Common Drug Review
Pharmacoeconomic Review Report

July 2015

Drug	lomitapide (Juxtapid) (oral capsules)
Indication	As an adjunct to a low-fat diet and other lipid-lowering drugs, with or without LDL apheresis, to reduce low-density lipoprotein cholesterol (LDL-C) in adult patients with homozygous familial hypercholesterolemia (HoFH).

Listing request	As per indication, plus:
	• Due to its benefit-risk profile, the prescribing of Juxtapid should be limited to physicians experienced in the diagnosis and treatment of familial hypercholesterolemia.
	
	The manufacturer proposes the following criteria be considered when assessing eligibility for Juxtapid in the treatment of HoFH:
	Typical clinical and lab criteria would include:
	• Untreated LDL-C > 10.3 mmol/L (400 mg/dL)
	OR:
	• Treated LDL-C > 5.2 mmol/L (200 mg/dL) with one or both of the following:
	  ○ Cutaneous or tendinous xanthomas (past or present); or
	  ○ Clinically evident premature CV disease and, when family history is available, evidence of FH in both parents
	OR:
	• DNA confirmation of 2 mutant alleles in genes for the LDL receptor, apo B, PCSK-9 or ARH.

Manufacturer	Aegerion Pharmaceuticals, Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in cardiology who provided input on the conduct of the review and the interpretation of findings.

Through the CADTH Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update — Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

CCA	cost-consequence analysis
CDR	CADTH Common Drug Review
CV	cardiovascular
HoFH	homozygous familial hypercholesterolemia
INESSS	Institut national d'excellence en santé et en services sociaux
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
MACE	major adverse cardiac event

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Lomitapide (Juxtapid)
Study Question	The objective was to present the disaggregated costs and clinical outcomes associated with lomitapide as compared to standard of care.
Type of Economic Evaluation	CCA
Target Population	Adult patients with HoFH
Treatment	Lomitapide + standard of care (low-fat diet + lipid-lowering drugs with or without plasma exchange)
Outcome(s)	Consequences assessed in the CCA included: • MI • coronary procedures (CABG, PTCA, heart valve procedures) • other vascular procedures (endarterectomy) • cerebrovascular events: TIA, stroke • cardiovascular (CV) death
Comparator	Standard of care (low-fat diet + lipid-lowering drugs + plasma exchange)
Perspective	Public payer
Time Horizon	5 years
Results for Base Case	Estimated annual costs to treat a patient with HoFH: • lomitapide + standard of care = $300,602 • standard of care alone = $14,078 Estimated 5-year costs to treat a patient with HoFH: • lomitapide + standard of care = $1,503,014 • standard of care alone = $70,392 Estimated reduction in risk of events over 5 years with lomitapide + standard of care compared with standard of care alone: • MI: 57% • coronary procedures: 54% • other vascular procedures: 49% • cerebrovascular procedures: 49% • CV death: 45%
Key Limitations	CDR noted a number of limitations with the manufacturer's submission: • As stated in the CDR clinical report, a true estimate of efficacy of lomitapide is unclear due to the absence of a comparator group in UP 1002/AEGR-733-005. • The validity of change in low-density LDL-C as a surrogate for outcomes such as CV events or CV death in patients with HoFH is not well established. The effects of treatment with lomitapide on CV morbidity and mortality are unknown. • The manufacturer assumed that patients receiving lomitapide would have a lower frequency of plasma exchanges (and related costs), which is not supported by any data. • The manufacturer's analysis did not include the costs incurred from additional monitoring of liver function tests that may be required with lomitapide due its effect on transaminases and hepatic fat. • The baseline patient data used in the model are based on a study with very small numbers of patients and data that were not specific to the Canadian population.

CDR Estimate(s)	Given the limitations identified with the clinical evidence and type of economic evaluation submitted, CDR was limited in the potential re-analyses. CDR multi-way reanalysis assumed all HoFH patients are eligible for drug coverage by public plans with no reductions in frequency of plasma exchange or apheresis sessions: • annual costs with lomitapide: $310,132 per patient • annual costs without lomitapide treatment: $14,339 per patient • annual incremental cost of lomitapide: $295,793 per patient The comparative effectiveness, the impact on quality of life, and, consequently, the cost-effectiveness of lomitapide + standard of care compared with standard of care alone remain unknown. Exploratory analyses by CDR based on suggested benefits by the manufacturer over 5 years resulted in incremental cost-effectiveness ratios ranging from $13.5 million per coronary procedure avoided to $512 million per CV event avoided.

CABG = coronary artery bypass graft; CCA = cost-consequence analysis; CDR = CADTH Common Drug Review; CV = cardiovascular; HoFH = homozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; TIA = transient ischemic attack.

EXECUTIVE SUMMARY

Background

Lomitapide (Juxtapid) is an oral lipid-lowering therapy that targets an atherogenic lipoprotein pathway. Lomitapide is indicated as an adjunct to a low-fat diet and other lipid-lowering drugs with or without low-density lipoprotein (LDL) apheresis to reduce LDL cholesterol (LDL-C) in adult patients with homozygous familial hypercholesterolemia (HoFH).[1] Lomitapide is available as 5 mg, 10 mg, and 20 mg capsules. The initial recommended dose of lomitapide is 5 mg daily to be titrated up to a maximum of 60 mg daily.[2] The manufacturer submitted a flat price of $1,040 per capsule, with a patient cap of $1,040 per day (the maximum cost per patient will not exceed $1,040 per day, irrespective of the dose prescribed and strengths dispensed). According to the manufacturer, the patient cap applies to all patients regardless of drug plan coverage and will be managed by a specialty pharmacy that will be the sole distribution point for lomitapide in Canada.[1]

