Common Drug Review
Pharmacoeconomic Review Report

June 2016

Drug	Ivacaftor (Kalydeco)
Indication	Treatment of cystic fibrosis in patients 18 years of age and older with a R117H mutation of the cystic fibrosis transmembrane conductance regulator (CFTR) gene
NOC	March 13, 2015
Dosage Form	Tablet 150 mg
Listing Request	As per indication
Manufacturer	Vertex 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 treating patients with 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The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions.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 CDR Clinical and Pharmacoeconomic Review Reports.

The information in this report is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. The information in this report should not be used as a substitute for the application of clinical judgment with respect to the care of a particular patient or other professional judgment in any decision-making process, nor is it intended to replace professional medical advice. While CADTH has taken care in the preparation of this document to ensure that its contents are accurate, complete, and up-to-date as of the date of publication, CADTH does not make any guarantee to that effect. CADTH is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in the source documentation. CADTH is not responsible for any errors or omissions or injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the information in this document or in any of the source documentation.

This document is intended for use in the context of the Canadian health care system. Other health care systems are different; the issues and information related to the subject matter of this document may be different in other jurisdictions and, if used outside of Canada, it is at the user's risk. This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

CADTH takes sole responsibility for the final form and content of this document, subject to the limitations noted above. The statements and conclusions in this document are those of CADTH and not of its advisory committees and reviewers. The statements, conclusions, and views expressed herein do not necessarily represent the views of Health Canada or any Canadian provincial or territorial government. Production of this document is made possible by financial contributions from Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Ontario, Prince Edward Island, Saskatchewan, and Yukon.

TABLE OF CONTENTS

ABBREVIATIONS

CDEC	Canadian Drug Expert Committee
CDR	CADTH Common Drug Review
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
FEV_1	forced expiratory volume in one second
$ppFEV_1$	per cent predicted forced expiratory volume in one second
QALY	quality-adjusted life-year
SOC	standard of care

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Ivacaftor (Kalydeco) 150 mg tablet
Study Question	To evaluate the cost-effectiveness of ivacaftor as an adjunct to current treatment for patients with CF who are aged 18 years and older and have an R117H mutation
Type of Economic Evaluation	Cost-effectiveness; cost-utility analyses
Target Population	Patients with CF aged 18 years and older who have an R117H mutation in Canada
Treatment	Ivacaftor + standard of care (could consist of, but is not limited to, respiratory, nutritional and rehabilitative support such as mucolytics, osmotic agents, antibiotics, bronchodilatation, pancreatic enzymes, dietetic therapy, and chest physiotherapy).
Outcomes	QALY Life-year
Comparator	SOC alone
Perspective	Public payer perspective
Time Horizon	Lifetime (up to age 80)
Results for Base Case	Ivacaftor + SOC vs. SOC alone: • Incremental cost of $926,776 per QALY gained • Incremental cost of $1.4 million per life-year gained
Key Limitations	CDR identified a number of limitations with the manufacturer's analysis: • Inappropriate assumption relating to enhanced effectiveness of ivacaftor over time • Uncertain utility estimates with likely double-counting • Inappropriate assumptions regarding the price of ivacaftor • Unvalidated assumption that ivacaftor would lead to reductions in other health care costs through improvements in FEV_1. In addition, no probabilistic analysis was conducted nor, given the design of the model, can it be conducted, so the underlying uncertainty regarding the results is unknown.
CDR Estimate	Analysis incorporating all of the above limitations resulted in an incremental cost of $4.6 million per QALY gained.

CDR = CADTH Common Drug Review; CF = cystic fibrosis; FEV_1 = forced expiratory volume in 1 second; QALY = quality-adjusted life-year; SOC = standard of care; vs. = versus.

EXECUTIVE SUMMARY

Background

Ivacaftor has previously been approved by Health Canada for treatment of cystic fibrosis (CF) in patients aged six years and older who have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or G970R. On August 12, 2014, a Notice of Compliance was issued for an expanded indication of the treatment of CF in patients aged 18 years and older who have an R117H mutation in the CFTR gene, which is the basis for the review by the CADTH Common Drug Review (CDR).[1]

Ivacaftor was previously reviewed by CDR in 2013 for CF patients with G551D mutation and in 2014 for patients who have one of the following mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or G970R. The CADTH Canadian Drug Expert Committee (CDEC) recommended in both cases that ivacaftor be listed with conditions, which included a substantial reduction in price.[2,3]

Ivacaftor is available as a 150 mg oral tablet. The Health Canada–recommended dose is 150 mg every 12 hours with fat-containing food. The manufacturer submitted a list price of $420 per tablet ($840 per day), or $306,600 annually.[4]

The manufacturer submitted a cost-utility analysis from a Canadian health care payer's perspective, comparing ivacaftor + standard of care (SOC) (defined as, but not limited to respiratory, nutritional, and rehabilitative support such as mucolytics, osmotic agents, antibiotics, bronchodilatation, pancreatic enzymes, dietetic therapy, and chest physiotherapy) with SOC alone, over the lifetime of a patient with CF (80 years).[5] The analysis is based on a complex model that is a combination of a Markov model and a patient-level simulation. Fifty patient profiles are used based on 50 patients aged 18 or older from the KONDUCT trial.[6] Patient profiles from the trial include age, gender, forced expiratory volume in one second (FEV_1), pancreatic sufficiency and weight-for-age. These are then combined with population data on the age-specific proportion of patients who have diabetes and are *Staphylococcus aureus*–infected or *Burkholderia cenocepacia*–infected. FEV_1 is modelled to change based on treatment and time. These data are then used to predict the exacerbation rates with and without ivacaftor and the proportion of patients who are alive or dead, based on a published survival model.[7] Thus, the model is akin to a two-state Markov model (alive and dead), with results averaged over the 50 distinct patient profiles. Results were reported in terms of the total cost, quality-adjusted life-years (QALYs), and life expectancy. No probabilistic analysis was conducted.

