturer calculated the drug costs of perindopril arginine/amlodipine based on the proportion of patients in the clinical trial (CL3-018) who were titrated to the three doses of perindopril arginine/amlodipine.² The total weighted average cost of primary comparators was calculated using estimates of utilization based on IMS Brogan claims data,² and on assumptions for the secondary comparators.

Key Limitations

- **Limited comparative evidence:** Direct evidence was provided comparing perindopril arginine/amlodipine and the individual components used as monotherapy. As noted in the CADTH Common Drug Review (CDR) clinical review, statistically significant reductions in DBP and SBP were observed in patients taking perindopril arginine/amlodipine compared with those taking the individual monotherapies, based on the results of CL2-005 and PATH. While this suggests that perindopril arginine/amlodipine may have superior efficacy when compared with its components used as monotherapy, no comparison was provided with perindopril arginine/amlodipine dosed at 7 mg/5 mg; therefore, there is uncertainty in the relative clinical effectiveness at this dose versus the individual monotherapies (perindopril arginine and amlodipine). Furthermore, it is unclear whether these results would be generalizable when comparing perindopril arginine/amlodipine with other monotherapies used as first-line treatments for hypertension (e.g., ARBs, ACE inhibitors, and CCBs).

Limited comparative effectiveness information was provided comparing perindopril arginine/amlodipine with combination therapies used to treat hypertension. In the CL3-018 titration study comparing perindopril arginine/amlodipine and valsartan/amlodipine, there was a statistically significant reduction in DBP and SBP at three months as well as at one, two, and six months.² While this suggests that perindopril arginine/amlodipine may be superior to the valsartan/amlodipine combination, this comparator is not licensed for use in Canada, and it is uncertain whether these results would be generalizable to other combination therapies.

In summary, the manufacturer did not provide any direct or indirect evidence to support the claim of similar efficacy of perindopril arginine/amlodipine with other antihypertensive drugs beyond those included as active comparators within the clinical trials. No cost-effectiveness model was submitted. In the absence of this information, only costs could be considered, which may not be sufficient to justify a price premium.

- **Questionable weighting for cost calculations:** Average annual costs were estimated for perindopril arginine/amlodipine and the comparators based on weighted averages. The average annual cost of perindopril arginine/amlodipine was calculated based on the distribution of patients taking each dose of perindopril arginine/amlodipine at six months in the CL3-018 titration study. While this was accepted as the best data available, there is uncertainty as to whether this would be representative of the usage of perindopril arginine/amlodipine in clinical practice.

For the primary comparators, the most recent full year of claims data from IMS Brogan² were used to approximate the distribution of patients on each of the different doses of each comparator drug, and these percentages were used to estimate the annual weighted average cost of each of the drugs. For the secondary comparators, the manufacturer considered classes of drugs (ACE inhibitors, ARBs, CCBs, CCBs plus ACE inhibitors, CCBs plus ARBs, CCBs plus beta blockers, FDCs containing CCBs, ACE inhibitors plus diuretics, and ARBs plus diuretics); the average cost per class was calculated as the average cost of the drugs within the class, with the weighted average cost of each drug having been calculated under the assumption that the use of different doses was evenly distributed across each drug.

The cost differential reported by the manufacturer between perindopril arginine/amlodipine and primary and secondary comparator drugs will only be realized if perindopril arginine/amlodipine, as per the assumed dosages, replaces existing comparator doses in the proportions assumed by

the manufacturer. The assumed dosages were based on clinical trial data (perindopril arginine/amlodipine), current claims data (primary comparators), and simple assumptions (secondary comparators). CDR reanalysis presented the maximum and minimum costs of perindopril arginine/amlodipine and comparators based on the recommended dosages defined in the product monographs to provide the full range of costs.

Issues for Consideration

- Perindopril arginine/amlodipine is the first ACE inhibitor/CCB combination product indicated as a first-line treatment for essential hypertension.⁵ As the FDC is more costly than individual products used as monotherapies, introducing this drug may lead to an increased impact on drug budget.
- Perindopril arginine/amlodipine is the second drug within the class of CCB-plus-ACE-inhibitor FDC tablets; verapamil/trandolapril (Tarka) was the first. Tarka is not currently reimbursed by any of the CDR-participating drug plans.
- Unlike other combination products for the treatment of hypertension, patients cannot be titrated on the individual components.

Results and Conclusions

At the manufacturer-submitted price, CDR 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 used as monotherapy (\$50 to \$131 annually) — not including markup or dispensing fees. The cost of perindopril arginine/amlodipine is within the range of the perindopril/indapamide FDC (\$309 to \$417 annually), and is generally less costly than the free-dose combination of perindopril erbumine and amlodipine (\$289 to \$544 annually) based on publicly available prices (Table 1, Table 2, Table 3, and Table 4). For secondary comparators (Table 8), the perindopril arginine/amlodipine FDC was generally more expensive than ACE inhibitors, ARBs, and CCBs when used as monotherapy (\$25 to \$543 per patient annually). Perindopril arginine/amlodipine was less costly than the other available ACE inhibitor/CCB combination (verapamil/trandolapril; \$629 to \$698 annually). It is generally less expensive than free-dose combinations of CCBs plus ACE inhibitors (\$160 to \$887 annually), CCBs plus ARBs (\$208 to \$953 annually), and CCBs plus beta blockers (\$131 to \$872 annually); however, the cost differential varies widely based on the combinations used. Perindopril arginine/amlodipine is more costly than FDCs with diuretics (ACE inhibitors plus diuretics: \$76 to \$392 annually; ARBs plus diuretics: \$103 to \$420 annually).

