Common Drug Review
Pharmacoeconomic Review Report

July 2015

Drug	ivacaftor (Kalydeco) 150 mg tablet
Indication	For treatment of cystic fibrosis (CF) in patients age 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.
Listing request	As per indication
Manufacturer	Vertex Pharmaceuticals 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 Respirology who provided input on the conduct of the review and the interpretation of findings.

This report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). 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The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions.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

CDR	CADTH Common Drug Review
CF	cystic fibrosis
CFFPR	US Cystic Fibrosis Foundation Patient Registry
CFTR	cystic fibrosis transmembrane conductance regulator
EQ-5D	EuroQol Five-Dimensions Questionnaire
FEV_1	forced expiratory volume in one second
ICER	incremental cost-effectiveness ratio
ICUR	incremental cost-utility ratio
QALY	quality-adjusted life-year
RCT	randomized controlled trial
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 age 6 years and older who have a non-G551D-CFTR mutation (G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P and G1349D)
Type of Economic Evaluation	Cost-effectiveness and cost-utility analyses
Target Population	Patients with CF aged 6 years and older who have a non-G551D-CFTR gating mutation in Canada (of note, the base case analysis included patients with G551D and non-G551D mutations)
Treatment	Ivacaftor plus SoC (could consist of, but not limited to, respiratory, nutritional and rehabilitative support such as mucolytic drugs, osmotic drugs, antibiotics, bronchodilators, pancreatic enzymes, dietetic therapy, and chest physiotherapy)
Outcome(s)	Cost per QALY and cost per life-year
Comparator	SoC alone
Perspective	Public payer perspective
Time Horizon	Lifetime (up to age 80)
Manufacturer's Results (Base Case)	ICUR = $356,349 per QALY ICER = $444,746 per life-year
Key Limitations and CDR Estimate(s)	CDR identified a number of limitations with the manufacturer's analysis: 1. The long-term comparative efficacy of ivacaftor relative to SoC is uncertain. CDR exploratory re-analysis assumed that the same decline in FEV_1 for ivacaftor and SoC would occur over time, leading to an ICUR of $1.2 million per QALY. 2. Uncertain survival equation. CDR could not estimate the impact of this uncertainty on the cost-effectiveness of ivacaftor. 3. Uncertain utility estimates. CDR re-analysis used trial-based utility estimates, resulting in an ICUR of $448,273 per QALY. 4. Uncertain cost estimates. CDR re-analysis considered that the price of ivacaftor will not be reduced after 12.5 years resulting in an ICUR of $547,346 per QALY. CDR alternative scenario considered, in addition to issues 3 and 4, an adherence rate of 93% and CF costs that are not a function of FEV_1, resulting in an ICUR of $850,932 per QALY.

CDR = CADTH Common Drug Review; CF = cystic fibrosis; FEV_1 = forced expiratory volume in 1 second; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SoC = standard of care.

EXECUTIVE SUMMARY OF THE PHARMACOECONOMIC SUBMISSION

Background

Ivacaftor is a first-in-class oral cystic fibrosis transmembrane conductance regulator (CFTR) potentiator approved by Health Canada for treatment of cystic fibrosis (CF) in patients age six years and older who have one of the following mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or G970R. Ivacaftor prolongs the time that activated CFTR channels remain open, thereby enhancing the regulation of chloride and water transport across cell membranes.[1] It is available as 150 mg oral tablets. 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.

Ivacaftor was previously reviewed by the CADTH Common Drug Review (CDR) in 2013 for CF patients with G551D mutation. The Canadian Drug Expert Committee (CDEC) recommended that ivacaftor be listed with conditions, which included a substantial reduction in price.[2] The current CDR review will focus on the full population identified in the approved Health Canada indication, which includes G551D and non-G551D mutations.