The manufacturer submitted a cost-consequence analysis (CCA) presenting the disaggregated costs and clinical outcomes associated with lomitapide used as an adjunct to standard of care, defined as lipid-lowering therapy (e.g., statins, ezetimibe, niacin, bile acid sequestrants, fibrates, and omega-3 fatty acids) with or without apheresis, in adult patients with HoFH compared with standard of care alone. LDL apheresis is currently available only in Quebec and Edmonton, while plasma exchange is more widely available in Canada; it was assumed that plasma exchange, and not LDL apheresis, is the current standard of care for HoFH patients in the majority of provincial drug plans.[3] The manufacturer estimated the number of patients covered by the CADTH Common Drug Review (CDR)–participating drug plans that could be expected to be treated with either lomitapide or plasma exchange (n = 11) multiplied by the annual cost of treatment per patient. The effects of lomitapide added on to standard of care in reducing cardiovascular (CV) event risks were based on measuring lomitapide effects on LDL-C lowering as a surrogate atherogenic marker for cardiac risk. This assumption was based on retrospective studies with statins (not involving lomitapide) that showed a modest reduction in LDL-C to have resulted in improvement in morbidity and mortality.[4] The perspective of this analysis includes the costs to the public payer associated with lomitapide and plasma exchange, as well as costs associated with major adverse cardiac events (MACEs: myocardial infarction, coronary procedures, other vascular procedures, cerebrovascular events, and cardiovascular death) over a five-year time horizon. The manufacturer assumed that 21% of patients would discontinue lomitapide in year 1.

The manufacturer reported that the total cost of lomitapide added on to standard of care is $1,503,014 per patient over five years ($300,602 per patient per year) compared to $70,392 per patient over five years ($14,078 per patient per year) for standard of care alone. Estimated reductions in CV events ranged from 45% to 57% for lomitapide added to standard of care compared to standard of care alone.

Summary of Identified Limitations and Key Results

There are a number of limitations with the available clinical evidence for lomitapide as an adjunct to standard of care that limit the determination of its comparative clinical effectiveness and, as a result, cost-effectiveness versus standard of care alone. The reduction in LDL-C with lomitapide shown in UP 1002/AEGR-733-005 is difficult to interpret, as the study did not include a comparator group. Further, the validity of change in LDL-C as a surrogate for outcomes such as CV events or CV death in HoFH patients is not well established. Another inappropriate assumption made by the manufacturer was that patients in the lomitapide added on to-standard-of-care group may discontinue or reduce the frequency of plasma exchange; this was deemed unlikely and suboptimal by the clinical expert involved in the

review, considering the severity and prognosis of HoFH. Also, the manufacturer's analysis did not include the costs incurred from periodic monitoring of liver function tests that might be needed due to the potential effect of lomitapide on transaminases and hepatic fat.[5] CDR reanalyses assumed higher estimates of HoFH patients in Canada and no reduction in plasma exchange frequency. Exploratory cost-effectiveness analyses by CDR based on suggested benefits by the manufacturer estimated incremental cost-effectiveness ratios ranging from $13.5 million per coronary procedure avoided to $512 million per cerebrovascular event avoided. However, given that the relationship between LDL change and the suggested benefits is uncertain; these results should be interpreted with caution.

Conclusions

There are a number of limitations with the available clinical evidence for lomitapide used as an adjunct to standard of care in patients with HoFH. These limitations restrict the assessment of its comparative clinical effectiveness and cost-effectiveness versus standard of care alone. Based on CDR reanalyses, treatment with lomitapide as an adjunct to standard of care over a five-year time horizon would be associated with incremental costs of $1,478,967 per patient ($295,793 per patient per year). CDR analysis may underestimate the true incremental cost of lomitapide, as potential additional monitoring costs due to hepatic adverse events observed with lomitapide were not considered.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-consequence analysis (CCA) presenting the disaggregated costs and clinical outcomes associated with lomitapide as an adjunct to standard of care, defined as lipid-lowering therapy with or without plasma exchange, in adult patients with homozygous familial hypercholesterolemia (HoFH) compared with standard of care alone. By definition, CCAs present a detailed listing of the various impacts on outcomes associated with intervention under review with no attempt to value the aggregated components in a single metric.[6] The analysis examines the estimated number of patients expected to be treated with either lomitapide or plasma exchange multiplied by the annual cost of treatment per patient.

According to the product monograph, the effects of lomitapide on cardiac morbidity and mortality have not been established.[2] In the submitted analysis, the effects of lomitapide in reducing cardiovascular (CV) event risks are based on measuring lomitapide effects on low-density lipoprotein cholesterol (LDL-C) lowering as a surrogate atherogenic marker for cardiac risk. This assumption was based on retrospective studies with statins (not involving lomitapide) that showed a modest reduction in LDL-C to have resulted in improvement in morbidity and mortality.[4]

The perspective of this analysis includes the costs to the public payer associated with lomitapide and plasma exchange (26 sessions per year), as well as costs associated with major adverse cardiac events (MACEs: myocardial infarction, coronary procedures, other vascular procedures, cerebrovascular events, and cardiovascular death) over a five-year time horizon. LDL apheresis is currently available only in Quebec and Edmonton, while plasma exchange is more widely available in Canada; it was assumed that plasma exchange, and not LDL apheresis, is the current standard of care for HoFH patients in the majority of provincial public plans.[3] In contrast to LDL apheresis, plasma exchange therapy is non-specific in that it eliminates almost all plasma proteins (including fibrinogen concentration, platelet counts, and high-density lipoprotein) from the blood, but these all return to normal levels within a week.

