Common Drug Review
Pharmacoeconomic Review Report

October 2016

Drug	lumacaftor/ivacaftor (Orkambi)
Indication	For the treatment of cystic fibrosis in patients age 12 years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator gene
Listing request	As per indication
Dosage form(s)	lumacaftor 200 mg/ivacaftor 125 mg tablets
NOC date	January 26, 2016
Manufacturer	Vertex Pharmaceuticals (Canada) Incorporated

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 *cystic fibrosis* 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The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions.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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TABLE OF CONTENTS

Tables

Figures

ABBREVIATIONS

AE	adverse event
CDR	CADTH Common Drug Review
CF	cystic fibrosis
CUA	cost-utility analysis
EQ-5D	EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire
FDC	fixed-dose combination
ICER	incremental cost-effectiveness ratio
IVA	ivacaftor
LUM	lumacaftor
LUM/IVA	lumacaftor/ivacaftor (Orkambi)
ppFEV$_1$	per cent predicted forced expiratory volume in one second
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
SoC	standard of care

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	LUM/IVA (Orkambi)
Study Question	What is the cost-effectiveness of LUM/IVA + SoC versus SoC alone for the treatment of CF in patients aged 12 years and older who are homozygous for the F508del-CFTR mutation
Type of Economic Evaluation	Cost-utility analysis
Target Population	Patients with CF who are 12 years of age or older and homozygous for the F508del-CFTR mutation. The age, gender, baseline $ppFEV_1$, and weight-for-age z score reflected the patient population in the TRAFFIC and TRANSPORT trials.
Treatment	LUM/IVA + SoC (which could include mucolytics, pancreatic enzymes, anti-inflammatory medications, and antibiotics for lung infections)
Outcome	QALYs
Comparator	SoC (treatment as in the control arm of the TRAFFIC and TRANSPORT trials)
Perspective	Canadian public health care system
Time Horizon	Lifetime horizon — 100 years
Results for Base Case (Provided by Manufacturer)	Incremental cost per QALY gained for LUM/IVA + SoC versus SoC alone: $485,767
Key Limitations and CDR Estimate(s)	• The manufacturer assumed that the benefit of therapy in terms of the improvement in absolute change in baseline in $ppFEV_1$ increased over time. This is a highly biased assumption. Addressing this issue led to an incremental cost per QALY gained of $1,373,109. • The manufacturer assumed reduced compliance with therapy but continued benefit. Addressing this issue led to an incremental cost per QALY gained of $541,019. • The manufacturer assumed that the cost of therapy would be reduced by 82% in 12 years' time. Addressing this issue led to an incremental cost per QALY gained of $667,973. • The manufacturer assumed that the exacerbation rate was affected both by $ppFEV_1$ and treatment choice. This led to potential double-counting of the benefits from treatment. Addressing this issue led to an incremental cost per QALY gained of $585,532. • Addressing all four issues led to an incremental cost per QALY gained of $4,773,615.

CDR = CADTH Common Drug Review; CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator; LUM/IVA = lumacaftor and ivacaftor; $ppFEV_1$ = per cent predicted forced expiratory volume in 1 second; QALY = quality-adjusted life-year; SoC = standard of care.

EXECUTIVE SUMMARY

Background

Orkambi is a fixed-dose combination (FDC) tablet containing 200 mg lumacaftor and 125 mg ivacaftor (LUM/IVA).[1] It is indicated for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.[2] This is most common CF-causing mutation worldwide and approximately half of all Canadian patients with CF are homozygous for the F508del mutation.[1] LUM/IVA is the first treatment specifically indicated for the treatment of patients who are homozygous for the F508del mutation in the CFTR gene. The manufacturer has requested that LUM/IVA be listed in accordance with the Health Canada–approved indication.[1]

The recommended dose is LUM 400 mg every 12 hours/IVA 250 mg every 12 hours.[2] This represents the higher of the dosages considered in both the TRANSPORT and TRAFFIC trials.[3,4] At the current marketed price of $170.54 per tablet, the daily cost of treatment per patient with LUM/IVA is $682 or $248,988 annually.[1]

The manufacturer submitted a cost-utility analysis to assess the cost-effectiveness of LUM/IVA + standard of care versus standard of care (SoC) alone in patients with CF who are 12 years of age or older and homozygous for the F508del-CFTR mutation.[5] The analysis is based on an individual patient simulation model estimating long-term health care costs and quality-adjusted life-years (QALYs) over a lifetime horizon (100 years), from the perspective of the Canadian public health care payer. In the manufacturer's submission, six replications for 1,000 patients were performed. During each cycle, the model updates a patient's age and per cent predicted forced expiratory volume in one second ($ppFEV_1$), leading to an estimate of cycle-specific mortality.

The manufacturer reported that LUM/IVA + SoC was associated with greater QALYs and higher costs than SoC alone, with an estimated incremental cost per QALY gained of $485,767.

Summary of Identified Limitations and Key Results

A number of limitations were identified with the model submitted by the manufacturer.