Summary of Identified Limitations and Key Results

Several limitations with the manufacturer's analysis were identified:

The long-term comparative efficacy of ivacaftor versus SOC is uncertain

In the base case, the manufacturer assumed that patients on SOC alone would have a continuous annual decline in lung function. This can be contrasted with the assumptions regarding ivacaftor, in which it was assumed there would be an immediate improvement in FEV_1 and the difference between ivacaftor and SOC would be exacerbated over time due to an assumed reduced annual decline in lung function with ivacaftor. This analysis can be considered highly speculative, given that data on the relative efficacy of ivacaftor were available only up to a 24-week time horizon and assumptions regarding continued benefit were inferred from open-label extension studies in a different patient population. CDR assumed that the

same decline in FEV_1 for ivacaftor and SOC would occur over time, leading to an incremental cost of $1.4 million per QALY gained (from the manufacturer base case of $927,000 per QALY).

Uncertain utility estimates
The manufacturer assumed a relationship between utility values, and FEV_1 and number of exacerbations. This is based on a study that is available only in abstract form and none of the data used as inputs in the model are reported in the abstract. Furthermore, it was assumed that a further utility gain from ivacaftor of [redacted] would be realized based on unpublished data, which will likely lead to double-counting of benefits for ivacaftor. Assuming that the latter is inappropriate, the incremental cost per QALY gained increases to $1.3 million based on CDR reanalyses. In addition, assuming no utility effect from FEV_1 and exacerbations would lead to an incremental cost per QALY gained of $1.6 million.

Inappropriate drug cost estimates
The manufacturer assumed that the cost of ivacaftor would be reduced by 82% after 11.5 years (patent expiry). In addition, it was assumed that a proportion of patients would not adhere to ivacaftor, which reduces the cost of treatment, although no related reduction in efficacy was assumed. It is highly uncertain that a generic alternative will be available following the expiry of the patent for ivacaftor and it is equally uncertain that it would be available at an 82% price reduction. It is not possible to adjust the effectiveness of ivacaftor within the model based on reduced adherence. CDR conducted an analysis in which the drug price and adherence were maintained over the time horizon, resulting in an incremental cost per QALY gained of $1.6 million.

Unvalidated effect of ivacaftor on health care costs
The manufacturer assumed reduced health care costs with ivacaftor based on improvements in FEV_1. However, the methods for deriving this effect from the available studies lacked transparency. Assuming no effect of FEV_1 on cost led to a slight increase in the incremental cost per QALY gained to $939,515.

No probabilistic analysis was conducted, nor, given the design of the model, was it possible to conduct one. As such, the underlying uncertainty regarding the results is unknown.

CDR conducted a further reanalysis assuming all of the following:
- Same decline in FEV_1 with ivacaftor + SOC as for SOC
- No independent utility effect from ivacaftor
- No price reduction after patent expiry and full adherence
- CF costs are not a function of FEV_1.

Based on the above assumptions, ivacaftor had an incremental cost of $4.6 million per QALY gained.

Conclusions
The manufacturer's base-case results suggested that the incremental cost per QALY gained from ivacaftor + SOC compared with SOC alone was $926,776. CDR identified several limitations with the submitted analysis. When considering more appropriate input estimates and assumptions, CDR noted that ivacaftor + SOC had an incremental cost of $4.6 million per QALY gained.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-utility analysis from a Canadian health care payer's perspective. The economic evaluation compared ivacaftor + standard of care (SOC) with SOC alone. SOC was as per the control arm of the KONDUCT trial, where SOC could consist of, but was not limited to, respiratory, nutritional, and rehabilitative support such as mucolytics, osmotic agents, antibiotics, bronchodilatation, pancreatic enzymes, dietetic therapy, and chest physiotherapy over the lifetime of CF patients (80 years).

The analysis is based on a complex model that is a combination of a Markov model and a patient-level simulation. Fifty patient profiles are used based on the 50 relevant patients aged 18 or older from the KONDUCT trial.[6] Patient profiles from the trial include age, gender, FEV_1, pancreatic sufficiency, and weight-for-age. These are then combined with population data on the age-specific proportion of patients who have diabetes and are *Staphylococcus aureus*–infected or *Burkholderia cenocepacia*–infected. These parameters are then simulated over time and are used to predict mortality. A Weibull survival model is used to develop hazard rates for survival based on data from the Canadian registry for patients born after 1990. These are assumed to apply to the typical cystic fibrosis (CF) patient within the registry. To obtain survival rates individualized to the characteristics of the KONDUCT patients, the model uses data from the predictive model, which is based on five-year survival data obtained from the Cystic Fibrosis Foundation Patient Registry data from the United States.[8] This allows estimation of the odds ratio of survival for the individual patients versus the typical patient characteristics based on the parameters mentioned above. The odds ratios are then applied to the underlying survival rates.