Summary of Economic Analysis

The manufacturer submitted a cost-utility analysis (CUA) from a Canadian health care payer's perspective. The economic evaluation compared ivacaftor plus standard of care (SoC) with SoC alone, where SoC could consist of, but not be limited to, respiratory, nutritional, and rehabilitative support such as mucolytic drugs, osmotic drugs, antibiotics, bronchodilators, pancreatic enzymes, dietetic therapy, and chest physiotherapy over the lifetime of CF patients (80 years). The model was based on a patient-level simulation to estimate clinical outcomes and costs associated with CF treatment. The model included four health states based on patients' lung function i.e. normal lung function (forced expiratory volume in one second [FEV_1] ≥ 90%), mild (FEV_1 70% to 90% predicted), moderate (FEV_1 40% to 70% predicted), severe (FEV_1 < 40% predicted), and one absorbing state (death). Transition between health states was based on CF survival prediction equations. The model used patient-level data from clinical trials (KONNECTION,[3] STRIVE,[4] ENVISION,[5] and PERSIST[6]). In the base case, the manufacturer assumed that ivacaftor would cause a persistent improvement of lung function, while patients on SoC alone would have a continuous annual decline in lung function. The manufacturer also assumed that the cost of ivacaftor would be reduced by 82% after 12.5 years (patent expiry). Costs and quality-adjusted life years (QALYs) for each individual patient were estimated based on assumptions relating to the relationship with per cent predicted FEV_1. Thus, the model predicted total cost, QALYs, and survival for each patient both with ivacaftor and without ivacaftor.

The model was a direct modification of the original ivacaftor cost-effectiveness analysis submitted to CDR, with a few updates, such as:

- Baseline characteristics of 39 patients with non-G551D mutations included in KONNECTION[3] were added to the model, leading to a total sample size of 252 individuals (G551D and non-G551D mutations).
- Utility values were obtained from a survey completed by seven directors of CF centres in Australia, while the previous submission used trial-based utility estimates.
- Mean values of FEV_1 were used instead of the median values used in the previous submission.
- Long-term data from the PERSIST[6] extension study were used to support sustained efficacy of ivacaftor up to 144 weeks.

- The manufacturer assumed that patients consume [redacted]% of the full dose of ivacaftor on an annual basis (to account for adherence and pharmacokinetic dose adjustments).

Results of Manufacturer's Analysis

The base-case results showed that the incremental cost-effectiveness ratio (ICER) for ivacaftor plus SoC compared with SoC alone was $356,349 per QALY and $444,746 per life-year gained.

Interpretations and Key Limitations

Several limitations with the manufacturer's analysis were identified:

The Long-Term Comparative Efficacy of Ivacaftor Versus SoC is Uncertain

The manufacturer's base case analysis assumed that ivacaftor would cause a persistent improvement of lung function, while patients on SoC alone would have a continuous annual decline in lung function. This analysis can be considered speculative given that despite open-label extension data the relative efficacy of ivacaftor beyond the 48-week time horizon of the clinical trials is unknown. The model did not allow CDR to perform an analysis that would incorporate waning of treatment effect over time. Therefore, in an exploratory analysis, CDR assumed that the same decline in FEV_1 for ivacaftor and standard care would occur over time, leading to an incremental cost-utility ratio (ICUR) of $1.2 million per QALY.

Uncertain Utility Estimates

The model estimated utilities based on a very small sample of directors of CF centres (N = 7) in Australia. Trial-based utility estimates were reported in the model, and they were used in the original submission to CDR. CDR considered these estimates to be more likely to present patients' perspectives of effects of ivacaftor. CDR re-analysis used trial-based utility estimates, resulting in an ICUR of $448,273 per QALY.

Uncertain Cost Estimates

The manufacturer assumed that the cost of ivacaftor would be reduced by 82% after 12.5 years (patent expiry). As it is uncertain whether a generic alternative will be available following the expiry of the patent, CDR considered an analysis where the drug price is maintained.

Results of CADTH Common Drug Review Analyses

CDR conducted reanalyses accounting for several of the limitations noted above. This analysis assumed the following:

- Trial-based utility would provide more accurate estimates than those used by the manufacturer, which came from a very small sample size (N = 7)
- No price reduction after patent expiry
- CF costs are not a function of FEV_1
- Patients consume 93% of the full dose of ivacaftor on an annual basis (based on Canadian data presented in the manufacturer's submission), instead of [redacted]% used in the manufacturer's base case (based on data from the United States).