The model simulates 1,000 individual patient profiles with six replications per profile. This approach allows some degree of consideration of the heterogeneity in patient profile, but limited consideration of heterogeneity in treatment response. This approach makes it difficult to verify the calculations within the model as the results are obtained directly from a macro and it is not possible to ascertain whether the sampling of the individual patients and their response is correct. Thus, the CADTH Common Drug Review (CDR) adopted an alternative approach of replacing the 1,000 patient profiles with one patient profile, which represents a typical (average) patient from across the patient profiles of the TRANSPORT and TRAFFIC studies, and obtaining 1,000 replications. Using this approach replicated the manufacturer's results of an incremental cost per QALY gained of $474,264, but allowed for a fuller consideration of the validity of the calculations within the model and facilitated further analyses.

Assumptions regarding the continued treatment effect appeared biased. The manufacturer assumed, based on the TRANSPORT and TRAFFIC studies, that LUM/IVA + SoC led to an improvement in $ppFEV_1$ compared with SoC alone; however, the manufacturer also assumed that over time, $ppFEV_1$ would decline at a lower annual rate for LUM/IVA + SoC than SoC. This assumption appears to be unsupported.

The model was revised to include a more appropriate assumption that the improvement in ppFEV1 would be maintained long-term, but that the rate of decline would be the same. This could still be considered biased in favour of LUM/IVA + SoC, as it assumes no waning of treatment effect. Analysis based on this revision leads to an estimated incremental cost per QALY gained of $1,373,109.

Analysis assumed that the compliance with LUM/IVA + SoC will be 88%. However, this is applied only to the drug costs of therapy and not to the treatment effects. Given the bias in assuming only a decrease in associated costs without any decrease in effectiveness, an alternative assumption whereby compliance was set at 100% was adopted. Under this assumption, the incremental cost per QALY gained was $541,019.

Analysis assumed that after 12 years, the cost of LUM/IVA + SoC would be reduced by 82% due to a generic equivalent becoming available. The basis of this assumption is highly questionable and would require at least three generic equivalents entering the market at this time point. To be in compliance with CADTH economic guidelines, the full treatment cost was assumed for the time horizon of the model. Under this assumption, the incremental cost per QALY gained was $667,973.

Analysis assumed that there was relationship between $ppFEV_1$ and the rate of exacerbations. Given that LUM/IVA + SoC was associated with an improvement in $ppFEV_1$, this would lead to lower exacerbations with LUM/IVA + SoC. However, the model also incorporated an assumption of a rate ratio of 0.44 with LUM/IVA + SoC. This would lead to double-counting the potential benefit from LUM/IVA + SoC. Reanalysis involved excluding the rate ratio (making it equal to 1) but allowing a long-term benefit from LUM/IVA + SoC in reducing exacerbation rates through the relationship with $ppFEV_1$. This analysis led to an incremental cost per QALY gained of $585,532.

Based on the limitations cited above, a revised CDR best estimate was obtained by using the revised assumptions relating to effectiveness, compliance, and drug costs. In this analysis, LUM/IVA + SoC was found to be more effective and more costly with an incremental cost per QALY gained of $4,773,615.

Based on the manufacturer's base case and on the revised CDR best estimate, reanalysis was conducted assuming alternate prices for LUM/IVA + SoC. Assuming an 86.5% price reduction, the manufacturer's base case suggested an incremental cost per QALY gained of approximately $50,000. However, the CDR reanalysis found that a 90% price reduction resulted in an incremental cost per QALY gained of $444,486.

Conclusions

The manufacturer's analysis suggested that LUM/IVA + SoC is both more effective in terms of QALYs and more costly than SoC with an incremental cost per QALY gained of $485,767. Several limitations favouring LUM/IVA + SoC were identified by CDR. Testing these limitations led to a CDR best estimate incremental cost per QALY of $4,773,615, which was largely driven by assumptions regarding the treatment effect with LUM/IVA. Using this more appropriate analysis, a 90% price reduction of LUM/IVA + SoC would lead to incremental cost per QALY of $444,486. A price reduction closer to 98.2% is required for the incremental cost per QALY gained to be close to a $50,000 valuation.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer's submission involves a cost-utility analysis (CUA) using a patient-level simulation model comparing lumacaftor and ivacaftor (LUM/IVA) plus standard of care (SoC) versus SoC alone.[5] The model incorporates the pooled individual patient data from the TRAFFIC and TRANSPORT clinical trials relating to baseline age, sex, per cent predicted forced expiratory volume in one second ($ppFEV_1$), and weight-for-age z score.[3,4] In the manufacturer's base analysis, these are sampled from 1,000 times and for each sample, six estimates of costs and outcomes are obtained from sampling form the related probability distributions replications. The same patients are sampled for both treatment comparators.

Model cycles are four weeks for the first two years and annual thereafter, for a lifetime horizon (100 years). In each cycle, the patient is at risk of death based on a published survival analysis adjusted to reflect the individual patient's characteristics.

During each cycle, the patient is at risk of various clinical events with associated costs, mortality, and utility values. Utility values were derived from the EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire (EQ-5D) completed within the TRAFFIC and TRANSPORT studies and are calculated based on $ppFEV_1$ and occurrence of exacerbations. Costs adjusted to 2015 included the cost of LUM/IVA + SoC, the annual cost of managing a patient with CF adjusted for $ppFEV_1$, the cost of exacerbations, the cost of adverse events, and the costs associated with lung transplantation.