Two of the parameters used to predict survival are assumed to change as a result of treatment with ivacaftor, thus leading to improved survival with ivacaftor. With SOC, the decline in per cent predicted forced expiry in one second ($ppFEV_1$) is assumed to be steady at a rate of 0.60% per annum based on a poster presentation that has not been subject to peer review.[9] For ivacaftor there is assumed to be an immediate improvement of 4.9647% in $ppFEV_1$ with treatment.[6] Subsequent to the improvement, the decline in $ppFEV_1$ is assumed to be 29% of the rate for SOC. This is based on an unpublished analysis.[10] Exacerbation rates are assumed to be a function of FEV_1. Thus, there is an assumed indirect relationship between treatment and the number of exacerbations. The relationship between exacerbations and FEV_1 is justified by a reference to a study that does not include any data relating to this.[11] The predictive equation was obtained from a previous health technology assessment, which cited an alternative source for the original data.[12,13]

Costs and QALYs for each individual patient are estimated based on assumptions relating to the relationship with FEV_1. Thus, the model predicts cost, QALYs and survival for each patient both with ivacaftor and without.

The model assumed a relationship between utility values and FEV_1 and number of exacerbations. This is based on a study that is available only in abstract form and none of the data used within the model are available within the abstract.[14] Furthermore, the model assumes a further utility gain from ivacaftor of [redacted] based on unpublished data, which will likely lead to double-counting as the benefit from FEV_1 is likely part of any such gain.

Costs other than ivacaftor were based on two Canadian studies. In a study by Guerriere, costs for 110 CF patients over a four-week period were obtained.[15] The submission takes the estimates of health care system costs and assumes they are outpatient only, inflates these by 3% per annum, annualizes these to obtain a cost per year, and then assumes a relationship between costs and FEV_1. The study specifically did not report a relationship between health care system cost and FEV_1. The data from which this is derived are unclear and the assumptions made lack transparency. Based on the results of a previous study, it is assumed that in-patient costs are one-third of total costs and that therefore total health care costs including in-patient costs can be obtained by simply weighting the costs from Guerriere and assuming the same relationship with FEV_1.[15,16] In the previous study, however, the relationship between costs and FEV_1 was not statistically significant.

The costs for ivacaftor are based on the submitted price ($306,600 per year). After 11.5 years, the price is assumed to drop by 82% and the adherence with ivacaftor is assumed to be only 85%. The reduction in cost due to adherence is double counted for the period after 11.5 years.

2. MANUFACTURER'S BASE CASE

In the base-case analysis, ivacaftor + SOC is more costly than SOC alone ($2.5 million versus $158,571). It is more effective in terms of life-years (13.4 versus 11.7) and QALYs (13.1 versus 10.6). This leads to an incremental cost of $926,776 per QALY gained and $1.4 million per life-year gained.

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

	Total Costs ($)	Incremental Cost of Ivacaftor ($)	Total QALYs	Incremental QALYs of Ivacaftor	Incremental Cost per QALY Gained
SOC alone	$158,571		10.6		
Ivacaftor + SOC	$2,481,034	$2,322,462	13.1	2.5	$926,776

QALY = quality-adjusted life-year; SOC = standard of care.

2.1 Summary of Manufacturer's Sensitivity Analyses

The manufacturer conducted a number of sensitivity analyses relating to adherence, discount rates, FEV_1 improvement, FEV_1 decline, utility effects, and costs. Only one analysis led to an incremental cost per QALY gained of less than $500,000. When a discount rate of 0% was applied, the incremental cost per QALY gained was $376,478.

3. LIMITATIONS OF MANUFACTURER'S SUBMISSION

There were a number of major limitations with the analysis that suggest that the true incremental cost per QALY gained from ivacaftor will be much higher than the manufacturer's estimate.

Estimation of long-term CF survival

The methods of estimating long-term CF survival based on the Canadian registry data are inappropriate. Ordinary least-squares (OLS) regression was used to fit a Weibull model. No other parametric forms were considered; a Weibull model was assumed appropriate because of the results of a previous analysis of a completely different data set.[7] The correct approach would have been to analyze the

individual data using alternate parametric forms and an appropriate parametric survival regression analysis, with the choice of survival function based on appropriate techniques.

The long-term comparative efficacy of ivacaftor versus SOC is uncertain

The manufacturer's base-case analysis assumed that patients on SOC alone would have a continuous annual decline in lung function — a decline in $ppFEV_1$ of 0.6%. This can be contrasted with the assumptions regarding ivacaftor that there would be an immediate improvement in $ppFEV_1$ of 4.965%. However, the model predicted that the difference between ivacaftor and SOC would be exacerbated over time due to an assumed reduced annual decline in lung function with ivacaftor. The decline in $ppFEV_1$ was assumed to be only 29% of the decline with SOC — i.e., a decline of 0.17%. This analysis can be considered highly speculative given that data on the relative efficacy of ivacaftor were available only up to a 24-week time horizon and assumptions around continued benefit were inferred from open-label extension studies in a different patient population.

Uncertain utility effects of ivacaftor

The model assumed a relationship between utility values and FEV_1 and number of exacerbations. This is based on a study that is available only in abstract form and none of the data used within the model are available within the abstract.[14] Furthermore, the model assumes a further utility gain from ivacaftor of [redacted] based on unpublished data from the manufacturer, which will likely lead to double-counting as the benefit from FEV_1 is likely part of any such gain.