CDR analysis showed that the incremental cost-effectiveness ratio (ICER) for ivacaftor plus SoC compared with SoC alone was $850,932 per QALY and $844,236 per life-year.

Conclusions

CDR identified several limitations with the submitted analysis. When considering more conservative input estimates and assumptions, CDR noted that the ICUR for ivacaftor plus SoC compared with SoC was $850,932 per QALY and the ICER was $844,236 per life-year.

REVIEW OF THE PHARMACOECONOMIC SUBMISSION

1. INTRODUCTION

1.1 Study Question

The aim of the submitted economic evaluation was to evaluate the cost-effectiveness of ivacaftor as an adjunct to current treatment for patients with cystic fibrosis (CF) aged six years and older who have a non-G551D CF transmembrane conductance regulator (CFTR) mutation.[7]

1.2 Treatment

Ivacaftor is used as an adjunct to current standard of care (SoC) — where SoC could consist of, but not be limited to, respiratory, nutritional, and rehabilitative support (e.g., mucolytic drugs, osmotic drugs, antibiotics, bronchodilators, pancreatic enzymes, dietetic therapy, and chest physiotherapy).

1.3 Comparators

Comparator is the current SoC used alone.

1.4 Type of Economic Evaluation

The manufacturer undertook a cost-utility analysis (CUA). The model predicted the incremental cost per life-year gained (LYG) and the incremental cost per quality-adjusted life-year gained (QALY) with the use of ivacaftor. This is appropriate given the potential impact of CF on life expectancy, as per CADTH *Guidelines for Economic Evaluations of Health Technologies*.[8]

The analysis takes a public-payer perspective. This is appropriate as per CADTH guidelines.[8]

1.5 Population

The Health Canada indication for ivacaftor is for the treatment of CF in patients age six years and older who have one of the following mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or G970R.

The submitted economic evaluation reported that the focus of the evaluation was for patients with CF age six years and older who have a non-G551D-CFTR gating mutation in Canada. However, the manufacturer noted that given the longer duration of follow-up, the larger sample size, and the similarities in response to ivacaftor seen in the G551D and non-G551D gating populations, the treatment effect of ivacaftor used in the economic model was based on results from the STRIVE and ENVISION randomized controlled trials (RCTs) (G551D patients).[9,10] Therefore, the base-case analysis included patients with G551D and non-G551D gating populations (N = 252).

The model was also tested using only the baseline characteristics of the non-G551D gating population (N = 39).

2. METHODS

Please see Table 10 for a summary of the key limitations associated with the methodology used by the manufacturer.

2.1 Model Structure

The economic evaluation was based on a patient-level simulation to estimate clinical outcomes and costs associated with CF treatment. The model included four health states representing patients living with CF of different severity and one absorbing state (death). The model considered four categories of disease severity that included normal lung function (forced expiratory volume in one second [FEV_1] ≥ 90%), mild (FEV_1 70% to 90% predicted), moderate (FEV_1 40% to 70% predicted), and severe (FEV_1 < 40% predicted). Transition between the states was based on CF survival prediction equations (Survival).

2.2 Clinical Inputs

2.2.1 Efficacy

The submitted model expressed efficacy in terms of average life expectancy (survival) of patients with CF. Sources on survival data and methods used to forecast patients' survival are presented in the Survival section. In brief, the model started by taking patient-specific characteristics (covariates) which are considered to impact on patient survival (i.e., age, gender, baseline per cent predicted FEV_1, pancreatic sufficiency, and weight-for-age z-score) from the individual patient data reported in the G551D and non-G551D gating populations collectively (i.e., 252 individuals reported in the KONNECTION, STRIVE, and ENVISION RCTs) and information on the age-specific rates of diabetes, *Staphylococcus aureus* and *Burkholderia cepacia* infection reported in the Canadian Cystic Fibrosis Foundation Patient Data Registry (CPDR) 2010. These data formed the individual baseline values for 252 individual patient cohorts that were tracked in both the SoC alone and ivacaftor plus SoC groups of the model compared with the time horizon of the economic analysis.

2.2.2 Harms

The submitted model did not include any harm outcomes. The CADTH Common Drug Review (CDR) considered this acceptable because of the reported tolerability of ivacaftor.