2. MANUFACTURER'S BASE CASE

The manufacturer's analysis estimated, over a lifetime horizon, a quality-adjusted life-year (QALY) gain with LUM/IVA + SoC versus SoC of 3.54 with incremental costs of $1,718,342. This leads to an estimated incremental cost per QALY gained of $485,767.

TABLE 2: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE

	LUM/IVA + SoC	SoC	LUM/IVA + SoC vs. SoC
Costs (2015$)			
Treatment costs	$ 1,800,132	$ 0	$ 1,800,132
Direct medical costs	$ 151,221	$ 233,012	$ –81,790
Total costs	$ 1,951,354	$ 233,012	$ 1,718,342
Effectiveness			
QALYs	11.33	7.79	3.54
Incremental cost per QALY gained			$ 485,767

LUM/IVA = lumacaftor and ivacaftor; QALY = quality-adjusted life-year; SoC = standard of care.
Source: Manufacturer's Pharmacoeconomic submission.[5]

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

A range of sensitivity analyses were included. Univariate sensitivity analyses were conducted whereby each input parameter was varied ± 20%. No variable was associated with reducing the incremental cost per QALY gained below $400,000.

Further analysis explored the impact of assumptions relating to change in $ppFEV_1$ with LUM/IVA + SoC, annual decline in $ppFEV_1$ with LUM/IVA + SoC and SoC, exacerbation rate ratio with LUM/IVA + SoC, lung transplantation, compliance, discontinuation, time horizon, discount rate, reduction in LUM/IVA + SoC cost, long-term costs, and health utility values. In all of these subsequent analyses, the incremental cost per QALY gained with LUM/IVA + SoC was at least $350,000; except for the analysis with a zero discount rate with a ratio of $212,811.

The manufacturer's probabilistic sensitivity analysis found the probability that LUM/IVA + SoC was cost-effective was 0%, assuming a willingness to pay for a QALY threshold of $300,000 or lower.

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

Modelling framework: The manufacturer's submission incorporated a complex modelling framework with the base analysis based on simulating a patient population of 1,000. For each patient profile, the long-term outcomes were estimated six times by taking random draws relating to the parameters within the model. Thus, 6,000 replications were required for each analysis. This takes approximately 21 minutes to run. This approach has two limitations. The computational complexity leads to difficulty with respect to running the analysis repeatedly and discerning which factors are affecting the results. Secondly, it precludes the ability of the reviewer to assess the validity of the model, as results are generated by a macro without any ability to verify the chosen values for parameters reflecting their underlying uncertainty and expected values.

Given that economic evaluation should be conducted in a homogenous patient population and heterogeneity should be assessed appropriately through stratified analysis, a reanalysis was conducted whereby a single patient profile was adopted, reflecting the expected values of parameters within the TRAFFIC and TRANSPORT studies.

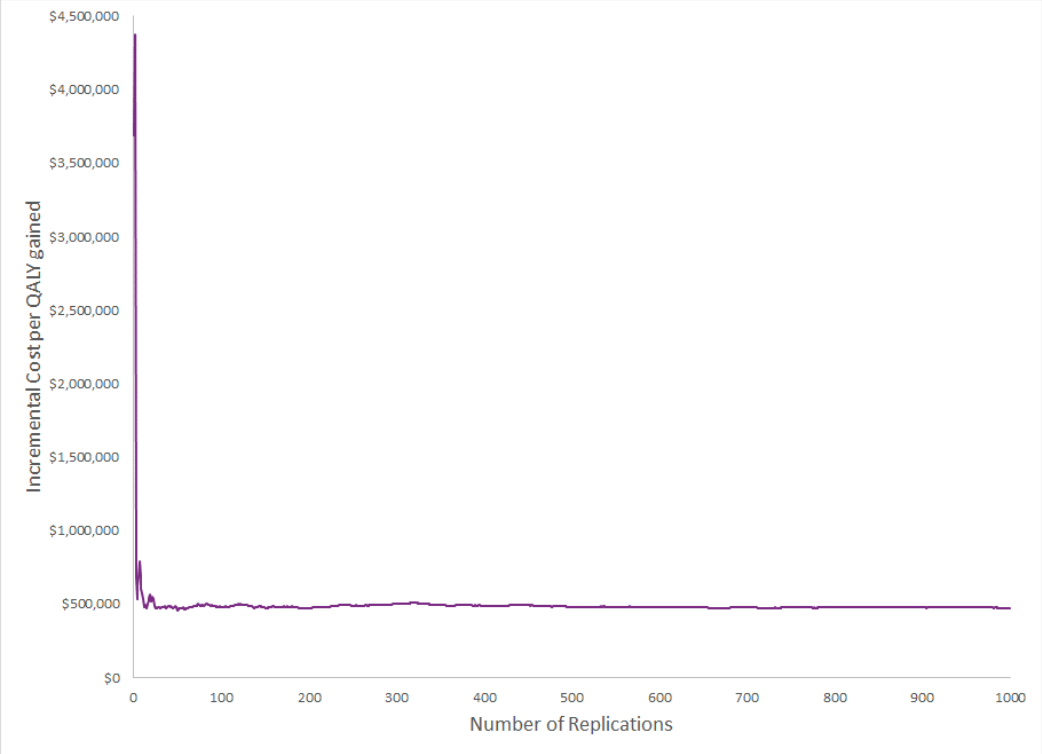
TABLE 3: REPRESENTATIVE PATIENT PROFILE ADOPTED IN CADTH COMMON DRUG REVIEW REANALYSIS

Age (Years)	$ppFEV_1$ (%)	Sex (Male = 0, Female = 1)	Weight-for-Age z Score	BMI	*Pseudomonas aeruginosa* infection	Pancreatic Sufficiency (Yes = 1, 0 = No)	Annual Acute Exacerbations
25.5	60	0	-0.405	21.2	1	0	0

BMI = body mass index; $ppFEV_1$ = per cent predicted forced expiratory volume in one second.