The manufacturer assumed a 21% treatment discontinuation rate in year 1 and no discontinuation in subsequent years. Patients who discontinue incur half a year's cost of lomitapide treatment and half a year's treatment benefit in the year of discontinuation. Patients treated with lomitapide were assumed to be 88% compliant in year 1 and 100% compliant in subsequent years.

2. MANUFACTURER'S BASE CASE

In the base-case analysis, the manufacturer reported the cumulative costs over a five-year time horizon for a cohort of 11 lomitapide-treated patients at $16,533,156 (annual cost of $300,602 per patient), with an incremental cost of $15,758,844 (annual incremental cost of $286,524 per patient) compared to the cohort of 11 patients not treated with lomitapide. Active treatment costs represented the majority of the total costs. Estimated reductions in cardiac events over a five-year time horizon ranged from 45% (CV-related deaths) to 57% (myocardial infarction) in lomitapide-treated patients compared to patients not treated with lomitapide (Table 8, Appendix 5).

2.1 Summary of Manufacturer's Sensitivity Analyses

The manufacturer conducted univariate sensitivity analyses on several parameters or parameter groups by using alternative values over ranges. The results reported by the manufacturer indicate that the proportion of patients included in the model and time horizon had the greatest impact on incremental costs, with incremental costs ranging from $3 million to $40 million (see Table 9 in Appendix 5). Inputs pertaining to LDL-C baseline levels and reductions, as well as baseline hazards and discontinuation rates, had the greatest impact on per cent change in MACE, with per cent change ranging from –21% to −40%, and −65% to −75%. Model results were minimally impacted by other sensitivity analyses performed.

3. LIMITATIONS OF MANUFACTURER'S SUBMISSION

3.1 Comparative Effectiveness of Lomitapide as an Adjunct to Standard of Care Versus Standard of Care Alone is Unknown

The comparative effectiveness of lomitapide added on to standard of care versus standard of care alone has not been determined from the currently available evidence. Although the reported reduction in LDL-C by lomitapide was 40.1% versus baseline after 26 weeks in the phase 3 study AEGR-733-005,[5] the study lacked a comparator group, which limits the interpretation of the magnitude of the treatment effect observed.

3.2 Validity of LDL-C Lowering as Surrogate Outcome in HoFH is Unknown

The effects of lomitapide added on to standard of care in reducing CV event risks were based on measuring its effects on LDL-C lowering as a surrogate marker for cardiac risk. The manufacturer's analysis was based on the results of studies with statins and other lipid-lowering therapies that established LDL-C lowering as a surrogate atherogenic marker for reduction in cardiovascular event risk. However, the validity of using change in LDL-C as a surrogate for outcomes such as CV events or CV-related death in HoFH patients is not well established.

3.3 Frequency of Plasma Exchanges

The manufacturer assumed that some patients treated with lomitapide may discontinue or reduce the frequency of plasma exchange. This was considered suboptimal by the clinical expert for this review; due to the severity of the condition and the emphasis of maintaining reduced levels of LDL-C, patients are expected to continue biweekly schedules of LDL apheresis or plasma exchange. A one-way sensitivity analysis by the manufacturer that varied the plasma exchange reduction and discontinuation resulted in incremental costs between $15,370,083 and $15,897,942 compared to the base case result of $15,758,844. No changes were observed on per cent change in MACE with varied frequency of plasma exchange.

3.4 Liver Testing Costs

Elevated transaminases and hepatic fat were identified as harms of interest in the study on lomitapide.[5] The clinical expert indicated that increased liver testing would be expected for patients treated with lomitapide. The manufacturer's analysis did not include the costs incurred from periodic monitoring of liver function tests and per cent hepatic fat from baseline, or costs related to the management of these adverse events.

3.5 Relevance to Canadian Clinical Practice

The baseline patient data used in the model are based on a study with very small numbers of patients and data that were not specific to the Canadian population. The study by Raal et al. (2011) was a

retrospective study based in South Africa.[4] Given the low prevalence of HoFH, the manufacturer relied on clinical expert opinion to establish the assumption that geographical distinctions do not play a significant role in disease trajectory for HoFH. This was confirmed by the clinical expert for this review.

3.6 CADTH Common Drug Review Analyses

The manufacturer's CCA was based on several assumptions: number of HoFH patients, proportion of HoFH patients with drug coverage from public plans, outcomes for plasma exchange and LDL apheresis being equivalent, and reduction of plasma exchange frequency and discontinuation after lomitapide treatment. The manufacturer addressed the impact of varying the aforementioned parameters in one-way sensitivity analyses. CDR conducted a multi-way sensitivity analysis that assumed the following:

- All 27 HoFH patients in Canada would be provided drug coverage by public plans.
- HoFH patients treated with lomitapide would continue using plasma exchange at biweekly sessions.

The results of the CDR reanalysis are aligned with the manufacturer's results that show the impact of treatment costs with lomitapide on the total costs in HoFH patients; the annual cost per HoFH patient treated with lomitapide was $310,132 compared to the annual cost with standard of care of $14,339 per HoFH patient (Table 10).

3.6.1 Exploratory Cost-Effectiveness Analyses

Based on suggested benefits by the manufacturer, CDR estimated incremental cost-effectiveness ratios for lomitapide as an adjunct to standard of care compared with standard of care alone ranging from $13.5 million per coronary procedure avoided to $512 million per cerebrovascular event avoided. However, given that the relationship between LDL change and the suggested benefits is uncertain, these results should be interpreted with caution (Table 10).