2.2.3 Natural History and Disease Progression

The submitted model reported that baseline values of the included 252 patients were modified according to available evidence from literature that described the natural history of CF progression. According to the model, patients treated with SoC alone have a natural annual decline in lung function (FEV_1) that ranged from 1.12% to 2.47% (Table 2).

TABLE 2: SUMMARY OF THE ANNUAL FEV_1 DECLINE APPLIED TO SOC ARM IN THE ECONOMIC MODEL

Patient Age	FEV_1 Decline (%)
6 to 8 years	–1.12%
9 to 12 years	–2.39%
13 to 17 years	–2.34%
18+ years	–2.47%

FEV1 = forced expiratory volume in 1 second; SoC = standard of care.

On the other hand, the model assumed that ivacaftor would cause a persistent improvement in lung function of 10% predicted for patients younger than 12 years and 10.5% for patients 12 years and older.

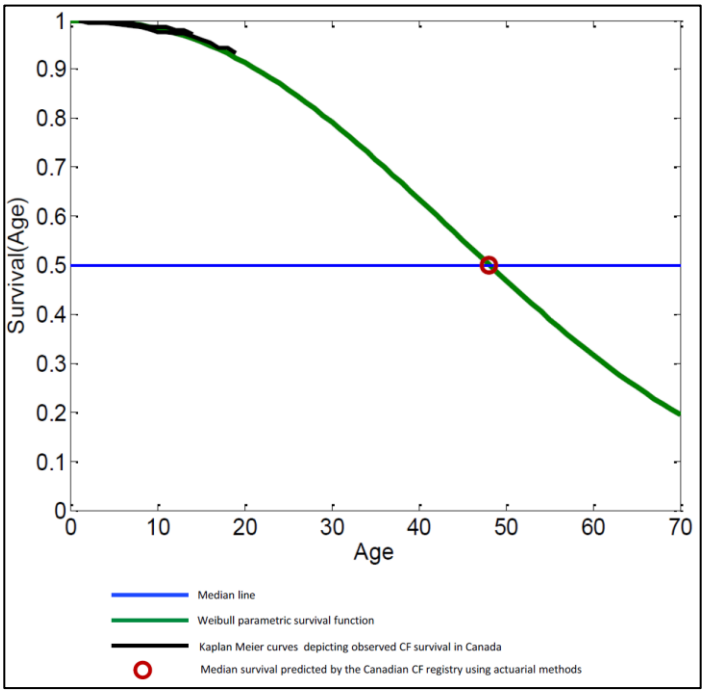
This assumption was not supported by solid evidence. Data from long-term extension trials showed that the results were not consistent throughout the follow-up period, which compromised the validity of the model assumption. It would have been more appropriate to incorporate waning effect equal to that seen with SoC.

2.2.4 Survival

The economic model used survival data based on CPDR for patients born after 1990. These data were used to estimate the baseline hazard of mortality in patients with CF in Canada treated with SoC alone.

To extrapolate survival data, the economic model used a Weibull parametric survival function that was fitted on the observed survivorship of 13,115 patients with CF from the US Cystic Fibrosis Foundation Patient Registry (CFFPR) dataset. A graphic presentation (Figure 1) of the observed and predicted survival showed that the observed survival might have been slightly higher than the predicted one, but the exact difference was not reported.

FIGURE 1: COMPARISON OF THE CANADIAN CYSTIC FIBROSIS SURVIVAL CURVES AND THE BASELINE WEIBULL SURVIVAL FUNCTION



Source: Manufacturer's pharmacoeconomic submission.[7]

To provide an individualized survival estimate, the economic model used multivariate Cox Proportional Hazards model developed by Liou et al. in 2001.[11] Liou's model used the CFFPR, which has collected longitudinal data on approximately 90% of cystic fibrosis patients diagnosed in the United States since 1986. Liou et al. found that age, gender, per cent predicted FEV_1, weight-for-age z-score, pancreatic sufficiency, diabetes mellitus, *S. aureus* infection, *B. cepacia* infection, and the number of acute pulmonary exacerbations a patient suffers were significant and independent predictors of survival in patients with CF. CDR has noted that Liou's model was partially based on data of patients who did not have access to dornase alfa and tobramycin treatments; these treatments improved the prognosis on

CF patients significantly,[12-14] and they are part of the current SoC. However, CDR could not estimate the impact of including these patients on Liou's model.