For this analysis, 1,000 replications were obtained for this patient profile. This appears reasonable, given the result in Figure 1, which highlights convergence, but at the same time, suggests the six replications for each of the 100 participants in the manufacturer's model may not be sufficient.

FIGURE 1: IMPACT OF NUMBER OF REPLICATIONS ON INCREMENTAL COST-EFFECTIVENESS RATIO



QALY = quality-adjusted life-year.

The model still does not provide sufficient transparency to determine whether the results are truly reflective of the underlying expected values and uncertainty of the input parameters.

Effectiveness: The manufacturer's submission makes the assumption that after the initial period represented by the clinical trial, $ppFEV_1$ will decline. This appears reasonable, but the manufacturer assumes a differential rate of decline favouring LUM/IVA + SoC. This is not based on any long-term evidence; rather, short-term data from two distinct observational studies. A more acceptable assumption, which would still favour LUM/IVA + SoC — in that it advocates a continuous treatment effect rather than any potential treatment waning — would be to assume the same percentage decline.

Drug Compliance: The manufacturer assumed that compliance with therapy would be 88% and adjusted costs accordingly. No such adjustment was made for treatment effectiveness. Given the likely bias of such an assumption, an alternative assumption of 100% compliance would be more reasonable.

Drug Costs: The manufacturer assumed that the cost of LUM/IVA + SoC would be reduced by 82% after 12 years because generic equivalents would be available. No justification for this assumption is provided, and this is counter to CADTH guidance. Full costs for LUM/IVA + SoC for the time horizon of the model should be included.

Exacerbation rates: The manufacturer assumed that exacerbation rates are a function of $ppFEV_1$. This appears reasonable. However, the manufacturer assumed a differential rate of exacerbation with LUM/IVA + SoC even with the effect of $ppFEV_1$. This is obvious double-counting and to allow for a more

reasonable assumption regarding the impact of LUM/IVA + SoC on exacerbations; the effect of $ppFEV_1$ on exacerbations was included, but with no additional relative reduction.

5. CADTH COMMON DRUG REVIEW REANALYSES

CADTH Common Drug Review Reanalyses

Single Patient Profile

To address the limitation with respect to the model design and to somewhat address transparency, analysis based on a single patient profile with 1,000 replications was conducted. With this analysis, results closely approximated the manufacturer's base analysis (thus justifying the approach taken by CDR), with an incremental cost per QALY gained of $474,264 compared with $485,767.

TABLE 4: CADTH COMMON DRUG REVIEW REANALYSIS USING SINGLE PATIENT PROFILE

	LUM/IVA + SoC	SoC	LUM/IVA + SoC vs. SoC
Costs (2015$)			
Treatment costs	$ 1,828,786	$ 0	$ 1,828,786
Direct medical costs	$ 149,001	$ 206,063	$ –57,061
Total costs	$ 1,977,787	$ 206,063	$ 1,771,525
Effectiveness			
QALYs	10.87	7.13	3.74
Incremental cost per QALY gained			$ 474,264

LUM/IVA = lumacaftor and ivacaftor; QALY = quality-adjusted life-year; SoC = standard of care; vs. = versus.

Treatment Effectiveness

CDR reanalysis adopted revised assumptions relating to the decline in $ppFEV_1$ over time. Using the same rate of decline with both LUM/IVA + SoC and SoC led to an incremental cost per QALY gained of $1,373,109 due primarily to a significant reduction in the forecasted QALY gain with LUM/IVA + SoC of – 1.16 versus 3.74.

TABLE 5: CADTH COMMON DRUG REVIEW REANALYSIS ASSUMING CONSTANT LONG-TERM EFFECT

	LUM/IVA + SoC	SoC	LUM/IVA + SoC vs. SoC
Costs (2015$)			
Treatment costs	$ 1,656,605	$ 0	$ 2,552,433
Direct medical costs	$ 146,636	$ 206,063	$ –59,427
Total costs	$ 1,803,241	$ 206,063	$ 1,597,178
Effectiveness			
QALYs	8.30	7.13	1.16
Incremental cost per QALY gained			$ 1,373,109

LUM/IVA = lumacaftor and ivacaftor; QALY = quality-adjusted life-year; SoC = standard of care; vs. = versus.

Exacerbations

CDR reanalysis included the relationship between $ppFEV_1$ and exacerbations but excluded the double-counting incorporated by also including a rate ratio. Under this assumption, the incremental cost per QALY gained was $585,532 due primarily to a reduction in QALY gains from 3.74 to 3.05.