The manufacturer's cost analysis was based on the assumption of similar efficacy between perindopril arginine/amlodipine and other antihypertensive drugs relying on the results of RCTs; however, there was uncertainty regarding the equivalent efficacy of perindopril arginine/amlodipine and the individual components as monotherapy at all dosages. Whether these results are generalizable to other monotherapies and combination therapies to treat hypertension also remains uncertain. Furthermore, no direct or indirect evidence was provided to support the equivalent efficacy of perindopril arginine/amlodipine beyond those considered within the clinical trials. As the manufacturer did not provide cost-effectiveness information, only cost information could be considered, which may not be sufficient to justify a cost premium for perindopril arginine/amlodipine.

Cost Comparison Tables

Clinical experts have deemed the comparator treatments presented in Table 1 to be appropriate. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are ODB Formulary list prices, unless otherwise specified. Existing product reimbursement agreements are not reflected in the table; as such, they may not represent the actual costs to public drug plans.

TABLE 1: COST COMPARISON TABLE FOR HYPERTENSION MEDICATIONS — ARB/CCB COMBINATIONS

Drug	Strength	Dosage Form	Price (\$)	Recommended Dose	Average Daily Drug Cost (\$)	Average Annual Drug Cost (\$)
Angiotensin-Converting Enzyme Inhibitors Plus Calcium Channel Blocker						
Perindopril arginine + amlodipine besylate (Viacoram)	3.5 mg/2.5 mg 7 mg/5 mg 14 mg/10mg	Tablet	0.9500 ^a 1.0500 ^a 1.1500 ^a	3.5 mg/2.5 mg (starting dose), 7 mg/5 mg, or 14 mg/10mg once daily	0.95 to 1.15	346 to 419
Verapamil + trandolapril (Tarka)	2 mg/240 mg 4 mg/240 mg	Tablet	1.7230 ^b 1.9121 ^b	2 mg/240 mg or 4 mg/240 mg once daily	1.72 to 1.91	629 to 698
Angiotensin II Receptor Blocker Plus Calcium Channel Blocker						
Telmisartan + amlodipine (Twynsta)	40 mg/5 mg 40 mg/10 mg 80 mg/5 mg 80 mg/10 mg	Tablet	0.7022 0.7022 0.7022 0.7022	40 mg/5 mg, 40 mg/10 mg, 80 mg/5 mg, or 80 mg/10 mg (one tablet) once daily	0.70	256

ARB = angiotensin II receptor blocker; CCB = calcium channel blocker.

^a Manufacturer's submission.

^b Régie de l'assurance maladie du Québec (June 2016).

Note: Pricing source is the Ontario Drug Benefit Formulary (June 2016), unless otherwise indicated.

TABLE 2: COST COMPARISON TABLE FOR HYPERTENSION MEDICATIONS — ACE INHIBITORS AND ACE INHIBITOR FIXED-DOSE COMBINATIONS

Drug	Strength	Dosage Form	Price (\$)	Recommended Dose	Average Daily Drug Cost (\$)	Average Annual Drug Cost (\$)
ACE Inhibitors						
Benazepril (generics)	5 mg 10 mg 20 mg	Tablet	0.5577 0.6595 0.7567	20 mg to 40 mg daily	0.76 to 1.51	276 to 552
Captopril (generics)	6.25 mg 12.5 mg 25 mg 50 mg 100 mg	Tablet	0.1237 ^a 0.2120 0.3000 0.5590 1.0395	25 mg to 50 mg two to three times daily	0.60 to 1.68	219 to 612
Cilazapril (generics)	1 mg 2.5 mg 5 mg	Tablet	0.1557 0.1795 0.2085	2.5 mg to 10 mg daily	0.18 to 0.42	66 to 152
Enalapril (generics)	2.5 mg 5 mg 10 mg 20mg	Tablet	0.1863 0.2203 0.2647 0.3195	10 mg to 40 mg once daily or 5 mg to 20 mg twice daily	0.26 to 0.64 or 0.44 to 0.64	97 to 233 or 161 to 233