2.2.5 Quality of Life

Quality of life was captured in STRIVE RCT using EQ-5D (EuroQol Questionnaire) scale. These data were used to estimate preference-based health-related quality of life weights (utility weights).

2.2.6 Utilities

The submitted model used two methods to estimate utility weights. The first was trial-based utility values transformed from EQ-5D values, and the second was based on EQ-5D-5L scales completed by proxy of seven directors of CF centres in Australia. The results of each method are presented Table 3. The model applied the second method for the base case analysis because it claimed that CF patients adapt to life with a chronic condition, and accordingly they rate their quality of life higher with less regard to the impact of the disease. CDR agreed that CF patients develop a certain level of tolerance for the disease; however, CDR considers that trial-based utility is more appropriate because it accounts for patients' perspectives of the disease, and is based on a larger sample size.

TABLE 3: UTILITY WEIGHTS BY HEALTH STATE APPLIED IN THE ECONOMIC EVALUATION

FEV_1 Category	Trial-Based Utility Values	Proxy-Based Utility Values[a]
Normal (≥ 90%)	0.97	0.98
Mild (70% to 89%)	0.95	0.88
Moderate (40% to 69%)	0.93	0.67
Severe (< 40%)	0.91	0.37

FEV_1 = forced expiratory volume in 1 second.
[a] Utility values used in the base-case analysis.
Source: Manufacturer's pharmacoeconomic submission.[7]

2.2.7 Costs

Costs related to SoC were based on available Canadian literature.[15,16] According to the model, outpatient costs presented 21% of the total costs associated with CF management in Canada, and outpatient and in-patient costs were functions of per cent predicted FEV_1 (Table 4). The consulted clinical expert expressed concerns about estimating costs in function of FEV_1, and commented that other factors could affect costs such as exacerbations and patient response to therapy. However, CDR considered that variations in SoC cost have minimal impact on the pharmacoeconomic analysis because these costs were applied to both groups.

TABLE 4: ESTIMATED COSTS OF SOC

Patient Category	Percentage of Patients	Cost in Function of FEV_1
Outpatient	21%	\$14,285 to \$97 × FEV_1% predicted
In-patient	79%	\$21,214 to \$145 × FEV_1% predicted

FEV_1 = forced expiratory volume in 1 second.
Source: Manufacturer's pharmacoeconomic submission.[7]

2.2.8 Drug Costs

The submitted price for ivacaftor was \$420 per tablet. The indicated dose is two tablets per day. The model assumed that adherence to the indicated dose would be [redacted]%, based on observed adherence rates

in the US reported in the literature. However, the manufacturer also reported Canadian data, which, although based on a small sample size (43 patients), showed an adherence rate of 93%.[7] The model also assumed that the price of ivacaftor would drop to 18% of its initial price once patent expiry occurs. The consulted clinical expert confirmed the adherence assumption. However, CDR doubted drop in price assumption after patent expiry because of the low prevalence of the disease; CDR considered that it would be unlikely to develop generic alternatives for ivacaftor. Summary of drug costs are presented in Table 5.

TABLE 5: SUMMARY OF IVACAFTOR DRUG COSTS

Description	Cost ($)
Price per tablet	$420
Price per day (2 tablets)	$840
Price per annum (365 days)	$306,600
Cost of ivacaftor per annum after adherence and pharmacokinetic dose adjustments are applied (i.e., a 23% reduction in the full dose of ivacaftor)	$236,082
Cost of ivacaftor per annum after patent expiry (i.e., 18% of initial price; OPDP, 2013)	$55,188

Source: Manufacturer's pharmacoeconomic submission.[7]

2.2.9 Time Horizon

The manufacturer presented the results of the economic evaluation using the patient's lifetime, or a maximum patient age of 80 years, whichever comes first. This time horizon was supported by the CADTH *Guidelines for the Economic Evaluation of Health Technologies* and the chronic nature of CF.[8] The economic model employed three-month cycles.