Inappropriate drug cost estimates

The manufacturer assumed that the cost of ivacaftor would be reduced by 82% after 11.5 years (patent expiry). In addition, it is assumed that a proportion of patients will not adhere to ivacaftor, which will reduce its cost by a further 85%. This is double counted in the post–patent-expiry period. However, there is no related reduction in efficacy assumed for this lower adherence. It is highly uncertain that a generic alternative will be available following the expiry of the patent and it is equally uncertain that it would be available at an 82% price reduction. Reanalysis was not possible to adjust the effectiveness of ivacaftor with the model based on reduced adherence.

Unvalidated effect of ivacaftor on health care costs

The analysis assumed reduced health care costs with ivacaftor based on improvements in FEV_1. However, the methods for deriving this effect from the available studies lacked transparency. When examining the two articles cited to support this assumption, problems were identified. In the Guerriere study, there was no reported impact of FEV_1 on health system costs.[15] Johnson does report total in-patient costs that could be used within the analysis. However, the study found no significant relationship between FEV_1 and in-patient costs.[16] Costs should have been increased using a consumer price index (CPI), not by using a constant by 3% per annum.

3.1 CADTH Common Drug Review Analyses

The long-term comparative efficacy of ivacaftor versus SOC

CDR reanalysis assumed that the same decline in FEV_1 for ivacaftor and SOC would occur over time, leading to an incremental cost of $1.4 million per QALY gained.

Uncertain utility estimates

CDR assumed no incremental QALY gain over the assumed impact on FEV_1 and exacerbations. This analysis found an incremental cost per QALY gained of $1.3 million. In addition, CDR conducted a further analysis whereby no utility effect from FEV_1 and exacerbations were assumed. This required normalizing

utility values based on baseline characteristics at a utility value of approximately 0.852. This led to an incremental cost per QALY gained of $1.6 million.

Inappropriate drug cost estimates
CDR conducted an analysis in which the drug price and adherence were maintained at the base price and level. The associated incremental cost per QALY gained was $1.6 million.

Unvalidated effect of ivacaftor on health care costs
CDR conducted a reanalysis assuming no effect of FEV_1 on cost. This led to an incremental cost per QALY gained of $939,515.

3.1.1 Combined Reanalysis

A combination of the above was conducted whereby CDR assumed:

- The same decline in FEV_1 for ivacaftor and SOC
- No incremental QALY gain for ivacaftor over the assumed impact on FEV_1 and exacerbations
- The drug price and adherence were maintained at the base price and level
- No effect of FEV_1 on cost.

TABLE 3: SUMMARY OF CADTH COMMON DRUG REVIEW REANALYSIS

CDR Reanalysis	Incremental Costs	Incremental QALYs	Incremental $/QALY
Same decline in FEV_1 for ivacaftor and standard of care	$2,267,696	1.6	$1,447,830
No incremental effect on utility over FEV_1 effect	$2,322,462	1.7	$1,338,757
No effect on utility	$2,322,462	1.4	$1,603,829
Revised drug costs	$4,105,031	2.5	$1,638,107
No effect of FEV_1 on costs	$2,354,386	2.5	$939,515
Combined reanalysis (CDR best estimate)	$3,846,035	0.8	$4,618,844

CDR = CADTH Common Drug Review; FEV_1 = forced expiratory volume in 1 second; QALY = quality-adjusted life-year.

The impact of the price of ivacaftor was examined both for the manufacturer's base case and the CDR multi-way analysis. To achieve a cost per QALY of $100,000, an 89% price reduction would be required using the manufacturer's base case or a 98% reduction when using the CDR reanalysis (Table 13).

3.2 Patient Input

Information was gathered through input from CF patients and their families. Respondents indicated that managing CF is demanding, with regular visits to specialized CF clinics. The treatments, CF-related infections, and hospitalizations take a toll on patients' emotional stamina and have a significant impact on day-to-day quality of life, affecting life decisions including education, career, travel, relationships, and family planning. They often have limited physical abilities and do not have the energy to enjoy time with their families and friends, complete their education, maintain employment, or travel. These aspects were included in the manufacturer's model.

Being a caregiver for a CF patient can have significant emotional, psychological, physical, and financial impacts. Caregivers may feel helpless and devastated watching their loved ones cope with a life-threatening disease. Caregiver burden was not discussed as part of the manufacturer's pharmacoeconomic submission.

Most CF patients take pancreatic enzymes, multivitamins, and nutritional supplements daily to maintain normal growth. Patients perform airway clearance techniques, which include physiotherapy and exercises, at least twice a day for about 30 to 45 minutes per session to improve the clearance of secretions from their lungs. Inhaled medications are used daily to open the airways. These aspects of patient care were included as part of SOC in the trials and in the manufacturer's pharmacoeconomic submission.

4. CONCLUSIONS

The manufacturer's analysis suggested that ivacaftor was more costly and more effective, leading to an incremental cost per QALY gained of $926,766. There were many major limitations with the manufacturer's analysis. Based on CDR's reanalysis, the best estimate of the true incremental cost per QALY gained is $4.6 million. For ivacaftor to be cost-effective, a price reduction of at least 98% would be necessary.

APPENDIX 1: COST COMPARISON

Clinical experts have deemed the comparators presented in Table 4 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 manufacturer list prices, unless otherwise specified.