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Drug	Strength	Dosage Form	Price (\$)	Recommended Dose	Average Daily Drug Cost (\$)	Average Annual Drug Cost (\$)
Fosinopril (Monopril)	10 mg 20 mg	Tablet	0.2178 0.2619	20 mg daily	0.26	96
Lisinopril (generics)	5 mg 10 mg 20 mg	Tablet	0.1347 0.1619 0.1945	10 mg to 40 mg daily	0.16 to 0.39	59 to 142
Perindopril (Coversyl)	2 mg 4 mg 8 mg	Tablet	0.6527 0.8168 1.1325	4 mg to 8 mg daily	0.82 to 1.13	298 to 412
Quinapril (generics)	5 mg 10 mg 20 mg 40 mg	Tablet	0.2321 0.2321 0.2321 0.2321	10 mg to 40 mg daily	0.92	334
Ramipril (generics)	1.25 mg 2.5 mg 5 mg 10 mg 15 mg	Capsule	0.1274 0.1470 0.1470 0.1862 0.5857 ^b	2.5 mg to 10 mg daily	0.15 to 0.19	54 to 68
Trandolapril (Mavik)	0.5 mg 1 mg 2 mg 4 mg	Capsule	0.2733 ^a 0.6901 0.7931 0.9785	1 mg to 2 mg daily	0.55 to 0.79	200 to 289
ACE Inhibitors + Diuretics						
Cilazapril + hydrochlorothiazide (generics)	5 mg/12.5 mg	Tablet	0.4170	5 mg/12.5 mg once daily	0.42	152
Enalapril + hydrochlorothiazide (generics)	5 mg/12.5 mg 10 mg/25 mg	Tablet	0.7493 ^a 1.0741 ^a	5 mg/12.5 mg or 10 mg/25 mg once daily	0.75 to 1.07	273 to 392
Lisinopril + hydrochlorothiazide (generics)	10 mg/12.5 mg 20 mg/12.5 mg 20mg/25 mg	Tablet	0.2084 0.2504 0.2504 ^b	10 mg/12.5 mg, 20 mg/12.5 mg, 20mg/25 mg once daily	0.21 to 0.25	76 to 91
Perindopril + indapamide (Coversyl Plus)	2 mg/0.625 mg 4 mg/1.25 mg 8 mg/2.5 mg	Tablet	0.8453 1.0225 1.1436	2 mg/0.625 mg, 4 mg/1.25 mg, or 8 mg/2.5 mg once daily	0.85 to 1.14	309 to 417
Quinapril + hydrochlorothiazide (generics)	10 mg/12.5 mg 20 mg/12.5 mg 20 mg/25 mg	Tablet	0.6865 0.6865 0.6512	10 mg/12.5 mg, 20 mg/12.5 mg, or 20 mg/25 mg once daily	0.65 to 0.69	238 to 251
Ramipril + hydrochlorothiazide (generics)	2.5 mg/ 12.5 mg 5 mg/12.5 mg 10mg/12.5 mg 5 mg/25 mg 10mg/25 mg	Tablet	0.2093 0.2069 0.2633 0.2069 0.2633	2.5 mg/12.5 mg, 5 mg/12.5 mg, 10mg/12.5 mg, 5 mg/25 mg, or 10mg/25 mg once daily	0.21 to 0.26	75 to 96

ACE = angiotensin-converting enzyme.

^aSaskatchewan Formulary (June 2016).

^bRégie de l'assurance maladie du Québec (June 2016).

Note: Pricing source is the Ontario Drug Benefit Formulary (June 2016), unless otherwise indicated.

TABLE 3: COST COMPARISON TABLE FOR HYPERTENSION MEDICATIONS — ARBs AND ARB FIXED-DOSE COMBINATIONS

Drug	Strength	Dosage Form	Price (\$)	Recommended Dose	Average Daily Drug Cost (\$)	Average Annual Drug Cost (\$)
ARBs						
Candesartan cilexetil (generics)	4 mg 8 mg 16 mg 32 mg	Tablet	0.1700 0.2850 0.2850 0.2932	8 to 32 mg once daily	0.29 to 0.34	104 to 124
Eprosartan mesylate (Teveten)	400 mg 600 mg	Tablet	0.7246 1.1079	400 to 600 mg once daily	0.73 to 1.11	265 to 404
Irbesartan (generics)	75 mg 150 mg 300 mg	Tablet	0.3025 0.3025 0.3025	150 to 300 mg once daily	0.30	110
Losartan (generics)	25 mg 50 mg 100 mg	Tablet	0.3147 0.3147 0.3147	50 to 100 mg once daily	0.31	115
Olmesartan medoxomil (Olmetec)	20 mg 40 mg	Tablet	1.1500 1.1500	20 to 40 mg once daily	1.15	420
Telmisartan (generics)	40 mg 80 mg	Tablet	0.2824 0.2824	80 mg once daily	0.28	103
Valsartan (generics)	40 mg 80 mg 160 mg 320 mg	Tablet	0.2912 ^a 0.2958 0.2958 0.2843	80 to 320 mg once daily	0.28 to 0.30	104 to 108
ARBs + Diuretics						
Candesartan + hydrochlorothiazide (generics)	16 mg/12.5 mg 32 mg/12.5 mg 32 mg/25 mg	Tablet	0.2995 0.3008 0.3008	16 mg/12.5 mg 32 mg/12.5 mg or 32 mg/25 mg (one tablet) once daily	0.30	109
Eprosartan + hydrochlorothiazide (Teveten Plus)	600 mg/12.5 mg	Tablet	1.1079	600 mg/12.5 mg (one tablet) once daily	1.11	404
Irbesartan + hydrochlorothiazide (generics)	150 mg/12.5 mg 300 mg/12.5 mg 300 mg/25 mg	Tablet	0.3024 0.3024 0.3004	150 mg/12.5 mg to 300 mg/25 mg (one tablet) once daily	0.30	110
Losartan + hydrochlorothiazide (generics)	50 mg/12.5 mg 100 mg/12.5 mg 100 mg/25 mg	Tablet	0.3147 0.3082 0.3147	50 mg/12.5 mg to 100 mg/25 mg (one tablet) once daily	0.31 to 0.32	112 to 115
Olmesartan + hydrochlorothiazide (Olmetec Plus)	20 mg/12.5 mg 40 mg/12.5 mg 40 mg/25 mg	Tablet	1.1500 1.1500 1.1500	50 mg/12.5 mg 40 mg/12.5 mg 40 mg/25 mg (one tablet) once daily	1.1500	420
Telmisartan + hydrochlorothiazide (generics)	80 mg/12.5 mg 80 mg/25 mg	Tablet	0.2824 0.2824	80 mg/12.5 mg or 80 mg/25 mg (one tablet) once daily	0.28	103