2.2.10 Discounting

The model applied a discount rate of 5% for both costs and survival, as per CADTH guidelines.[8] However, the manufacturer demanded that CDR consider a lower discount rate due to the high sensitivity of ICER to discounting. This sensitivity was due to a forecasted survival benefit in young patient population. CDR acknowledged the sensitivity of the pharmacoeconomic analysis relative to the discounting rate, but decided to report results generated with 5% discount in order to ensure consistency with CADTH guidelines.[8]

2.2.11 Validation

The submitted evaluation did not report any validation method.

3. RESULTS

3.1 Manufacturer's Base Case

The base-case results, based on individual trial data from the 252 patients included in KONNECTION, STRIVE, and ENVISION (i.e., both G551D and non-G551D populations) showed that the cost-effectiveness of ivacaftor plus SoC compared with SoC alone was $444,746 per life-year and $356,349 per QALY (see Table 6).

TABLE 6: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE (DISCOUNTED AT 5%)

	Total Costs ($)	Incremental Cost ($)	Total Effect	Incremental Effect	ICER and ICUR
Incremental cost per life-year gained					
SoC	$130,922	$2,402,735	10.2	5.4	$444,746
Ivacaftor plus SoC	$2,533,657		15.6		
Incremental cost per quality-adjusted life-year gained					
SoC	$130,922	$2,402,735	6.8	6.7	$356,349
Ivacaftor plus SoC	$2,533,657		13.5		

ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; SoC = standard of care.
Source: Manufacturer's pharmacoeconomic submission.[7]

3.2 Summary of the Manufacturer's Sensitivity Analyses

3.2.1 One-Way Sensitivity Analyses

The manufacturer conducted several sensitivity analyses, two of which provided significant changes from the base case analysis; these were varying adherence rates to ivacaftor and varying discount rate (Table 7).

TABLE 7: SENSITIVITY ANALYSIS OF INTEREST

Sensitivity Analysis	ICUR
Base case analysis	$356,349
Use of only the 39 non-G551D mutation patients from KONNECTION to inform the baseline characteristics of patients included in the economic analysis (removing the G551D mutation patients from the economic analysis)	$345,489
Patients consume 93% of the full dose of ivacaftor on an annual basis (instead of [redacted]%)	$430,113
Discount rate of 0%	$161,673
Discount rate of 3.5%	$289,515

ICUR = incremental cost-utility ratio.
Source: Manufacturer's pharmacoeconomic submission.[7]

3.3 CADTH Common Drug Review Analyses

CDR identified a number of limitations with the manufacturer's analysis:

The Long-Term Comparative Efficacy of Ivacaftor Versus Standard of Care is Uncertain

The assumption that per cent predicted FEV_1 will be maintained with ivacaftor beyond one year such as the difference in per cent predicted FEV_1 between those receiving ivacaftor and those receiving SoC actually increases over time is not justified due to lack of long-term controlled clinical data. The model

did not allow CDR to perform an analysis that would incorporate waning of treatment effect over time. Therefore, in an exploratory analysis, CDR assumed that the same decline in FEV_1 for ivacaftor and standard care would occur over time.

Uncertain Survival Equation

The model used multivariate Cox Proportional Hazards model developed by Liou et al. in 2001.[11] Liou's model used the CFFPR, which has collected longitudinal data on approximately 90% of cystic fibrosis patients diagnosed in the United States since 1986. CDR has noted that Liou's model was partially based on data of patients who did not have access to dornase alfa and tobramycin treatments; these treatments improved the prognosis and survival of CF patients significantly,[12-14] and they are part of the current SoC. However, CDR could not estimate the impact of including these patients on Liou's model.

Uncertain Utility Estimates

The model estimated utilities based on EQ-5D-5L scales completed by seven directors of CF centres in Australia. Trial-based utility estimates were reported in the submitted model, and they were used in the previous ivacaftor CDR submission for patients with G551D-CFTR. These estimates are more likely to present patients' perspectives and are based on a larger sample size.