TABLE 6: CADTH COMMON DRUG REVIEW REANALYSIS AVOIDING DOUBLE-COUNTING OF POTENTIAL BENEFIT RELATING TO EXACERBATIONS

	LUM/IVA + SoC	SoC	LUM/IVA + SoC vs. SoC
Costs (2015$)			
Treatment costs	$ 1,790,576	$ 0	$ 1,790,576
Direct medical costs	$ 203,479	$ 206,063	$ –2,584
Total costs	$ 1,994,054	$ 206,063	$ 1,787,992
Effectiveness			
QALYs	10.19	7.13	3.05
Incremental cost per QALY gained			$ 585,532

LUM/IVA = lumacaftor and ivacaftor; QALY = quality-adjusted life-year; SoC = standard of care; vs. = versus.

Drug Price

CDR reanalysis assumed the brand price for LUM/IVA + SoC for the time horizon of the model. Under this assumption, the incremental cost per QALY gained was $667,973, due primarily to an increase in costs associated with LUM/IVA + SoC.

TABLE 7: CADTH COMMON DRUG REVIEW REANALYSIS EMPLOYING BRANDED DRUG PRICE

	LUM/IVA + SoC	SoC	LUM/IVA + SoC vs. SoC
Costs (2015$)			
Treatment costs	$ 2,552,433	$ 0	$ 2,552,433
Direct medical costs	$ 149,001	$ 206,063	$ –57,061
Total costs	$ 2,701,434	$ 206,063	$ 2,495,371
Effectiveness			
QALYs	10.87	7.13	3.74
Incremental cost per QALY gained			$ 667,973

LUM/IVA = lumacaftor and ivacaftor; QALY = quality-adjusted life-year; SoC = standard of care; vs. = versus.

Treatment Compliance

CDR reanalysis assumed 100% compliance with LUM/IVA + SoC to avoid the disconnect between compliance and effectiveness. Under this assumption, the incremental cost per QALY gained was $541,109, due primarily to an increase in costs associated with LUM/IVA + SoC.

TABLE 8: CADTH COMMON DRUG REVIEW REANALYSIS ASSUMING 100% COMPLIANCE

	LUM/IVA + SoC	SoC	LUM/IVA + SoC vs. SoC
Costs (2015$)			
Treatment costs	$ 2,078,166	$ 0	$ 2,078,166
Direct medical costs	$ 149,001	$ 206,063	$ –57,061
Total costs	$ 2,227,167	$ 206,063	$ 2,021,105
Effectiveness			
QALYs	10.87	7.13	3.74
Incremental cost per QALY gained			$ 541,019

LUM/IVA = lumacaftor and ivacaftor; QALY = quality-adjusted life-year; SoC = standard of care; vs. = versus.

CADTH Common Drug Review Best Estimate

To address concerns regarding long-term outcomes, exacerbation rates, drug costs, and compliance, the CDR best estimate employed the revised assumptions from each of the above analyses. Under this scenario, the incremental cost per QALY gained was $4,773,615.

TABLE 9: SUMMARY OF RESULTS OF THE CADTH COMMON DRUG REVIEW BEST ESTIMATE

	LUM/IVA + SoC	SoC	LUM/IVA + SoC vs. SoC
Costs (2015$)			
Treatment costs	$ 2,010,589	$ 0	$ 2,010,589
Direct medical costs	$ 190,794	$ 206,063	$ –15,269
Total costs	$ 2,201,383	$ 206,063	$ 1,995,321
Effectiveness			
QALYs	7.55	7.13	0.42
Incremental cost per QALY gained			$ 4,773,615

LUM/IVA = lumacaftor and ivacaftor; QALY = quality-adjusted life-year; SoC = standard of care; vs. = versus.

A probabilistic sensitivity analysis was not possible based on the CDR reanalysis, as the manufacturer's model returned a runtime error.

Price Reduction Scenarios

Reanalysis was conducted assuming alternate prices for LUM/IVA + SoC. Assuming an 86.5% price reduction, the manufacturer's base case suggested an incremental cost per QALY gained of approximately $50,000. The CDR reanalysis found that a 90% price reduction resulted in an incremental cost per QALY gained of $444,486. A reduction in price of 98.2% was associated with an incremental cost per QALY gained of approximately $50,000.

TABLE 10: CADTH COMMON DRUG REVIEW REANALYSIS PRICE REDUCTION SCENARIOS

ICERs of Submitted Drug Versus Comparator		
Price	**Base-case analysis submitted by manufacturer**	**CDR best estimate**
Submitted	$485,767	$4,773,615
10% reduction	$434,878	$4,292,601
20% reduction	$383,989	$3,811,586
30% reduction	$333,100	$3,330,572
40% reduction	$282,211	$2,849,558
50% reduction	$231,323	$2,368,543
60% reduction	$180,434	$1,887,529
70% reduction	$129,545	$1,406,515
80% reduction	$78,656	$925,500
90% reduction	$27,767	$444,486
98.2% reduction	$2,323	$50,054

CDR = CADTH Common Drug Review; ICER = incremental cost-effectiveness ratio.

6. ISSUES FOR CONSIDERATION

The lack of transparency within the model made it difficult to validate the analysis provided by the manufacturer.