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Drug	Strength	Dosage Form	Price (\$)	Recommended Dose	Average Daily Drug Cost (\$)	Average Annual Drug Cost (\$)
Valsartan + hydrochlorothiazide	80 mg/12.5 mg 160mg/12.5 mg 160 mg/25 mg 320 mg/12.5 mg 320 mg/25 mg	Tablet	0.2958 0.2958 0.2958 0.2912 0.2912	80 mg/12.5 mg 160 mg/12.5 mg 320 mg/12.5 mg or 320 mg/25 mg (one tablet) once daily	0.29 to 0.30	106 to 108

ARB = angiotensin II receptor blocker.

^a Manufacturer's submission.

Note: Pricing source is the Ontario Drug Benefit Formulary (June 2016) unless otherwise indicated.

TABLE 4: COST COMPARISON TABLE FOR HYPERTENSION MEDICATIONS – OTHER MONOTHERAPIES AND FIXED-DOSE COMBINATIONS

Drug	Strength	Dosage Form	Price (\$)	Recommended Dose	Average Daily Drug Cost (\$)	Average Annual Drug Cost (\$)
Beta Blockers						
Acebutolol (generics)	100 mg 200 mg 400 mg	Tablet	0.0787 0.1177 0.2466	200 to 400 mg twice daily	0.24 to 0.4932	86 to 180
Atenolol (generics)	50 mg 100 mg	Tablet	0.1437 0.2362	50 mg to 100 mg daily	0.14 to 0.24	52 to 86
Bisoprolol (generics)	5 mg 10 mg	Tablet	0.0994 0.1450	5 mg to 20 mg daily	0.10 to 0.29	36 to 106
Carvedilol (generics)	3.125 mg 6.25 mg 12.5 mg 25 mg	Tablet	0.3377 0.3377 0.3377 0.3377	3.125 mg, 6.25 mg, 12.5 mg, or 25 mg twice daily	0.68	247
Labetalol (Trandate)	100 mg 200 mg	Tablet	0.3474 0.6141	200 mg to 600 mg twice daily	1.08 to 3.24	394 to 1,181
Metoprolol (generics)	50 mg 100 mg	Tablet	0.0624 0.1361	50 mg to 100 mg twice daily	0.12 to 0.27	46 to 99
	100 mg 200 mg	SR Tablet	0.1415 0.2568	100v to 200 mg daily	0.14 to 0.26	52 to 94
Nadolol (generics)	40 mg 80 mg 160 mg	Tablet	0.2465 0.3515 1.2046	80 mg to 320 mg daily	0.35 to 2.41	128 to 858
Nebivolol (Bystolic)	2.5 mg 5 mg 10 mg 20 mg	Tablet	1.2607 ^a 1.2607 ^a 1.2607 ^a 1.2607 ^a	5 mg daily	1.30	475
Pindolol (generics)	5 mg 10 mg 15 mg	Tablet	0.1361 0.2323 0.3370	15 mg to 45 mg daily	0.34 to 1.01	123 to 369
Propranolol (generics)	10 mg 20 mg 40 mg 80 mg 120 mg	Tablet	0.0689 0.1107 0.1225 0.2034	160 mg to 320 mg daily	0.11 to 0.20	37 to 74
	60 mg 80 mg 120 mg 160 mg	LA Capsule	0.6296 ^b 0.7101 ^b 1.0932 ^b 1.2928 ^b	60 mg to 320 mg daily	0.63 to 1.30	230 to 945
Sotalol (generics)	80 mg 160 mg	Tablet	0.2966 ^b 0.1623	160 mg to 320 mg daily	0.16 to 0.32	59 to 118