4. ISSUES FOR CONSIDERATION

The clinical expert for this review indicated the possibility of off-label use of lomitapide in patients with heterozygous familial hypercholesterolemia and possibly in patients with non-familial hypercholesterolemia who may be statin-intolerant and presenting LDL-C levels greater than 5 mmol/L.

The daily cost of lomitapide is based on the patient cap submitted by the manufacturer. Should the patient cap not be maintained or operationalized by drug plans, the cost of lomitapide could be as high as $3,120 daily per patient (for the maximum daily dose of 60 mg).

4.1 Patient Input

One patient group, the FH Canada Patient Network, provided input. Patients who had no experience with lomitapide expected that it would improve cholesterol levels and would allow for fewer apheresis treatments. A reduction in the frequency of apheresis treatments was expected to help reduce stress, improve quality of life, and increase the amount of time for work, school, family, and social activities. Patients who had experience with lomitapide reported improved LDL levels, energy, and quality of life. Side effects were considered mild and were reduced when a low-fat diet was maintained concurrently. The number of apheresis treatments required was reduced, and patients cited a beneficial short-term effect of the drug.

As noted previously, the clinical expert involved in the CDR review indicated that given the severity of the disease, frequency of plasma exchange should not be reduced in patients using lomitapide.

5. CONCLUSIONS

There are a number of limitations with the available clinical evidence for lomitapide used as an adjunct to standard of care in patients with HoFH. These limitations restrict the assessment of its comparative clinical effectiveness and cost-effectiveness versus standard of care alone. Based on CDR reanalyses, treatment with lomitapide as an adjunct to standard of care over a five-year time horizon would be associated with incremental costs of $1,478,967 per patient ($295,793 per patient per year).
CDR analysis may underestimate the true incremental cost of lomitapide, as potential additional monitoring costs due to hepatic adverse events observed with lomitapide were not considered.

APPENDIX 1: COST COMPARISON

The comparators presented in the table in this appendix have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice rather than actual practice. Comparators are not restricted to drugs but may be devices or procedures. Costs are manufacturer list prices unless otherwise specified. Existing Product Listing Agreements are not reflected in the table, and thus, this table may not represent the actual costs to public drug plans.

TABLE 2: COST COMPARISON TABLE OF DRUGS USED FOR THE MANAGEMENT OF HOFH

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Daily Use	Daily Drug Cost ($)
Lomitapide (Juxtapid)[a]	5 mg 10 mg 20 mg	cap	1,040 per day	Initial: 5 mg daily Max: 60 mg daily	1,040.00[b]
HMG-CoA reductase inhibitors					
Lovastatin (Mevacor and generics)	20 mg 40 mg	tab	0.4919 0.8985	20 mg to 80 mg at bedtime	0.49 to 1.80
Fluvastatin sodium (Lescol XL)	80 mg	tab	1.5392	80 mg daily	1.54
Fluvastatin sodium (Lescol and generics)	20 mg 40 mg	cap	0.2202 0.3092	20 mg to 40 mg at bedtime	0.22 to 0.31
Rosuvastatin calcium (Crestor and generics)	5 mg 10 mg 20 mg 40 mg	tab	0.2311 0.2437 0.3046 0.3582	10 mg to 40 mg daily	0.23 to 0.36
Atorvastatin calcium (Lipitor and generics)	10 mg 20 mg 40 mg 80 mg	tab	0.3138 0.3922 0.4216 0.4216	10 mg to 80 mg at bedtime	0.31 to 0.42
Pravastatin sodium (Pravachol and generics)	10 mg 20 mg 40 mg	tab	0.4050 0.4778 0.5755	10 mg to 40 mg at bedtime	0.41 to 0.58
Simvastatin (Zocor and generics)	5 mg 10 mg 20 mg 40 mg 80 mg	tab	0.1841 0.3642 0.4501 0.4501 0.4501	10 mg to 80 mg at bedtime	0.36 to 0.45
Niacin products					
Niacin extended-release (Niaspan FCT)[c]	500 mg 750 mg 1,000 mg	tab	1.3300	1,000 mg to 2,000 mg at bedtime[d]	1.33 to 2.66
Niacin[c,e]	50 mg 100 mg 500 mg	tab	0.0153 0.0326 0.0365	1.5 to 6 grams per day in 3 divided doses	0.11 to 0.44
Fibrates					
Fenofibrate (Lipidil EZ)	48 mg 145 mg	tab	0.3560 0.9113	48 mg to 145 mg daily	0.36 to 0.91

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Daily Use	Daily Drug Cost ($)
Bezafibrate (Bezalip and generics)	400 mg	tab	2.1113	400 mg every morning or at bedtime	2.11
Micro-coated fenofibrate (Lipidil Supra and generics)	160 mg	tab	0.3116	160 mg daily	0.31
Fenofibrate (Lipidil and generics)	100 mg	cap	0.6105	3 to 4 caps divided three times daily before meals	1.83 to 2.44
Fenofibrate (Lipidil Micro and generics)	67 mg 200 mg	cap	0.4844[e] 0.2723	67 mg to 200 mg daily	0.27 to 0.48
Gemfibrozil (Lopid and generics)	300 mg	cap	0.1340	600 mg twice daily before meals	0.27
Cholesterol absorption inhibitor					
Ezetimibe (Ezetrol)	10 mg	tab	0.4612	10 mg daily	0.46
Binders					
Colesevelam (Lodalis)	625 mg	tab	1.1000	2.5 g to 4.5 g daily	4.40 to 7.70
Cholestyramine resin (Questran and generics)	4 g/packet	oral powder	1.3167	one packet 1 to 6 times daily	1.32 to 7.90
Colestipol HCl Colestid Regular Colestid Orange	5 g/packet 7.5 g/ packet	oral powder	0.9463 0.9463	1 to 6 packets in divided doses daily	0.95 to 5.68