Uncertain Cost Estimates

The methods for deriving cost data were a function of FEV_1, based on available Canadian literature.[15,16] It should be noted that the model used a published study by Guerriere that did not report impact of per cent predicted FEV_1 on health system costs — the only reported covariate was pancreatic sufficiency.[15] Further, the assumption around a reduced price of ivacaftor after patent expiry was not justified. CDR re-analysis considered that cost is not a function of FEV_1, and the price of ivacaftor will not be reduced after patent expiry.

A summary of CDR reanalyses is provided in Table 8.

TABLE 8: CDR REANALYSES

CDR Re-analyses	ICUR	ICER
Assuming same decline in FEV_1 for ivacaftor and standard care would occur over time (exploratory analysis)	$1,213,514	$1,163,967
Using trial-based utility estimates	$448,273	$444,746
Assuming no price reduction after patent expiry	$547,346	$683,123
Assuming CF costs are not function of FEV_1[a]	$371,987	$464,264
CDR alternative scenario[b]	$850,932	$844,236

CDR = CADTH Common Drug Review; CF = cystic fibrosis; FEV_1 = forced expiratory volume in one second; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio.

[a] The manufacturer's analysis estimated the cost based on Johnson's formula (cost = $21,214 -145 × $\%FEV_1$);[16] CDR analysis assumed that cost is not related to FEV_1 (i.e., cost = $21,214).

[b] CDR alternative scenario included the following:

- using trial-based utility estimates
- assuming no price reduction after patent expiry
- assuming that CF costs are not a function of FEV_1
- assuming that patients consume 93% of the full dose of ivacaftor on an annual basis instead of [redacted]%(based on Canadian data accounting for adherence and pharmacokinetic dose adjustments, as presented in the manufacturer's submission[7]).

CDR conducted additional re-analysis considering price reductions and implications on the cost-effectiveness of ivacaftor, where the CDR "alternative scenario" was used. Table 9 summarizes the results of the cost minimization analysis.

TABLE 9: CDR ANALYSIS OF ICURS BASED ON VARIOUS PRICE REDUCTION SCENARIOS

Scenario	Based on Manufacturer's Analysis		Based on CDR "Alternative Scenario"	
	ICUR	ICER	ICUR	ICER
No price reduction	$356,349	$444,746	$850,932	$844,236
10% price reduction	$320,850	$400,441	$767,977	$761,934
20% price reduction	$258,351	$356,136	$685,022	$679,632
30% price reduction	$311,831	$249,852	$602,067	$597,330
40% price reduction	$214,353	$267,526	$519,112	$515,027
50% price reduction	$178,854	$223,221	$436,257	$432,725
60% price reduction	$143,355	$178,916	$353,202	$350,423
70% price reduction	$107,856	$134,611	$270,247	$268,121
80% price reduction	$72,357	$90,307	$187,293	$185,819
90% price reduction	$36,858	$46,002	$104,338	$103,517

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

4. DISCUSSION

The submitted analysis estimated the cost-effectiveness of ivacaftor plus SoC relative to SoC alone. CDEC already reviewed ivacaftor for use in patients who have G551D mutation in the CFTR, and recommended its listing with conditions, including a substantial reduction in price.[2] The current submission is very similar to the previous one, with the exception of including patients who have non-G551D mutations. When only patients with the non-G551D mutation were considered, the economic analysis showed that cost-effectiveness was similar to the one reported for both groups of patients together (Table 7). CDR analysis included both types of patients in order to be consistent with Health Canada's indication, and because, as indicated by the manufacturer, estimates from the full population are likely to be more robust. Another difference between the current submission and the previous one was the use of utility values obtained from a survey completed by seven directors of CF centres in Australia, while the previous submission used trial-based utility estimates. CDR considered that trial-based utilities were more appropriate as they were more likely to present patients' perspectives and were based on a larger sample size. The previous model used the median of the efficacy outcome (FEV_1), while the current submission used the mean values. CDR considered that the use of the mean values was a more appropriate choice.

The analysis had several limitations summarized in Table 10. A key limitation of the submitted analysis was that it assumed a persistent improvement of lung functions for patients treated with ivacaftor, and it assumed that lung functions of patients treated with SoC alone would have a continuous annual decline. The manufacturer reported some evidence from the literature to support the natural disease progression; however, there is no evidence to support the long-term comparative efficacy of ivacaftor compared with SoC in terms of FEV_1.