7. PATIENT INPUT

Patient input was received from the Cystic Fibrosis Canada (CF Canada). In its feedback, CF Canada noted that managing CF requires regular visits to specialized CF clinics, CF treatments, treatment of CF-related infections, and hospitalizations. These aspects affect the quality of life of patients and their ability to participate in activities of daily living, including spending time with family and friends, pursuing educational goals, maintaining employment, or travelling. Caregiver burden was also noted as a significant issue.

The manufacturer attempted to capture the impact of treatment on health care resources and patient aspects in its model. Caregiver burden was not captured as part of the manufacturer's economic evaluation.

8. CONCLUSIONS

The manufacturer's analysis suggested that LUM/IVA + SoC is both more effective in terms of QALYs and more costly than SoC with an incremental cost per QALY gained of $485,767. However, multiple limitations favouring LUM/IVA + SoC were identified by CDR, which relate to continually improving treatment effect, drug compliance, and costs and effect on exacerbation rates.

Addressing these limitations led to a CDR best estimate incremental cost per QALY of $4,773,615. Using this scenario, a 98.2% price reduction for LUM/IVA + SoC is needed for an incremental cost per QALY approaching $50,000.

APPENDIX 1: COST COMPARISON

The comparators presented in Table 11 have been deemed appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified.

TABLE 11: COST COMPARISON TABLE FOR DRUGS USED FOR CYSTIC FIBROSIS

Drug/ Comparator	Strength	Dosage Form	Unit Cost ($)	Recommended Treatment Regimen	Average Daily Cost ($)	Average Annual Cost ($)
Lumacaftor/ ivacaftor (Orkambi)	**200 mg/125 mg**	**Tab**	**170.5357**[a]	**400 mg/250 mg every 12 hours**	**$682.14**	**248,982**
Treatments indicated for the management of cystic fibrosis patients						
Aztreonam (Cayston)	75 mg/vial	Inhaled solution	48.1600	Alternating 75 mg 3 times daily for 28 days, followed by 28 days off	144.48[b]	26,367[b]
Dornase alfa (Pulmozyme)	1 mg/mL (2.5 mL)	Inhaled solution	39.3900	2.5 mg once or twice daily	39.39 to 78.78	14,377 to 28,755
Ivacaftor (Kalydeco)	150 mg	Tab	420.0000	150 mg twice daily	840.00	306,600
Tobramycin (generic)	300 mg/ 5 mL (60 mg/mL)	Inhaled solution (single-dose ampoule)	41.0800	Alternating 300 mg twice daily for 28 days, followed by 28 days off	82.16[b]	14,994[b]
Tobramycin (TOBI Podhaler)	28 mg	Inhalation capsule	13.4500	4 capsules (112 mg) twice daily for 28 days, followed by 28 days off	107.60[b]	19,637[b]
Treatments used for the management of cystic fibrosis patients — not indicated						
Colistimethate sodium	150 mg vial	IV	33.7397[c]	75 mg twice daily	33.74	12,315
Tobramycin (generic)	40 mg/mL	IV	2.7250[c]	300 mg inhaled twice daily for 28 days, followed by 28 days off	40.88[b]	7,460[b]

IV = intravenous; tab = tablet.
[a] Manufacturer's submitted and current market price.
[b] Daily cost is for days of use; annual cost includes off days.
[c] Alberta Blue Cross Formulary (April 2016).[6]
Source: Saskatchewan Drug Benefit Formulary (April 2016), unless otherwise indicated. Administration costs are not included.[7]

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 12: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS LUMACAFTOR AND IVACAFTOR RELATIVE TO THE SOC?

Adalimumab Vs. SoC	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	Manufacturer $485,767 per QALY CDR $4,773,615 per QALY					

CDR = CADTH Common Drug Review; CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year; SoC = standard of care.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 13: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?			X
Comments *Reviewer to provide comments if checking "no"*	The model is complex and is coded to such an extent to make it difficult to follow without some time commitment. The use of macros to generate individual patient simulations lacks transparency and makes it difficult to validate the results.		
Was the material included (content) sufficient?		X	
Comments *Reviewer to provide comments if checking "poor"*	None		
Was the submission well organized and was information easy to locate?	X		
Comments *Reviewer to provide comments if checking "poor"*	None		

TABLE 14: AUTHORS' INFORMATION

Authors of the Pharmacoeconomic Evaluation Submitted to the CADTH Common Drug Review			
☐ Adaptation of global model/Canadian model done by the manufacturer ☒ Adaptation of global model/Canadian model done by a private consultant contracted by the manufacturer ☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the manufacturer ☐ Other (please specify)			
	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 LUMACAFTOR/IVACAFTOR