cap = caplet; HoFH = homozygous familial hypercholesterolemia; tab = tablet.
[a] Source: Manufacturer's submission.[3]
[b] The submitted price for lomitapide is $1,040.0000 per day (list price) regardless of the patient's required dosing and strengths dispensed. The patient cap applies to all patients regardless of drug plan coverage. The patient cap will be managed by a specialty pharmacy (Innomar) that will be the sole distribution point for lomitapide in Canada.[3]
[c] Flush-free niacin, available over-the-counter, would not be a relevant comparator as it contains no free nicotinic acid and is therefore not effective in the treatment of dyslipidemia; it is therefore not included.
[d] Starting dose: 500 mg daily for four weeks; maintenance: 1,000 mg to 2,000 mg at bedtime (depending on response and concomitant statin use).
[e] Source: Newfoundland and Labrador drug formulary, January 2015.[7]
Source: Ontario online drug plan formulary January 2015 unless indicated otherwise.[8]

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 3: WHEN CONSIDERING ONLY COSTS, OUTCOMES AND QUALITY OF LIFE, HOW ATTRACTIVE IS LOMITAPIDE PLUS STANDARD CARE RELATIVE TO STANDARD CARE?

Lomitapide + Standard Care Versus Standard Care	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes						X
Quality of life						X
Incremental CE ratio or net benefit calculation	NA					

CE = cost-effectiveness; NA = not applicable.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 4: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?	X		
Comments	None		
Was the material included (content) sufficient?	X		
Comments	None		
Was the submission well organized and was information easy to locate?	X		
Comments	None		

TABLE 5: AUTHOR INFORMATION

Authors	Affiliations		
None specified	Aegerion Pharmaceuticals United BioSource Corporation		
	Yes	**No**	**Uncertain**
Authors signed a letter indicating agreement with entire document.		X	
Authors had independent control over the methods and right to publish analysis.		X	

APPENDIX 4: SUMMARY OF OTHER HEALTH TECHNOLOGY ASSESSMENT REVIEWS OF DRUG

Lomitapide was reviewed by the Institut national d'excellence en santé et en services sociaux (INESSS). The review by INESSS was based on the open-label, single-group, phase 3 study AEGR733-005 (Cuchel et al. 2013), which looked at the efficacy and safety of lomitapide in combination with other lipid-lowering drugs with or without low-density lipoprotein (LDL) apheresis in 29 adult patients with homozygous familial hypercholesterolemia (HoFH).[5] INESSS considered the level of evidence to be low owing to the design of the study (open-label, single-group) and the small number of patients included.

A recommendation was issued in October 2014 to not include lomitapide on the Quebec formulary.[9] The recommendation was based on the following reasons:

- The clinical benefits on cardiovascular morbidity and mortality and quality of life for lomitapide were not demonstrated in HoFH patients who already had the vast majority of cases of cardiovascular history.
- The long-term risk of hepatic fat accumulation was unclear and raised concerns.

Following the October 2014 recommendation, the manufacturer has requested a reconsideration and has submitted additional information to INESSS. A final recommendation is expected in June 2015.

APPENDIX 5: REVIEWER WORKSHEETS

1. Manufacturer's Model Structure

The manufacturer submitted a cost-consequence analysis (CCA) presenting the disaggregated costs and clinical outcomes associated with lomitapide use as an adjunct to standard of care in adult homozygous familial hypercholesterolemia (HoFH) patients. By definition, cost-consequence analyses present a detailed listing of the various impacts on outcomes associated with the intervention under review with no attempt to value the aggregated components in a single metric.[6] According to the product monograph, the effects of lomitapide on cardiac morbidity and mortality have not been established.[2] In the submitted analysis, the effects of lomitapide in reducing cardiovascular (CV) event risks are based on measuring lomitapide effects on low-density lipoprotein cholesterol (LDL-C) lowering as a surrogate atherogenic marker for cardiac risk. This assumption was based on retrospective studies with statins (not involving lomitapide) that showed a modest reduction in LDL-C to have resulted in improvement in morbidity and mortality.[4]

The perspective of this analysis includes the costs to CADTH Common Drug Review (CDR)–participating drug plans associated with lomitapide and plasma exchange as well as costs associated with major adverse cardiac events (MACEs: myocardial infarction, coronary procedures, other vascular procedures, cerebrovascular events, and cardiovascular death) over a five-year time horizon. LDL apheresis is currently only available in Quebec and Edmonton, while plasma exchange is more widely available in Canada; it was assumed that plasma exchange, and not LDL apheresis, is the current standard of care for HoFH patients in the majority of provincial public plans.[3] In contrast to LDL apheresis, plasma exchange therapy is non-specific in that it eliminates almost all plasma proteins (including fibrinogen concentration, platelet counts, and high-density lipoprotein cholesterol) from the blood, but these all return to reach normal levels within a week.

The analysis examines the estimated number of patients expected to be treated with either lomitapide or plasma exchange multiplied by the annual cost of treatment per patient (Figure 1). The HoFH patient population was modelled as a fixed cohort, with the number of HoFH patients entering the model determined based on Canadian adviser input.[3] To assess the incremental costs and MACE rates associated with lomitapide treatment, a cohort of treated and untreated patients were followed longitudinally in the model, and total events and costs were calculated at the end of the specified time horizon. Based on adviser input from Canadian physicians treating HoFH patients, it is assumed there are 27 patients currently identified with HoFH in CDR-participating provinces. It was assumed that 40% of these 27 patients have drug coverage from public plans (n = 11 publicly covered patients).