Another major limitation in the manufacturer's analysis was that it assumed a price reduction after 12 years (patent expiry). However, the prevalence of CF is very small, and the development of generic alternatives is unlikely. CDR reanalyses were conducted to reduce the uncertainty in the manufacturer's assumption; consequently, the cost-effectiveness estimates are considerably higher than the manufacturer's estimates.

The key limitations associated with the manufacturer's submission are summarized in Table 10.

TABLE 10: KEY LIMITATIONS OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Parameter or Assumption	Issue	Impact
Efficacy input	Lung function improvement overestimated	Potentially overestimates long-term efficacy of ivacaftor
Uncertain utility estimates	Utility estimation was based on very small sample of directors of CF centres (N = 7)	Overestimated cost-effectiveness; CDR estimate of ICUR is $448,273
Uncertain cost reduction	Model assumed 82% price reduction after 12.5 years	Overestimated cost-effectiveness; CDR estimate of ICUR is $547,346

CDR = CADTH Common Drug Review; CF = cystic fibrosis; ICUR = incremental cost-utility ratio.

4.1 Patient Input

The received patient inputs were about young CF patients, and they presented the caregivers' perspectives. They showed that caregivers have high expectations for the efficacy of ivacaftor and the positive impact it would have on patients. However, the high cost of ivacaftor put significant financial strain on the caregiver.

5. CONCLUSIONS

CDR identified several limitations with the submitted analysis. When considering more conservative input estimates and assumptions, CDR noted that the ICUR for ivacaftor plus SoC compared with SoC was $850,932 per QALY and the ICER was $844,236 per life-year.

APPENDIX 1: COST COMPARISON TABLE FOR DRUGS USED FOR CYSTIC FIBROSIS

Clinical experts have deemed the comparators presented in Table 11 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 11: COST COMPARISON TABLE FOR DRUGS USED FOR CYSTIC FIBROSIS

Drug or Comparator	Strength	Dosage Form	Unit Cost ($)	Recommended Treatment Regimen	Average Daily Cost ($)	Average Annual Cost ($)
Ivacaftor (Kalydeco)	**150 mg**	**Tab**	**420.000[a]**	**150 mg twice daily**	**840.00**	**306,600**
Treatments indicated for the treatment of patients with CF						
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	26,366
Tobramycin (Tobi)	300 mg/5mL (60 mg/mL)	Inhaled solution (single-dose ampoule)	52.2100	Alternating 300 mg twice daily for 28 days, followed by 28 days off	104.42	19,056
Tobramycin (Tobi Podhaler)	28 mg	Inhalation capsule	13.0500	4 capsules (112 mg) twice daily for 28 days, followed by 28 days off	104.40	19,053
Treatments used for the treatment of patients with CF — not indicated						
Colistimethate sodium	150 mg vial	IV	33.7397[b]	75 mg twice daily	33.74	12,315
Tobramycin	80 mg/2mL (40 mg/mL)	IV	4.5000	300 mg twice daily for 28 days, followed by 28 days off	36.00	6,570

IV = intravenous; mg = milligram; mL= millilitre; tab = tablet.
Source: Saskatchewan Drug Benefit Formulary (effective July 17, 2014) unless otherwise indicated. Doses based on product monographs unless otherwise stated. Administration costs are not included.
[a] Manufacturer's submitted price.
[b] Alberta Formulary (July 2014).

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 12: WHEN CONSIDERING ONLY COSTS, OUTCOMES AND QUALITY OF LIFE, HOW ATTRACTIVE IS IVACAFTOR RELATIVE TO STANDARD OF 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	ICUR: $850,932 per QALY ICER: $844,236 per life-year					

CE = cost-effectiveness; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; NA = not applicable.
The ICUR is based on CADTH Common Drug Review reanalysis.

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"*	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		

TABLE 14: AUTHOR INFORMATION

Authors	Affiliations
Kyle Hvidsten	Vertex Pharmaceuticals Incorporated

	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

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