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Drug	Strength	Dosage Form	Price (\$)	Recommended Dose	Average Daily Drug Cost (\$)	Average Annual Drug Cost (\$)
Timolol (generics)	5 mg 10 mg 20 mg	Tablet	0.1649 0.2572 0.5005	20 mg twice daily to 60 mg daily	1.001 to 1.5015	365 to 548
Beta Blockers + Diuretics						
Atenolol + chlorthalidone (generics)	50 mg/25mg 100 mg/25mg	Tablet	0.3195 0.5236	50 mg/25 mg or 100 mg/25 mg (one tablet) once daily	0.32 to 0.52	117 to 191
Pindolol + hydrochlorothiazide (Viskazine)	10 mg/25 mg 10 mg/50 mg	Tablet	1.1007 1.1007	10 mg/25 mg or 20 mg/100 mg (1 to 2 tablets) once daily	1.10 to 2.20	402 to 804
Calcium Channel Blockers						
Amlodipine (generics)	2.5 mg 5 mg 10 mg	Tablet	0.1380 ^c 0.2417 0.3587	5 mg to 10 mg daily	0.24 to 0.36	88 to 131
Felodipine (generics)	2.5 mg 5 mg 10 mg	ER Tablet	0.3170 0.4620 0.6733	2.5 mg to 10 mg daily	0.32 to 0.67	116 to 246
Nifedipine (generics, Adalat XL)	5 mg 10 mg 20 mg 30 mg 60 mg	ER Tab	0.3679 0.4877 1.2725 0.6171 0.9374	30 mg to 90 mg daily	0.62 to 1.56	225 to 567
Diltiazem (generics)	120 mg 180 mg 240 mg 300 mg 360 mg	ER Tablet	0.8590 1.1418 1.1562 1.5117 1.5161	240 mg to 360 mg daily	1.16 to 1.72	422 to 627
	120 mg 180 mg 240 mg 300 mg	LA Capsule	0.3634 0.4824 0.6399 0.7999	240 mg to 360 mg daily	0.64 to 0.96	234 to 352
	120 mg 180 mg 240 mg 300 mg 360 mg	SR Capsule	0.2133 0.2889 0.3832 0.4720 0.5778	180 mg to 240 mg daily	0.29 to 0.38	105 to 140
Verapamil (generics)	80 mg 120 mg	Tablet	0.2735 0.4250	80 mg to 160 mg three times daily	0.8500 to 1.7000	303 to 605
	120 mg 180 mg 240 mg	LA Tablet	0.4250 0.5204 0.5075	180 mg to 480 mg daily	0.52 to 1.02	190 to 370
Diuretics						
Chlorthalidone (generics)	50 mg	Tablet	0.1242	25 mg to 100 mg three times daily	0.12 to 0.25	45 to 91
Hydrochlorothiazide (generics)	12.5 mg 25 mg 50 mg 100 mg	Tablet	0.0322 ^b 0.0157 0.0217 0.1250 ^d	12.5 mg to 200 mg once or twice daily	0.03 to 0.25	12 to 91
Indapamide (generics)	1.25 mg 2.5 mg	Tablet	0.0745 0.1182	1.25 mg to 2.5 mg once daily	0.07 to 0.12	26 to 43
Direct Renin Inhibitor						
Aliskiren (Rasilez)	150 mg 300 mg	Tablet	1.1539 ^e 1.1539 ^e	150 mg to 300 mg once daily	1.15	421
Direct Renin Inhibitor + Diuretics						
Aliskiren (Rasilez) +	150 mg/12.5 mg	Tablet	1.1100 ^e	150 mg/12.5 mg,	1.11	405

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Drug	Strength	Dosage Form	Price (\$)	Recommended Dose	Average Daily Drug Cost (\$)	Average Annual Drug Cost (\$)
hydrochlorothiazide	150 mg/25 mg 300 mg/12.5 mg 300 mg/25 mg		1.1100 ^e 1.1100 ^e 1.1100 ^e	150 mg/25 mg, 300 mg/12.5 mg, or 300 mg/25 mg (one tablet) once daily		
Angiotensin II Receptor Blocker Plus Calcium Channel Blocker						
Telmisartan + amlodipine (Twynsta)	40 mg/5 mg 40 mg/10 mg 80 mg/5 mg 80 mg/10 mg	Tablet	0.7022 0.7022 0.7022 0.7022	40 mg/5 mg, 40 mg/10 mg, 80 mg/5 mg, or 80 mg/10 mg (one tablet) once daily	0.70	256

ER = extended release; LA = long-acting; SR = sustained release.

^a Delta, PA wholesale price (June 2016).

^b Saskatchewan Formulary (June 2016).

^c Alberta Drug Formulary (June 2016).

^d Nova Scotia Drug Formulary (June 2016).

^e Régie de l'assurance maladie du Québec (June 2016).

Note: Pricing source is the Ontario Drug Benefit Formulary (June 2016), unless otherwise indicated.