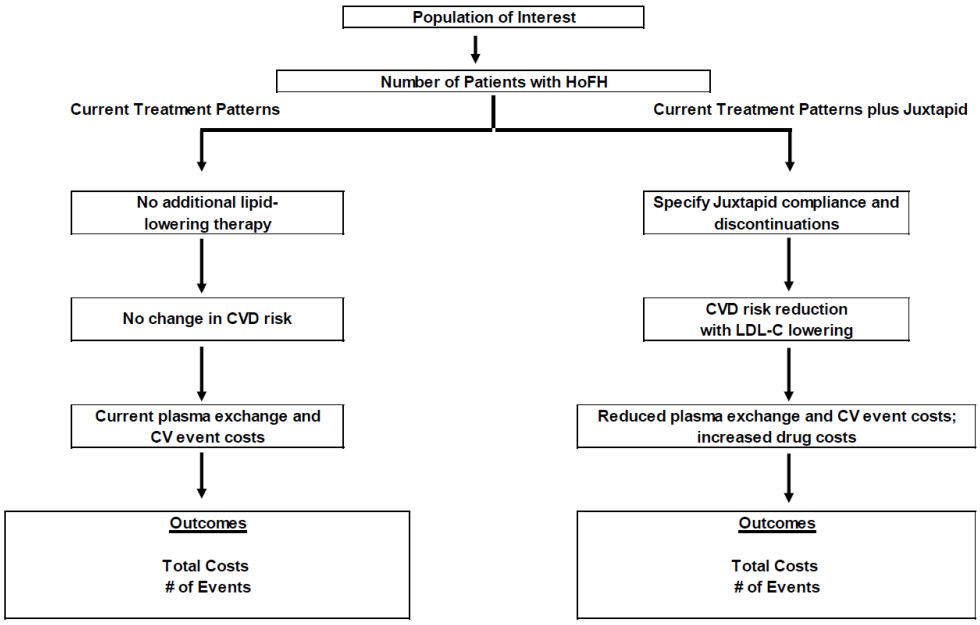
In the base case, and based on input from Canadian advisers treating HoFH patients, it was assumed that of the 27 currently identified HoFH patients in Canada, 19 of them are currently on plasma exchange. Therefore 70% (19 of 27) of HoFH patients eligible for treatment with lomitapide are undergoing plasma exchange treatment.

Based on post-hoc analysis of the AEGR733-005 trial, there was no significant difference observed in the degree of LDL-C lowering achieved among patients who received apheresis compared with patients who did not receive apheresis (Cuchel et al. 2013).[5] According to the manufacturer's submission, of the 13 patients who were receiving apheresis and completed the 26-week efficacy phase, 6 patients (46%) stopped apheresis (n = 3) or reduced the frequency of procedures (n = 3) during the subsequent 52-week safety phase, during which changes in lipid-lowering therapy were allowed (Cuchel et al. 2013).[5]

Based on this evidence, it was assumed that 23% of patients treated with lomitapide and on LDL apheresis would discontinue apheresis completely at the beginning of the first year, and 23% of patients would reduce their apheresis frequency to monthly. The residual 54% of apheresis-treated patients (100% – 23% – 23%) are assumed to continue on biweekly apheresis treatment.

The risks of cardiac events and death were calculated from published survival curves for an HoFH population; piecewise linear fits were used to approximate published survival curves for all-cause mortality and MACE in HoFH patients (Raal et al. 2011).[4] Subsequently, the risks of MACE and all-cause mortality as functions of age were determined from the estimated survival curves using statistical methods. The risk of CV-related death was determined by partitioning the survival curve for all-cause mortality into non-CV-related death and CV-related death, assuming that 77% of all deaths were CV-related. The risk of non-fatal MACE was determined by calculating the hazard for first CV events from the MACE survival curve and multiplying by the ratio of the overall hazard for all MACE to the overall hazard for first-event MACE. The hazards for non-CV-related death, CV-related death, and non-fatal MACE were tabulated in the model as a function of age, enabling identification of age-appropriate hazards following specification of the population mean age by the user. The age-appropriate hazards were then adjusted to account for the difference between baseline LDL-C in the HoFH population of Raal et al. (2011) and the user-specified population mean LDL-C (Raal et al. 2011).[4] This adjustment was analogous to the adjustment of risks due to LDL-C reductions with lomitapide treatment. Non-fatal MACE was partitioned into event classes consistent with the breakdown of events described by Raal et al. (2011).[4] For each of these event classes, an appropriate hazard ratio was selected from the Cholesterol Treatment Trialists' Collaboration 2010 meta-analysis for reductions in risk due to LDL-C reductions.[10]

FIGURE 1: SCHEMATIC OVERVIEW OF PHARMACOECONOMIC MODEL FOR LOMITAPIDE IN HOFH



CV = cardiovascular; CVD = cardiovascular disease; HoFH = homozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol.
Source: Manufacturer's Pharmacoeconomic Submission, page 18.[3]