Agency	**NICE (March 2016)**[8]
Treatment	LUM 200 mg/IVA 125 mg: 2 tablets every 12 hours
Price	£8,000 per 112-tablet pack (excluding VAT; company's evidence submission) Cost of 1-year course is £104,000 (excluding VAT).
Similarities to CDR submission	Mfr appears to have submitted the same general model structure: individual patient-level simulation comparing LUM/IVA + SoC vs. SoC in people 12 years and older with CF who are homozygous for the F508del mutation. Baseline characteristics were taken from the TRAFFIC and TRANSPORT studies, and 6 replications of 1,000 were simulated. Model cycle was the same: 4 weekly for the first 2 years. Both models were run over a lifetime time horizon; the actual length differed slightly, based on country-specific information used. A multivariate MMRM regression analysis was used to model the relationship between EQ-5D utility values, lung function, and pulmonary exacerbations reported in TRAFFIC and TRANSPORT; utility for patients varied over the time horizon.
Differences from CDR submission	Submission to CDR used data from a Canadian CF Registry data (2000 to 2012); data for NICE submission based on UK CF Registry (2013). Costs of managing CF based on retrospective 24-month study in UK, while data for CDR based on Canadian chart review. Other health system and drug costs based on country-specific sources. Utility values for lung transplant derived from a weighted average from Whiting et al. (2014), while for CDR, time-dependent utility values were sourced from Santana et al. and Singer et al.
Manufacturer's results	Base-case ICER for LUM/IVA + SoC vs. SoC: £218,248 per QALY; PSA: £214,838 per QALY. OWSAs suggested that ICERs were sensitive to rate of $ppFEV_1$ decline for LUM/IVA, discount rate, and cost of managing CF. Subgroup analyses suggest baseline $ppFEV_1$ also affected ICER.
Issues noted by the review group	ERG indicated model appeared to capture important features of CF, but noted it wasn't possible to compare baseline characteristics of trial population with patients in UK CF Registry; thus, unclear whether differences in mean age and $ppFEV_1$ were due to different characteristics between subtypes of CF or differences between trial population and UK CF population. ERG noted that mfr highlighted challenges with registry data, but concluded that difference in populations was an important consideration. Averaging absolute difference in $ppFEV_1$ for 16 and 24 weeks favoured LUM/IVA vs. 24 weeks alone. ERG noted assumption that short-term benefits persisted long-term was based on 48-week data, and use of non-randomized data sets for long-term extrapolations may bias estimates; no long-term data were presented to support benefits of LUM/IVA on pulmonary exacerbations and weight-for-age z scores, leading to uncertainty. Impact of LUM/IVA on pulmonary exacerbations was independent from its effect on $ppFEV_1$, which led to a risk of double-counting. No robust rationale for assumed price reduction after 12 years (i.e., generic availability). CF management costs taken from population that included a different mutation (G551D). Assumption that pre-transplant HRQoL depended on $ppFEV_1$ and pulmonary exacerbations not justified if other treatment-related factors affect HRQoL (e.g., AEs).

Results of reanalyses by the review group (if any)	ERG exploratory analysis with higher adherence rate included annual stopping rate from week 24 onward and mean absolute change in $ppFEV_1$ based on the 24-week data, resulting in ICER of £221,992 per QALY. If no price reduction, ICER increases to £330,385 per QALY. Testing 95% confidence intervals for annual $ppFEV_1$ decline estimated from weeks 4 to 48 for LUM/IVA resulted in ICER ranging from £135,464 to £459,045 per QALY.
Recommendation	LUM/IVA not recommended for treating CF in people 12 years and older who are homozygous for F508del mutation in the CFTR gene. Acute improvements in $ppFEV_1$ with LUM/IVA were modest and unlikely to be clinically significant. ICERs were considerably higher than what is normally considered a cost-effective use of NHS resources.

AE = adverse event; CDR = CADTH Common Drug Review; CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator; EQ-5D = EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire; ERG = Evidence Review Group; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; LUM/IVA = lumacaftor and ivacaftor; mfr = manufacturer; MMRM = mixed-effect model repeated measures; NHS = National Health Service (UK); NICE = National Institute of Health and Care Excellence; OWSA = one-way sensitivity analysis; $ppFEV_1$ = per cent predicted forced expiratory volume in 1 second; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year; SoC = standard of care; UK = United Kingdom; VAT = value-added tax; vs. = versus.