APPENDIX 1: REVIEWER WORKSHEETS

TABLE 5: SUMMARY OF MANUFACTURER’S SUBMISSION

Drug Product	Perindopril arginine/amlodipine (Viacoram)
Treatment	<ul style="list-style-type: none"> Perindopril arginine 3.5 mg/amlodipine 2.5 mg as first-line therapy Perindopril arginine 7 mg/amlodipine 5 mg in patients non-controlled by perindopril 3.5 mg/amlodipine 2.5 mg Perindopril arginine 14 mg/amlodipine 10 mg in patients non-controlled by perindopril 7 mg/amlodipine 5 mg
Comparators	<p>Primary comparators in the base case:</p> <ul style="list-style-type: none"> Perindopril/indapamide (Coversyl Plus) (2 mg/0.625 mg, 4 mg/1.25 mg, 8 mg/2.5 mg once daily) Perindopril (Coversyl) (2 mg, 4 mg, 8 mg once daily) Amlodipine (2.5 mg, 5 mg once daily) Free-dose combination of perindopril erbumine (2 mg, 4 mg, 8 mg once daily) and amlodipine (2.5 mg, 5 mg, 10 mg once daily) <p>Secondary comparators:</p> <ul style="list-style-type: none"> ACE inhibitors, ARBs, CCBs used as monotherapies CCBs in free-dose combination with ACE inhibitors, ARBs, and BBs FDCs of ACE inhibitors and ARBs with diuretics Other FDCs (amlodipine + telmisartan; trandolapril + verapamil)
Study Question	“From the Ministry of Health perspective and utilizing the Ontario Public Drug Programs proxy for CDR-participating drug plans, what is the cost of Viacoram relative to alternative antihypertensive agents used as a first-line agent and for treated albeit uncontrolled patients? Comparators may be monotherapies, free-dose combinations, and single-pill combinations used in the treatment of adult patients with mild-to-moderate hypertension.”
Type of Economic Evaluation	Cost analysis (drug costs only)
Target Population	Adult patients with mild-to-moderate hypertension
Perspective	Canadian publicly funded health care system
Outcomes Considered	DBP, SBP; from manufacturer-sponsored clinical trials
Key Data Sources	
Cost	The cost of perindopril arginine/amlodipine was obtained from the manufacturer. The cost of comparators was obtained from the Ontario Drug Benefit formulary and the Régie de l’assurance maladie du Québec. ⁴ Costs included dispensing fees (\$8.83) and markup (8%). Other potential health care resource use, including those associated with drug-related adverse events, were not included.
Clinical Efficacy	Three manufacturer-sponsored, randomized, double-blind, active-controlled trials (phase 2: CL2-005; phase 3: PATH, CL3-018)
Harms	Manufacturer-sponsored clinical trials
Market Share	IMS Brogan PharmaStat database ⁶
Time Horizon	1 year
Results for Base Case	The total cost of perindopril arginine/amlodipine in ██████ per patient annually, which is ██████ more costly than perindopril erbumine and amlodipine used as monotherapies and the free-dose combination of perindopril erbumine and indapamide, and is ██████ less costly than the free-dose combination of perindopril erbumine and amlodipine.
Results for Secondary Analysis	For the secondary comparators, the total cost of perindopril arginine/amlodipine was reported to be higher than that of ACE inhibitors, ARBs, and CCBs when used as monotherapies; less expensive than free-dose combinations of CCBs + ACE inhibitors, CCBs + ARBs, and CCBs + BBs; less expensive than FDCs containing CCBs; and more expensive than FDCs with diuretics (ACE inhibitors + diuretics,

ARBs + diuretics). The manufacturer conducted sensitivity analyses on the maximum and minimal doses of the comparators, and the inclusion of markups and dispensing fees. Varying these parameters did not change the rank order of the treatments.

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; BB = beta blocker; CCB = calcium channel blocker; CDR = CADTH Common Drug Review; DBP = diastolic blood pressure; FDC = fixed-dose combination; SBP = systolic blood pressure.

Manufacturer's Results

The manufacturer submitted a cost comparison of perindopril arginine/amlodipine with monotherapies, free-dose combinations, and fixed-dose combinations (FDCs) used in the treatment of patients with mild-to-moderate hypertension. In the manufacturer's base case, the primary comparators were the individual components used as monotherapy (perindopril erbumine [Coversyl], amlodipine), the individual components used as a free-dose combination (perindopril erbumine plus amlodipine), and an FDC product that includes perindopril (perindopril/indapamide [Coversyl Plus]).² The manufacturer also included secondary comparisons with typical monotherapies (angiotensin-converting enzyme [ACE] inhibitors), angiotensin II receptor blockers [ARBs], and calcium channel blockers [CCBs]), free-dose combinations (CCBs plus ACE inhibitors, CCBs plus ARBs, and CCBs plus beta blockers), and FDCs (amlodipine plus telmisartan, trandolapril plus verapamil, ACE inhibitors plus diuretics, and ARBs plus diuretics).² The analysis was conducted from the perspective of a publicly funded health care payer using a one-year time horizon.²

The manufacturer assumed that all aspects of patient management were equivalent across the treatments and comparators; therefore, only drug costs were considered. Drug costs were obtained from the Ontario Drug Benefit (ODB) Formulary or the Régie de l'assurance maladie du Québec *Liste des médicaments* (RAMQ).^{3,4} The prices included dispensing fees (\$8.83) and markup (8%).² The manufacturer presented the drug costs for one year (Table 7). The average annual cost of perindopril arginine/amlodipine was calculated based on the distribution of patients taking each dose of perindopril arginine/amlodipine at six months in the CL3-018 titration study (Table 6).² For the primary comparators, the most recent full year of claims data from IMS Brogan² was used to approximate the distribution of patients on each of the different doses of each comparator drug; these percentages were used to estimate the weighted average cost of each of the drugs (Table 6). Finally, for the secondary comparators, the manufacturer considered classes of drugs (ACE inhibitors, ARBs, CCBs, CCBs plus ACE inhibitors, CCBs plus ARBs, CCBs plus beta blockers, FDCs containing CCBs, ACE inhibitors plus diuretics, and ARBs plus diuretics); the average cost per class was calculated as the average cost of the drugs within the class, the weighted average cost of each drug having been calculated under the assumption that the use of different doses was evenly distributed across each drug (Table 7).