2. Data Sources

TABLE 6: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy	The efficacy of lomitapide on lowering LDL-C levels was drawn from one phase 3 trial, AEGR733-005 (NCT00730236).[3,5,11] Study AEGR733-005 was a single-group, open-label trial with a small number of patients (n = 23) and a duration of 78 weeks that was not adequately powered to compare between lomitapide and placebo.[3,5,11]	Comparative efficacy of lomitapide added on to standard of care versus standard of care alone is unknown.
Natural history and mortality	The risks of CV death and MACE were calculated from survival curves published by Raal et al. 2011.[4]	
Utilities	Not assessed	Appropriate considering the type of analysis used.
Resource use	Expert opinion	
Adverse events	Not assessed	Consideration of elevated transaminases and hepatic fat associated with lomitapide (and associated costs) would have been important.
Costs		
Drug	The cost of lomitapide included in the analysis was $1,040 (list price) per day regardless of the patient's required dose.	
LDL apheresis and plasma exchange	Calculated from the 2007 Ontario Health Technology Assessment of LDL apheresis and inflated to 2014 Canadian dollars (OHTAC 2007),[12] LDL apheresis and plasma exchange, on a biweekly schedule, were estimated to represent an annual cost of $40,000 and $19,335, respectively. This results in a cost per session of $743.65 for plasma exchange and $1,538.46 for LDL apheresis assuming biweekly treatment (26 sessions per year). Manufacturer indicated that no updated inclusive cost for LDL apheresis or plasma exchange is available, and that inflation may not have captured all cost updates since publication of the 2007 report.	Clinical expert indicated appropriateness of biweekly schedule
Event	Cardiac event costs of hospitalization were taken from the Ontario Case Costing Initiative (OCCI) and Canadian Institute for Health Information (CIHI) (CIHI 2014; OCCI, 2014).[13,14] Physician costs were not included; therefore, an additional 10% was added to each event cost to account for physician fees.	

CV = cardiovascular; LDL-C = low-density lipoprotein cholesterol; MACE = major adverse cardiac events.

3. Manufacturer's Key Assumptions

TABLE 7: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
The population of treatment-eligible patients is a fixed cohort over the time horizon of the model.	Likely inappropriate. Since HoFH is a genetic disorder, it is expected that newly diagnosed cases would be added to the cohort population of the model over time.
Lomitapide is used as an add-on therapy and does not replace existing therapies (except for plasma exchange in some cases) even though lomitapide is indicated as an adjunct to other lipid-lowering treatments, including LDL apheresis where available.	Appropriate.
The risks of CV events and death from the Raal et al. publication on HoFH in South Africa[4] apply to the HoFH populations of interest.	Uncertain.
Patients who discontinue lomitapide incur half of the annual treatment costs and achieve a half-year reduction in the risk of CV events (non-fatal and fatal) in the year of discontinuation.	Appropriate.
Treatment efficacy is achieved instantly with respect to reductions in the risk of CV events (non-fatal and fatal).	Uncertain. No long-term data to support this assumption.
Patients treated with lomitapide are assumed to be 88% compliant in year 1 and 100% compliant in subsequent years, with the exception of those who explicitly discontinue treatment.	Appropriate.
All assumptions about reduction of CV events are theoretical and solely for modelling purposes. The effect of lomitapide on CV morbidity and mortality has not been established.	Appropriate.
Dose escalation at the start of lomitapide treatment is not considered explicitly, so first-year treatment costs will be somewhat overestimated.	Irrelevant. The pricing of lomitapide was on a per day basis regardless of the patient's required dose.
Some patients treated with lomitapide may discontinue or reduce the frequency of plasma exchange.	Considered highly unlikely by clinical expert; patients are expected to continue biweekly schedules of LDL apheresis or plasma exchange.
The log of relative risk is linearly related to LDL-C, so the CTTC (2010)[10] risk reductions for MACE per mmol/L reduction in LDL-C can be used in the HoFH population.	Appropriate.
Only acute costs of CV events are considered; no follow-up costs in years subsequent to an event are included.	Uncertain. Addition of follow-up costs may impact the differences in costs between strategies.

CTTC = Cholesterol Treatment Trialists' Collaborators; CV = cardiovascular; HoFH = homozygous familial hypercholesterolemia; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; MACE = major adverse cardiac events.

4. Manufacturer's Results

In the base-case analysis, the manufacturer reported the cumulative costs over the five-year time horizon for a cohort of 11 lomitapide-treated patients at $16,533,156 (annual cost of $300,602 per patient), with an incremental cost of $15,758,844 (annual cost of $286,524 per patient) compared to the cohort of 11 patients not treated with lomitapide with a cumulative cost of $774,313 (annual cost of $14,078 per patient). Active treatment costs dominate the total costs. Results indicate estimated reductions in cardiac events over a five-year time horizon ranging from 45% (CV-related death) to 57% (myocardial infarction) in lomitapide-treated patients compared to patients not treated with lomitapide (Table 8).

TABLE 8: SUMMARY OF RESULTS OF MANUFACTURER'S BASE CASE (FIVE-YEAR TIME HORIZON)

Parameter	Without Lomitapide Treatment	With Lomitapide Treatment	Difference (With – Without)	
Patients (n)	11	11	–	
Total costs				
Lomitapide	–	$15,997,349[a]	$15,997,349	
Plasma exchange	$718,618	$509,405	–$209,213	
Cardiovascular event costs	$55,695	$26,402	–$29,293	
Total costs	**$774,313**	**$16,533,156**	**$15,758,844**	
Total cost per patient (5 years)	**$70,392**	**$1,503,014**	**$1,432,622**	
Annual cost per patient	**$14,078**	**$300,602**	**$286,524**	
Total events				**% change**
MI	0.353	0.151	–0.202	–57%
Coronary procedures	2.177	0.996	–1.181	–54%
Other vascular procedures	0.257	0.132	–0.125	–49%
Cerebrovascular events	0.064	0.033	–0.031	–49%
CV-related deaths	0.565	0.308	–0.257	–45%