TABLE 4: 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 ($)
Ivacaftor (Kalydeco)	**150 mg**	**Tablet**	**420.0000[a]**	**150 mg twice daily**	**840.00**	**306,600**
Treatments indicated for the management of cystic fibrosis patients						
Dornase alfa (Pulmozyme)	1 mg/mL (2.5 mL)	Inhaled solution	38.2800	2.5 mg once or twice daily	38.28 to 76.56	13,972 to 27,944
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]
Tobramycin (TOBI)	300 mg/ 5 mL (60 mg/mL)	Inhaled solution (single-dose ampoule)	52.4200	Alternating 300 mg twice daily for 28 days, followed by 28 days off	104.84[b]	19,133[b]
Tobramycin (TOBI Podhaler)	28 mg	Inhalation capsule	13.1038	4 capsules (112 mg) twice daily for 28 days, followed by 28 days off	104.83[b]	19,132[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	40 mg/mL	IV	2.7250[c]	300 mg twice daily for 28 days, followed by 28 days off	40.88[b]	7,460[b]

IV = intravenous.
[a] Manufacturer's submitted and current market price.[5]
[b] Daily cost is for days of use; annual cost includes off days.[5]
[c] Alberta Formulary (June 2015).[17]
Source: Saskatchewan Drug Benefit Formulary (June 2015) unless otherwise indicated. Administration costs are not included.[18]

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 5: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS IVACAFTOR + STANDARD OF CARE RELATIVE TO STANDARD OF CARE?

Ivacaftor + SOC Versus 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	$926,776 per QALY gained (manufacturer's estimate) $4.6 million per QALY gained (CDR estimate)					

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

Results are from the health care system perspective and are presented for both the manufacturer's base analysis and the CADTH Common Drug Review reanalysis.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 6: 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"*	None		
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		

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 — uncertain; no information provided

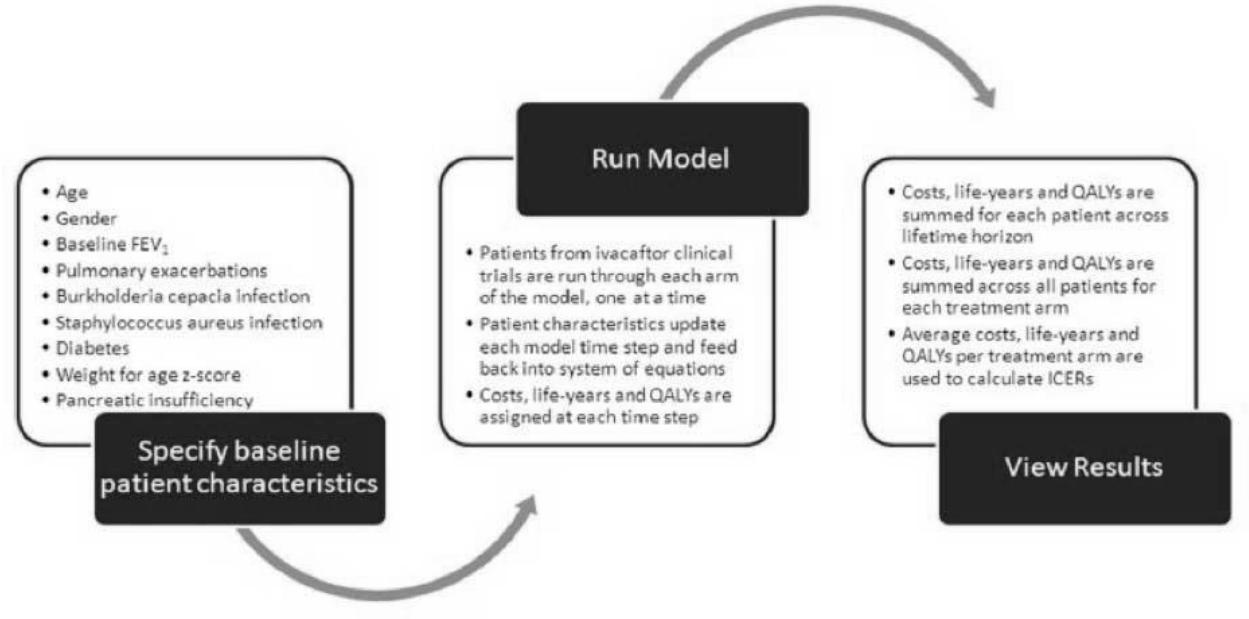
	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document		X	
Authors had independent control over the methods and right to publish analysis		X	

APPENDIX 4: REVIEWER WORKSHEETS

Manufacturer's Model Structure

The analysis is based on a complex model that is a combination of a Markov model and a patient-level simulation.[5] Fifty patient profiles are used based on the 50 relevant patients from the KONDUCT trial.[6] Patient profiles from the trial include age, gender, forced expiratory volume in one second (FEV_1), pancreatic sufficiency, and weight-for-age. These are then combined with population data on the age-specific proportion of patients who have diabetes and are *Staphylococcus aureus*–infected or *Burkholderia cenocepacia*–infected. FEV_1 is modelled to change based on treatment and time. These data are then used to predict the exacerbation rates with and without ivacaftor and the proportion of patients who are alive or dead based on a published survival model.[7]

FIGURE 1: OVERVIEW OF THE ECONOMIC MODEL — SURVIVAL AND COST ESTIMATION



FEV_1 = forced expiratory volume in 1 second; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.
Source: Manufacturer's pharmacoeconomic submission.[5]

Thus, the model is akin to a two-state Markov model (alive and dead), with results averaged over the 50 distinct patient profiles. Results were reported in terms of the total cost, quality-adjusted life-years (QALYs) and life expectancy.

No details of model validation were provided.