For the base-case analysis (primary comparators) (Table 7), the total cost of perindopril arginine/amlodipine was reported to be ██████ per year; this is ██████ more costly than perindopril erbumine monotherapy (\$459.01 per year), amlodipine monotherapy (\$211.57 per year), and perindopril/indapamide FDC (\$534.60 per year), but is ██████ less costly than the free-dose combination of perindopril erbumine and amlodipine (\$670.58 per year).

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For the secondary analysis (secondary comparators) (Table 7), perindopril arginine/amlodipine was reported to be more expensive than ACE inhibitors, ARBs, and CCBs as monotherapies (incremental: ██████████); less expensive than free-dose combinations of CCBs plus ACE inhibitors, CCBs plus ARBs, and CCBs plus beta blockers (incremental: ██████████); less expensive than FDCs containing CCBs (incremental: ██████████); and more expensive than FDCs with diuretics (ACE inhibitors plus diuretics, ARBs plus diuretics) (incremental: ██████████).

The manufacturer conducted sensitivity analyses on the maximum and minimum doses of the comparators, and the inclusion of markups and dispensing fees. Varying these parameters did not change the rank order of the treatments.

TABLE 6: ASSUMED PATIENT DISTRIBUTION BY DOSE FOR PRIMARY COMPARATORS

Comparators		Cost Per Day	Patient Distribution
Perindopril arginine/amlodipine (Viacoram)	3.5 mg/2.5 mg	\$0.9500	████
	7 mg/5 mg	\$1.0500	████
	14 mg/10 mg	\$1.1500	████
Included as primary comparators within the manufacturer's analysis			
Perindopril erbumine/indapamide (Coversyl Plus)	2 mg/0.625 mg	\$0.8453	████
	4 mg/1.25 mg	\$1.0225	████
	8 mg/2.5 mg	\$1.1436	████
Perindopril erbumine (Coversyl)	2 mg	\$0.6527	████
	4 mg	\$0.8168	████
	8 mg	\$1.1325	████
Amlodipine	2.5 mg	\$0.1380	████
	5 mg	\$0.2417	████
	10 mg	\$0.3587	████

Note: Adapted from the manufacturer's submission.²

TABLE 7: MANUFACTURER'S RESULTS

Comparators	Cost Per Day	Annual Cost	Incremental Per Day	Incremental Per Year
Included as primary comparators within the manufacturer's analysis				
Perindopril arginine/ amlodipine (Viacoram)	████	████	████	████
Perindopril erbumine/ indapamide (Coversyl plus)	████	████	████	████
Perindopril erbumine (Coversyl)	████	████	████	████
Amlodipine	████	████	████	████
Perindopril erbumine (Coversyl) + amlodipine	████	████	████	████
Included as secondary comparators within the manufacturer's analysis				
ACE inhibitors	████	████	████	████
ARBs	████	████	████	████
CCBs	████	████	████	████
Free-dose combinations				
CCBs + ACE inhibitors	████	████	████	████
CCBs + ARBs	████	████	████	████
CCBs + BB	████	████	████	████
Single-pill combinations with CCBs	████	████	████	████

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Comparators	Cost Per Day	Annual Cost	Incremental Per Day	Incremental Per Year
Single-pill combinations with diuretics				
ACE inhibitor + diuretics	■	■	■	■
ARBs + diuretics	■	■	■	■

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; BB = beta blocker; CCB = calcium channel blocker.
 Note: Adapted from the manufacturer's submission.²

CADTH Common Drug Review Results

CADTH Common Drug Review (CDR) compared the annual drug cost per patient for perindopril arginine/amlodipine versus alternative antihypertensive drugs. Updated ODB list prices were used. Where a drug cost was not available on the ODB Formulary,³ the cost was taken from other CDR-participating drug plans (Saskatchewan, Alberta, and Nova Scotia),⁷⁻⁹ or the RAMQ *Liste des médicaments*.⁴ Drug cost was obtained from IMS Brogan DeltaPA when no public drug plan price was available.⁶ The CDR base case excluded markups and dispensing fees.

The manufacturer assumed the proportion of patients on each of the dosing options of perindopril arginine/amlodipine based on the titration study (CL3-018) (Table 6). The impact of this assumption was tested by CDR by assuming 100% of patients received either the lowest or highest dosage; the full range of costs was reported (Table 8). The rank order of the comparison between perindopril arginine/amlodipine and the comparators did not vary when applying the two extreme scenarios. The manufacturer's assumption was accepted in the base case even if uncertain, having been judged acceptable.

For the primary comparators, the manufacturer applied weighted averages to determine the total cost of comparators based on market share data from IMS Brogan Rx Dynamics (Table 6).⁶ For the secondary analysis, the manufacturer considered classes of drugs (ACE inhibitors, ARBs, CCBs, CCBs plus ACE inhibitors, CCBs plus ARBs, CCBs plus beta blockers, single-pill combinations containing CCBs, ACE inhibitor plus diuretics, and ARBs plus diuretics), and calculated the average cost per class as the average cost of the drugs within the class, since the weighted average cost of each drug had been calculated under the assumption that the use of different doses was evenly distributed across each drug. For these comparators (primary and secondary), the CDR reanalysis presented the maximum and minimum cost within each of the comparator classes by assuming 100% use of the most expensive and least expensive dose of each comparator within the class, in order to provide the full range of cost differences that may arise from the introduction of perindopril arginine/amlodipine (Table 8).