CV = cardiovascular disease; MI = myocardial infarction.
[a] 21% treatment discontinuation rate in year 1, and no discontinuation in subsequent years; 88% compliance rate in year 1 and 100% compliance in subsequent years.
Source: Adapted from Manufacturer's Submission, Pharmacoeconomic Evaluation, page 25.[3]

Summary of Manufacturer's Sensitivity Analyses

The manufacturer conducted univariate sensitivity analyses on several parameters or parameter groups by using alternative values over ranges. The results reported by the manufacturer indicate that the proportion of patients included in the model and time horizon had the greatest impact on incremental costs, with incremental costs ranging from $3 million to $40 million (Table 9). Inputs pertaining to LDL-C baseline levels and reductions, as well as baseline hazards and discontinuation rates, had the greatest impact on per cent change in MACE, with per cent change ranging from 21% to 40%, and 65% to 75%, respectively. Model results were minimally impacted by other sensitivity analyses performed.

TABLE 9: UNIVARIATE SENSITIVITY ANALYSES (FIVE-YEAR TIME HORIZON)

Analysis (No. of Patients = 11)			Incremental Cost
Base case			$15,758,844
Epidemiology and market uptake	Proportion of publicly insured patients	**10%**	**$3,939,711**
		100%	**$39,397,109**
	Age (years)	18	$15,836,610
		55	$14,618,641
	Baseline LDL-C (mg/dl)	220	$15,805,638
		750	$15,153,069
Hazard	Death and MACE hazards	+15%	$15,604,431
		–15%	$15,830,450
Clinical	LDL-C reduction	31%	$15,735,220
		57%	$15,777,421
	First-year discontinuation rates	**0%**	**$19,432,089**
		50%	**$10,686,267**
	Baseline plasma exchange rate	0%	$15,968,056
		100%	$15,670,754
	Plasma exchange discontinuation	0%	$15,897,942
		100%	$15,370,083
	Plasma exchange reduction	0%	$15,833,743
		100%	$15,648,279
	Standard plasma exchange frequency 52/year (reduced to 26/year)		$15,530,331
Cost and resource use	CV event costs (collective)	0$	$15,788,137
		2 × base case	$15,720,177
	Plasma exchange cost	0$	$15,968,056
		2 × base case	$15,549,631
Time horizon		**1 year**	**$3,222,040**
		10 years	**$30,152,955**
Comparator cost	LDL apheresis		$15,535,240

CV = cardiovascular; LDL-C = low-density lipoprotein cholesterol; MACE = major adverse cardiac events.
Source: Adapted from Manufacturer's Submission, Pharmacoeconomic Evaluation, page 25.[3]

5. CADTH Common Drug Review Reanalysis

The manufacturer's CCA was based on several assumptions: number of HoFH patients, proportion of HoFH patients with drug coverage from public plans, outcomes for plasma exchange and LDL apheresis being equivalent, and reduction of plasma exchange frequency and discontinuation after lomitapide treatment. The manufacturer addressed the impact of varying the aforementioned parameters in one-way sensitivity analyses. CDR conducted a multi-way sensitivity analysis that assumed the following:

- All 27 HoFH patients in Canada would be provided drug coverage by public plans.
- HoFH patients treated with lomitapide would continue using plasma exchange at biweekly sessions.

The results of the CDR reanalysis are aligned with the manufacturer's results that show the impact of treatment costs with lomitapide on the total costs in HoFH patients (Table 10).

Finally, although the submitted economic evaluation was a cost-consequence analysis, the availability of incremental costs and incremental changes in MACE rates between lomitapide with standard of care and standard of care alone resulted in exploratory cost-effectiveness analyses by CDR for each reported MACE. The cost-effectiveness analyses were based on the results of the CDR reanalysis in terms of cost (i.e., for 27 patients). The output of the cost-effectiveness analyses was expressed as the incremental cost per event avoided ratio for each MACE (Table 10). The resulting ratios ranged from $13.5 million to close to $512 million.

TABLE 10: SUMMARY OF RESULTS OF CDR MULTI-WAY SENSITIVITY ANALYSIS

Parameter	Without Lomitapide Treatment	With Lomitapide Treatment	Difference (With – Without)		ICER[a] ($/Event Avoided)
Patients (n)	27	27	–		
Total costs					
Lomitapide	–	$39,993,373	$39,993,373		
Plasma exchange	$1,796,545	$1,808,505	11,960		
Cardiovascular event costs	$139,237	$66,005	–$73,232		
Total costs	**$1,935,782**	**$41,867,883**	**$39,932,101**		
Total cost per patient (5 years)	**$71,696**	**$1,550,662**	**$1,478,967**		
Annual cost per patient	**$14,339**	**$310,132**	**$295,793**		
Total events				**% change**	
MI	0.883	0.377	–0.506	–57%	$78,917,196
Coronary procedures	5.442	2.489	–2.953	–54%	$13,522,554
Other vascular procedures	0.643	0.331	–0.312	–49%	$127,987,503
Cerebrovascular events	0.161	0.083	–0.078	–49%	$511,950,013
CV-related deaths	1.411	0.769	–0.642	–45%	$62,199,534

CDR = CADTH Common Drug Review; CV = cardiovascular disease; ICER = incremental cost-effectiveness ratio; MI = myocardial infarction.

[a] ICER results calculated by CDR by dividing the difference in total costs ($39,932,101) by the respective difference in total events (e.g., for MI, 0.506).

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