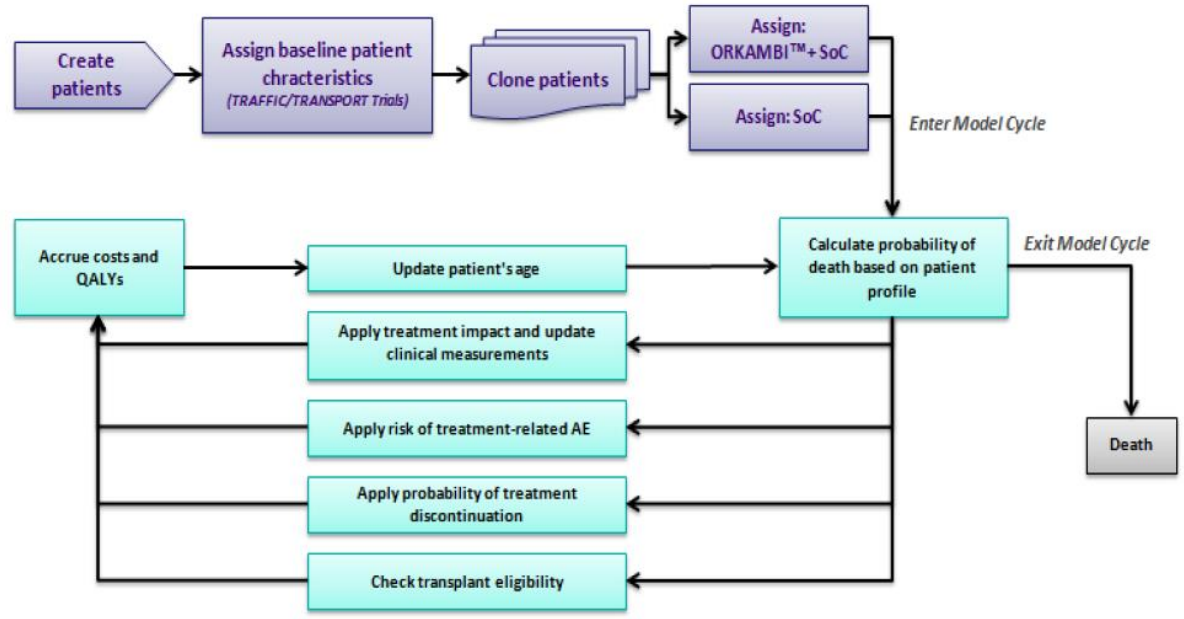
APPENDIX 5: REVIEWER WORKSHEETS

Manufacturer's Model Structure

- Individual patient simulation model (Figure 2)
- 1,000 patients simulated based on TRAFFIC and TRANSPORT patient populations[3,4]
- Estimates based on six replications per patient
- 4 week cycle for first two years — annual thereafter
- In each cycle, patient has risk of death derived from the Stephenson analysis of the Canadian CF cohort adjusted by the Liou predictive model[9,10]
- EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire (EQ-5D) scores based on per cent predicted forced expiratory volume in one second ($ppFEV_1$) and exacerbations
- $ppFEV_1$ is updated each cycle based on treatment-specific estimates from the TRAFFIC and TRANSPORT studies for the first 24 weeks and then assumed differential rates of decline thereafter[3,4]
- Exacerbations assumed a function of both $ppFEV_1$ and an independent treatment effect with lumacaftor and ivacaftor (LUM/IVA)
- Adverse events from treatments come from the TRAFFIC and TRANSPORT studies[3,4]
- Costs include costs of LUM/IVA costs of managing cystic fibrosis (CF), which is assumed a function of $ppFEV_1$, costs of exacerbations, and costs of adverse events.[5,11,12]
- Analysis incorporates the probability of lung transplantation and the associated costs and utilities.

Model Design

FIGURE 2: MODEL SCHEMATIC



Abbreviations: AE=Adverse event; QALY=Quality-adjusted life-year; SoC=Standard of care

Source: Manufacturer's Pharmacoeconomic Submission.[5]

Data Inputs

TABLE 15: DATA SOURCES

Data Input	Description of Data Source	Comment
24-week impact on $ppFEV_1$	TRAFFIC and TRANSPORT studies	Appropriate
$ppFEV_1$ beyond 24 weeks	For LUM/IVA — 24-week extension data from PROGRESS For SoC — cohort studies	Inappropriate — long-term data available for SoC and short-term data only for LUM/IVA. Data are not randomized; therefore, inferences cannot be made
Exacerbation rate as a function of $ppFEV_1$	Analysis of US CF Registry data	Possibly appropriate, although standard errors of coefficients not provided
Incremental effect of LUM/IVA on exacerbations	TRAFFIC and TRANSPORT studies	Appropriate; but inclusion of this and the effect of $ppFEV_1$ on exacerbations involves double-counting of LUM/IVA benefit, so inappropriate
Lung transplantation probabilities. Costs and utilities	Canadian data	Appropriate
Adverse event rates	TRAFFIC and TRANSPORT studies	Appropriate
Discontinuation/compliance	American clinical practice data	Possibly appropriate; however, incorporating the effect of this on costs but not effectiveness is biased
Costs of managing CF	Unpublished chart review for quantities of resource use Various sources for costs of resources	Unpublished data are hard to verify. Most differences based on $ppFEV_1$ are estimated through expert opinion, not chart review. Costs sources appear appropriate, but some are old
Costs of exacerbations	Johnson study from 1999 Mittman study from 2008 in patients with chronic obstructive pulmonary disease Unpublished data Expert opinion	Impact is to assume higher per exacerbation in-patient costs for SoC than LUM/IVA — inappropriate, although negligible impact on results if included — not considered essential to incorporate in review
Costs of adverse events	One general practitioner visit	Possibly biased in favour of LUM/IVA
Utility values for CF	Unpublished regression analysis	Possibly appropriate

CF = cystic fibrosis; LUM/IVA = lumacaftor and ivacaftor; $ppFEV_1$ = per cent predicted forced expiratory volume in 1 second; SoC = standard of care.

TABLE 16: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
Cost of Orkambi will be reduced by 82% after 12 years. Inappropriate, unless manufacturer willing to guarantee a price reduction. Compliance with Orkambi will be 88% with no effect on effectiveness but with reduced costs	Inappropriate — biased to assume reduced costs, but no reduced effectiveness
$ppFEV_1$ will decline at a lower rate long-term for Orkambi than SoC.	Unjustified, given follow-up data are not randomized beyond 24 weeks. Assumption assumes that benefit from Orkambi becomes greater with continued usage. Alternative assumption of treatment effect waning with time is equally plausible

$ppFEV_1$ = per cent predicted forced expiratory volume in 1 second; SoC = standard of care.

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