TABLE 7: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy	KONDUCT[6]	Biased due to assumed increased benefit over time
Natural history/mortality	Liou 2001[8] Canadian Cystic Fibrosis registry[19]	Inappropriate but unclear if biased
Utilities	Solem 2014;[14] data on file	Inappropriate and biased
Costs		
Drug	Manufacturer	Biased
Health care costs	Johnson 1999,[16] Guerriere 2006[15]	Inappropriate and biased

TABLE 8: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
Utility increment from ivacaftor of [redacted]	Likely involves double-counting due to assumed utility benefit from FEV_1 improvement and impact on exacerbations
Utility values are a function of FEV_1 and number of exacerbations	Basis for this assumption is reference to a conference abstract that does not contain the data for the analysis
Costs are a function of FEV_1	Basis for this assumption is two references, neither of which contain data that seem to be relevant to the analysis
Assumed that a proportion of patients will not adhere to ivacaftor, which will reduce the cost of ivacaftor by 85%	Would need to assume some degree of reduction in efficacy with inadequate adherence. The model does not allow for this; nor did the manufacturer's analysis consider this
Generic version of ivacaftor will be available once the patent expires and at 18% of current cost	Highly uncertain that a generic version of ivacaftor will be available, and especially at this price
The difference between ivacaftor and SOC in FEV_1 would be exacerbated over time due to an assumed reduced annual decline in lung function with ivacaftor	Highly speculative as data on the relative efficacy of ivacaftor were available only up to a 24-week time horizon and assumptions regarding continued benefit were inferred from open-label extension studies in a different patient population

FEV_1 = forced expiratory volume in 1 second; SOC = standard of care.

Manufacturer's Results

Based on the manufacturer's base case, they report an incremental cost per QALY of $927,000 or an incremental cost per life-year of $1.3 million:

TABLE 9: INCREMENTAL COST-EFFECTIVENESS, BASE CASE (DISCOUNTED AT 5%)

Treatment	Total Cost	Total Effect	Incremental Costs	Incremental Effect	ICER
Incremental cost per life-year gained					
SOC	$158,571	11.7	$2,322,462	1.7	$1,366,144
SOC + ivacaftor	$2,481,034	13.4			
Incremental cost per QALY gained					
SOC	$158,571	10.6	$2,322,462	2.5	$926,776
SOC + ivacaftor	$2,329,581	13.1			

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SOC = standard of care.
Note: Figures may not balance due to rounding.
Source: Manufacturer's pharmacoeconomic submission.[5]

TABLE 10: MANUFACTURER'S SENSITIVITY ANALYSIS

Description of Sensitivity Analysis	Incremental Costs	Incremental QALYs	Incremental $ per QALY
Base case	**$2,322,816**	**2.5**	**$926,776**
Reduced dose of ivacaftor	$2,086,510	2.5	$832,619
0% discount rate			$376,478
1.5% discount rate			$517,876
3.5% discount rate			$742,161
FEV_1 improvement due to ivacaftor treatment increased to upper 95% CI for all patients (i.e., 8.7796%)	$2,382,363	3.1	$757,815
FEV_1 improvement due to ivacaftor treatment decreased to lower 95% CI for all patients (i.e., 1.1497%)	$2,254,984	1.8	$1,232,372
Increase the utility gain due to ivacaftor by 20% ([redacted])	$2,322,462	2.6	$907,847
Decrease the utility gain due to ivacaftor by 20% ([redacted])	$2,322,462	2.4	$969,806
Remove SOC costs from the analysis	$2,283,816	2.5	$911,354
Increase the SOC costs in the analysis by 50%	$2,357,828	2.5	$940,888
Increase decline in FEV_1 over time in SOC arm by 20% from 0.6 to 0.72 percentage points per annum	$2,319,622	2.7	$870,916
Decrease decline in FEV_1 over time in SOC arm by 20% from 0.6 to 0.48 percentage points per annum	$2,325,347	2.3	$993,653
Double decline in FEV_1 over time in ivacaftor arm from 0.174 to 0.348 percentage points per annum	$2,308,208	2.3	$1,023,556
Half decline in FEV_1 over time in ivacaftor arm from 0.174 to 0.085 percentage points per annum	$2,333,025	2.7	$865,870

CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; QALY = quality-adjusted life-year; SOC = standard of care.
Source: Adapted from manufacturer's pharmacoeconomic submission.[5]

CADTH Common Drug Review Reanalysis

a) The Long-Term Comparative Efficacy of Ivacaftor Versus Standard Of Care (SOC)

The manufacturer's base-case analysis assumed that patients on SOC alone would have a continuous annual decline in lung function, a decline in ppFEV$_1$ of 0.6%.

This can be contrasted with the assumptions regarding ivacaftor, in which it was assumed there would be an immediate improvement in ppFEV$_1$ of 4.965%. However, the difference between ivacaftor and SOC would be exacerbated over time due to an assumed reduced annual decline in lung function with ivacaftor. The decline in ppFEV$_1$ was assumed to be only 29% of the decline with SOC — i.e., a decline of 0.17.

This analysis can be considered highly speculative, given that data on the relative efficacy of ivacaftor were available only up to a 24-week time horizon and assumptions regarding continued benefit were inferred from open-label extension studies in a different patient population.

CDR assumed that the same decline in FEV$_1$ for ivacaftor and SOC would occur over time, leading to an incremental cost of $1.4 million per QALY gained.

b) Uncertain Utility Estimates

The manufacturer assumed a relationship between utility values and FEV$_1$ and number of exacerbations.