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 (\$50 to \$131 per patient annually) used as monotherapy. It is within the range of the perindopril/indapamide FDC (\$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 (Table 1, Table 2, Table 3, and Table 4). In summary, a price reduction of 2% to 85% is required for perindopril arginine/amlodipine compared with the individual components used as monotherapy (perindopril and amlodipine), 0% to 11% compared with perindopril erbumine/indapamide, and up to 17% compared with the free-dose combination of perindopril erbumine plus amlodipine at lower doses.

For the secondary comparators (Table 8), the total cost of perindopril arginine/amlodipine was generally more expensive than the cost of ACE inhibitors, ARBs, and CCBs when used as monotherapy (\$25 to

\$543 per patient annually). Perindopril arginine/amlodipine was less costly than the other available ACE inhibitor plus CCB combination (verapamil plus trandolapril: \$629 to \$698 annually). It is generally less expensive than free-dose combinations of CCBs plus ACE inhibitors (\$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 (ACE inhibitors with diuretics: \$76 to \$392 per patient annually; ARBs with diuretics: \$103 to \$420 per patient annually).

TABLE 8: CADTH COMMON DRUG REVIEW RESULTS

Comparators	Cost Per Day	Annual Cost	Incremental Per Day	Incremental Per Year
Included as primary comparators within the manufacturer's analysis				
Perindopril arginine/amlodipine (Viacoram)	\$1.09 (\$0.95 to \$1.15)	\$397.49 (\$346.75 to \$419.75)	Reference	
Perindopril erbumine/indapamide (Coversyl Plus)	\$1.08 (\$0.85 to \$1.14)	\$395.52 (\$308.53 to \$417.41)	-\$0.01 (-\$0.03 to -\$0.10)	-\$1.97 (-\$2.34 to -\$38.22)
Perindopril erbumine (Coversyl)	\$0.89 (\$0.65 to \$1.13)	\$325.54 (\$238.24 to \$413.36)	-\$0.20 (-\$0.02 to -\$0.30)	-\$71.95 (-\$6.39 to -\$108.51)
Amlodipine	\$0.26 (\$0.14 to \$0.36)	\$96.42 (\$50.37 to \$130.93)	-\$0.83 (-\$0.79 to -\$0.81)	-\$301.07 (-\$288.82 to -\$296.38)
Perindopril erbumine (Coversyl) + amlodipine	\$1.15 (\$0.79 to \$1.49)	\$421.96 (\$288.61 to \$544.29)	\$0.06 (-\$0.16 to \$0.34)	\$24.47 (-\$58.14 to \$124.54)
Included as secondary comparators within the manufacturer's analysis				
ACE inhibitors	\$0.34 (\$0.15 to \$0.96)	\$125.39 (\$53.66 to \$379.42)	-\$0.75 (-\$0.19 to -\$0.80)	-\$273.75 (-\$69.35 to -\$292.00)
ARBs	\$0.50 (\$0.28 to \$1.14)	\$183.33 (\$103.08 to \$419.75)	-\$0.59 (-\$0.01 to -\$0.67)	-\$215.35 (-\$3.65 to -\$244.55)
CCBs	\$0.72 (\$0.29 to \$1.47)	\$262.98 (\$105.45 to \$542.61)	-\$0.37 (-\$0.66 to \$0.32)	-\$135.05 (-\$240.90 to \$116.80)
BBs	\$0.30 (\$0.07 to \$0.92)	\$108.97 (\$25.12 to \$336.79)	-\$0.79 (-\$0.23 to -\$0.88)	-\$288.35 (-\$83.95 to -\$321.20)
Free-dose combinations				
CCBs + ACE inhibitors	\$1.06 (\$0.44 to \$2.43)	\$388.37 (\$160.60 to \$886.95)	-\$0.03 (-\$0.51 to \$1.28)	-\$10.95 (-\$186.15 to \$467.20)
CCBs + ARBs	\$1.22 (\$0.57 to \$2.61)	\$446.31 (\$208.05 to \$952.65)	\$0.13 (-\$0.38 to \$1.46)	\$47.45 (-\$138.70 to \$532.90)
CCBs + BB	\$1.02 (\$0.36 to \$2.39)	\$371.95 (\$131.40 to \$872.35)	-\$0.07 (-\$0.59 to \$1.24)	-\$25.55 (-\$215.35 to \$452.60)
Single-pill combinations with CCBs	\$1.25 (\$0.70 to \$1.91)	\$456.25 (\$256.30 to \$697.92)	\$0.16 (-\$0.25 to \$0.76)	\$58.40 (-\$91.25 to \$277.40)
Single-pill combinations with diuretics				
ACE inhibitor + diuretics	\$0.45 (\$0.21 to \$1.07)	\$164.25 (\$76.07 to \$392.05)	-\$0.64 (-\$0.08 to -\$0.74)	-\$233.60 (-\$29.22 to -\$270.10)
ARBs + diuretics	\$0.54 (\$0.28 to \$1.15)	\$197.10 (\$103.08 to \$419.75)	-\$0.55 (-\$0.67 to \$0.00)	-\$200.75 (-\$244.55 to \$0)

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; BB = beta blocker; CCB = calcium channel blocker.

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