TABLE 11: REGRESSION FORMULA FOR UTILITY APPLIED IN THE ECONOMIC MODEL

$$U = \beta_0 + \beta_1 \, x \, \%FEV_1 - \beta_2 \, x \, \%FEV_1^{\,2} - \beta_3 \, x \, Experiencing \; a \; PE$$

Parameter	Coefficient	SE
β0	0.6782	0.0674
β1	0.5614	0.1932
β2	-0.2941	0.1352
β3	-0.0256	0.013

Source: Coefficient values are taken from Solem and standard errors are derived from the reported data [8, 22]

Abbreviations: FEV$_1$, forced expiratory volume in 1 second; PE, pulmonary exacerbation; SE, standard error; U, utility value

Source: Manufacturer's pharmacoeconomic submission.[5]

This is based on a study that is available only in abstract form and none of the data used within the model are available within the abstract. Furthermore, the model assumes a further utility gain from ivacaftor of [redacted] based on unpublished data; this will likely lead to double-counting, as the benefit from FEV$_1$ is likely part of any such gain. CDR assumed no incremental QALY gain over the assumed impact on FEV$_1$ and exacerbations. This analysis found an incremental cost per QALY gained of $1.3 million.

In addition, CDR conducted a further analysis whereby no utility effect from FEV$_1$ and exacerbations were assumed; this required normalizing utility values based on baseline characteristics at a utility value of approximately 0.852. This led to an incremental cost per QALY gained of $1.6 million.

c) Inappropriate Drug Cost Estimates

The manufacturer assumed that the cost of ivacaftor would be reduced by 82% after 11.5 years (patent expiry). In addition, it is assumed that a proportion of patients will not adhere to ivacaftor, which will reduce its cost by a further 85%. However, there is no related reduction in efficacy assumed for this lower adherence.

It is highly uncertain that a generic alternative will be available following the expiry of the patent and it is equally uncertain that it would be available at an 82% price reduction. Reanalysis was not possible to adjust the effectiveness of ivacaftor with the model based on reduced adherence.

CDR conducted an analysis in which the drug price and adherence were maintained at the base price and level. The associated incremental cost per QALY gained was $1.6 million.

d) Unvalidated Effect of Ivacaftor on Health Care Costs

Analysis assumed reduced health care costs with ivacaftor based on improvements in FEV_1. However, the methods for deriving this effect from the available studies lacked transparency. When examining the two articles cited to support this assumption, problems were identified.

In the Guerriere study,[15] there was no reported impact of FEV_1 on health system costs. Johnson does report total in-patient costs, which could be used within the analysis.[16] Costs should have been increased using a CPI, not by using a constant 3% per annum. Due to the lack of transparency, a reanalysis was conducted assuming no effect of FEV_1 on cost. Costs were standardized at $22,638.05 per annum based on average baseline FEV_1. This led to an incremental cost per QALY gained of $939,515.

e) Combined Reanalysis

A combination of the above was conducted whereby CDR assumed:

- The same decline in FEV_1 for ivacaftor and standard care
- No incremental QALY gain for ivacaftor over the assumed impact on FEV_1 and exacerbations
- The drug price and adherence were maintained at the base price and level
- No effect of FEV_1 on cost.

TABLE 12: SUMMARY OF CADTH COMMON DRUG REVIEW REANALYSES

Scenario	Incremental Costs	Incremental QALYs	Incremental $/QALY
A – same decline in FEV_1	$2,267,696	1.6	$1,447,830
B1 – no incremental gain from ivacaftor	$2,322,462	1.7	$1,338,757
B2 – B1 and normalizing utility values	$2,322,462	1.44807	$1,603,829
C – drug price and adherence maintained throughout time horizon	$4,105,031	2.5	$1,638,107
D – no effect on FEV_1 on costs	$2,354,386	2.5	$939,515
E – combined (A, B1, C, D)	$3,846,035	0.8	$4,618,844

FEV_1 = forced expiratory volume in 1 second; QALY = quality-adjusted life-year.

Price Scenarios

The impact of the price of ivacaftor was examined both for the manufacturer's base case and the CDR multi-way analysis. To achieve a cost per QALY of $100,000, an 89% price reduction would be required using the manufacturer's base case or a 98% reduction when using the CDR reanalysis.

TABLE 13: CDR ANALYSIS BASED ON VARIOUS PRICE-REDUCTION SCENARIOS ($/QALY)

Scenario	Incremental Cost per QALY Gained	
	Based on Manufacturer's Analysis	CDR Reanalysis
Manufacturer's base case ($420)	$926,776	$4,618,844
10% price reduction ($378)	$834,360	$4,159,179
20% price reduction ($336)	$741,944	$3,699,515
30% price reduction ($294)	$649,528	$3,239,850
40% price reduction ($252)	$557,113	$2,780,185
50% price reduction ($210)	$464,697	$2,320,520
60% price reduction ($168)	$372,281	$1,860,855
70% price reduction ($126)	$279,866	$1,401,191
80% price reduction ($84)	$187,450	$941,526
89.46% price reduction ($44)	**$100,000**	
90% price reduction ($42)	$95,034	$481,861
94.87% price reduction ($22)	**$50,000**	
98.31% price reduction ($7)		**$100,000**
99.39% price reduction ($3)		**$50,000**

CDR = CADTH Common Drug Review; QALY = quality-adjusted life-year.

REFERENCES

1. [Pr]Kalydeco® (Ivacaftor): 150mg tablets [product monograph]. Laval (QC): Vertex Pharmaceuticals (Canada), Inc.; 2015 Mar 16.
2. Common Drug Review. CDEC final recommendation: IVACAFTOR (Kalydeco - Vertex Pharmaceuticals Inc.). Indication: cystic fibrosis with G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or G970R mutation [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2014 Dec 19. [cited 2015 Aug 7]. Available from: https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_SR0379_Kalydeco_Dec-23-14.pdf
3. Common Drug Review. Final CDEC recommendation: IVACAFTOR (Kalydeco - Vertex Pharmaceuticals (Canada) Incorporated). Indication: cystic fibrosis with G551D mutation [Internet]. Ottawa (ON): Canadian Agency for Drug and Technologies in Health; 2013 Mar 22. [cited 2015 Aug 7]. Available from: https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_Kalydeco_March-25-13_e.pdf
4. CDR submission: [Pr]Kalydeco® (ivacaftor) 150 mg tablets. Company: Vertex Pharmaceuticals (Canada) Incorporated [**CONFIDENTIAL** manufacturer's submission]. Mississauga (ON): Vertex Pharmaceuticals (Canada) Inc.; 2015.
5. Pharmacoeconomic evaluation. In: CDR submission: [Pr]Kalydeco® (ivacaftor) 150 mg tablets. Company: Vertex Pharmaceuticals (Canada) Incorporated [**CONFIDENTIAL** manufacturer's submission]. Mississauga (ON): Vertex Pharmaceuticals (Canada), Inc.; 2015.
6. Clinical Study Report: VX11-770-110. A Phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of Ivacaftor in subjects with cystic fibrosis who have the R117H-CFTR mutation [**CONFIDENTIAL** internal manufacturer's report]. Version 4.0. Cambridge (MA): Vertex Pharmaceuticals Incorporated; 2013 Jun 11.
7. Jackson AD, Daly L, Jackson AL, Kelleher C, Marshall BC, Quinton HB, et al. Validation and use of a parametric model for projecting cystic fibrosis survivorship beyond observed data: a birth cohort analysis. Thorax [Internet]. 2011 Aug [cited 2015 Jul 31];66(8):674-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3142345
8. Liou TG, Adler FR, Fitzsimmons SC, Cahill BC, Hibbs JR, Marshall BC. Predictive 5-year survivorship model of cystic fibrosis. Am J Epidemiol [Internet]. 2001 Feb 15 [cited 2015 Jul 31];153(4):345-52. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2198936
9. Shteinberg M, Beattie D. Clinical characteristics of CF patients with R117H mutation and different polythymidine tract variants. Poster presented at: NACFC. 28th Annual North American Cystic Fibrosis Conference; 2014 Oct 9 to 11 Oct 2014; Atlanta (GA).
10. Sawicki GS, Pasta DJ, Wagener JS, Johnson CA, Konstand MW. The effect of Ivacaftor on the rate of lung function decline in CF patients with a G551D-CFTR mutation. Poster presented at: ECFS. 37th Meeting of the European Cystic Fibrosis Society; 2014 Jun 11 to 14 Jun 2014; Gothenburg (SW).
11. Goss CH, Quittner AL. Patient-reported outcomes in cystic fibrosis. Proc Am Thorac Soc [Internet]. 2007 Aug 1 [cited 2015 Jul 31];4(4):378-86. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2647603

12. Goss CH, Burns JL. Exacerbations in cystic fibrosis. 1: Epidemiology and pathogenesis. Thorax [Internet]. 2007 Apr [cited 2015 Jul 31];62(4):360-7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2092469

13. Whiting P, Al M, Burgers L, Westwood M, Ryder S, Hoogendoorn M, et al. Ivacaftor for the treatment of patients with cystic fibrosis and the G551D mutation: a systematic review and cost-effectiveness analysis. Health Technol Assess. 2014 Mar;18(18):1-106.

14. Solem C, Llonch MV, Liu S, Botteman MF, Lasch K, Rodriguez S, et al. Responsiveness of the EQ-5D index and Visual Analog Scale to changes in lung function in patients with cystic fibrosis. Poster presented at: International Society of Pharmacoeconomics and Outcomes Research. ISPOR 19th Annual International Meeting; 2014 May 31 to 4 Jun 2014; Montreal (QC).

15. Guerriere DN, Tullis E, Ungar WJ, Tranmer J, Corey M, Gaskin L, et al. Economic burden of ambulatory and home-based care for adults with cystic fibrosis. Treat Respir Med. 2006;5(5):351-9.

16. Johnson JA, Connolly MA, Jacobs P, Montgomery M, Brown NE, Zuberbuhler P. Cost of care for individuals with cystic fibrosis: a regression approach to determining the impact of recombinant human DNase. Pharmacotherapy. 1999 Oct;19(10):1159-66.

17. Interactive drug benefit list [Internet]. Edmonton (AB): Alberta Health; 2015. [cited 2015 Aug 10]. Available from: https://idbl.ab.bluecross.ca/idbl/load.do

18. Drug Plan and Extended Benefits Branch. Saskatchewan online formulary database [Internet]. Regina: Government of Saskatchewan; 2015. [cited 2015 Aug 10]. Available from: http://formulary.drugplan.health.gov.sk.ca/

19. 2013 Annual report: The Canadian Cystic Fibrosis registry [Internet]. Toronto (ON): Cystic Fibrosis Canada; 2015. [cited 2015 Jul 28]. Available from: http://www.cysticfibrosis.ca/wp-content/uploads/2015/02/Canadian-CF-Registry-2013-FINAL.pdf