



FINAL CDEC RECOMMENDATION

IVACAFTOR

(Kalydeco – Vertex Pharmaceuticals (Canada) Incorporated)

Indication: Cystic Fibrosis with G551D Mutation

Recommendation:

The Canadian Drug Expert Committee (CDEC) recommends that ivacaftor be listed for the treatment of cystic fibrosis (CF) in patients age six years and older who have a G551D mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, only if both of the following conditions are met:

Conditions:

1. Substantial reduction in price: ivacaftor will not be considered cost-effective without a substantial reduction in the submitted price.
2. Clinical criteria for the discontinuation of ivacaftor treatment in patients who fail to demonstrate a meaningful response must be developed in consultation with CF treatment clinics.

Reasons for the Recommendation:

1. In two double-blind randomized controlled trials (RCTs) (ENVISION and STRIVE), ivacaftor was superior to placebo for improvement in percent predicted forced expiratory volume in one second (FEV₁) and weight gain. In STRIVE, compared with placebo, ivacaftor-treated patients demonstrated statistically significant and clinically meaningful improvements in patient-reported respiratory symptoms.
2. At the submitted price of \$306,600 per year, the Common Drug Review (CDR) estimated that the incremental cost per quality-adjusted life-year (QALY) for ivacaftor ranges from approximately \$2 million to \$9 million; therefore, ivacaftor is not considered cost-effective at the submitted price.
3. Up to 25% of ivacaftor-treated patients in the included RCTs failed to demonstrate an improvement in the percent predicted FEV₁ of at least 5%; therefore, discontinuation criteria are required to ensure appropriate use of ivacaftor.
4. Patient groups identified unmet need in the treatment of CF that CDEC concluded could potentially be met by ivacaftor.

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Of Note:

1. The Committee noted that a proportion of ivacaftor-treated patients (up to 25%) failed to demonstrate a meaningful response in clinical trials. Given the high cost of ivacaftor, the Committee concluded that it is important to develop appropriate discontinuation criteria for non-responders. This issue will require broad consultation within the CF treatment community to ensure appropriate use of ivacaftor.
2. The Committee noted that the clinical benefits of ivacaftor must be viewed in conjunction with the high cost and unfavourable cost-effectiveness of this treatment.

Background:

Ivacaftor is a CFTR potentiator that works by prolonging the time that activated CFTR channels remain open; thereby, enhancing the regulation of chloride and water transport across cell membranes. It has a Health Canada indication for the treatment of CF in patients age six years and older who have a G551D mutation in the CFTR gene. Ivacaftor is available as 150 mg oral tablets and the product monograph recommends a dose of 150 mg every 12 hours with fat-containing food.

Summary of CDEC Considerations:

The Committee considered the following information prepared by CDR: a systematic review of RCTs of ivacaftor, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

Patient Input Information

The following is a summary of the information provided by two patient groups that responded to the CDR Call for Patient Input for this review:

- Outcomes of importance to patients include improved survival, improved quality of life, elimination or reduction in the need CF therapies, and delaying the need for lung transplantation.
- Patients and their caregivers can be substantially impacted emotionally, psychologically, physically, and financially by CF. In addition, a considerable amount of time (two to seven hours per day) is spent on airway clearance activities to maintain lung health. In the event of acute pulmonary exacerbations, patients can spend at least two weeks in hospital.

Clinical Trials

The systematic review included two similarly designed, 48-week, double-blind, placebo-controlled RCTs (STRIVE and ENVISION) comparing ivacaftor 150 mg every 12 hours with placebo added to a stable regimen of CF background therapies in patients with a G551D-CFTR mutation on at least one allele. Patients receiving inhaled hypertonic saline (a mucolytic agent) had to discontinue that treatment before study enrolment.

STRIVE (N = 167) studied adolescent and adult patients with CF at least 12 years old with an FEV₁ score of 40% to 70% (inclusive) of the predicted normal; while ENVISION (N = 52) studied pediatric patients with CF six to 11 years old with an FEV₁ score of 40% to 105% (inclusive) of the predicted normal. North American patients comprised 62% and 52% of the STRIVE and ENVISION patients respectively.

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Patients with more severe disease ($FEV_1 < 40\%$) were excluded from the trials; therefore, the included studies are applicable to patients with mild to moderate CF. Since children younger than age six were not studied in these trials, there is no information on the efficacy or safety of ivacaftor in this population. The use of inhaled tobramycin therapy was also noted to be lower than expected, which could overestimate the added benefit of ivacaftor to standard care.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following:

- Percent predicted FEV_1 – maximal amount of air forcefully exhaled in one second. The measured volume is converted to a percentage of predicted normal value. Measured at 24 weeks and 48 weeks in the included studies.
- Pulmonary exacerbations – defined as treatment with new or changed antibiotic therapy for any of four or more sinopulmonary signs and symptoms.
- Revised Cystic Fibrosis Questionnaire – validated health-related, quality of life measure for CF that includes three modules: quality of life, symptoms, and health perception. Each scale yields a standardized score from 0 to 100, with higher scores indicating better quality of life.
- Changes in body weight.
- Total adverse events, serious adverse events, and withdrawals due to adverse events.

The primary efficacy outcome for each study was the absolute change in the percent predicted FEV_1 through 24 weeks. The absolute change from baseline in the percent predicted FEV_1 through week 48 was a secondary outcome.

Results

Efficacy

- Compared with placebo, patients treated with ivacaftor demonstrated statistically significant improvements in the percent predicted FEV_1 in both STRIVE (mean difference [MD] 10.6% [95% confidence interval (CI), 8.6 to 12.6]) and ENVISION (MD [95% CI], 12.5% [6.6 to 18.3]) through 24 weeks. The improvement in the percent predicted FEV_1 was sustained through 48 weeks in both STRIVE (MD [95% CI], 10.5% [8.5 to 12.5]) and ENVISION (MD [95% CI], 10.0% [4.5 to 15.5]).
- The improvement in FEV_1 was consistent across subgroups based on baseline FEV_1 and age; however, statistical significance of subgroup findings was achieved only in STRIVE.
- Both pulmonary exacerbations and total hospitalization rates, during 48 weeks, were statistically significantly lower for patients treated with ivacaftor compared with placebo in STRIVE. Pulmonary exacerbations and hospitalization rates were not evaluated in ENVISION due to the small number of patients experiencing events.
- Statistically significant and clinically important improvements in respiratory symptoms, as measured by the Cystic Fibrosis Questionnaire – Revised were reported for ivacaftor compared with placebo, at both 24 and 48 weeks in STRIVE. In ENVISION, respiratory symptom improvement was not statistically significant as reported in the child version of the questionnaire, but it was both statistically and clinically significant at 24 weeks as reported in the parent/caregiver version of the questionnaire.

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- Patients treated with ivacaftor demonstrated an increase in body weight compared with placebo at 24 weeks (MD [95% CI], 2.8 kg [1.8 to 3.7]) and at 48 weeks (MD [95% CI], 2.7 kg [1.3 to 4.1]) in STRIVE. Similar results were observed in ENVISION, where the mean body weight of patients treated with ivacaftor increased by 1.9 kg (95% CI: 0.9 to 2.9) at 24 weeks and 2.8 kg (95% CI: 1.3 to 4.2) at 48 weeks, relative to placebo.

Harms (Safety and Tolerability)

- Most patients in the included trials, whether randomized to ivacaftor or placebo, experienced at least one adverse event (98.8% versus 100.0% in STRIVE; 100.0% versus 96.2% in ENVISION, respectively). Adverse events that occurred numerically more often in the ivacaftor groups compared with placebo in both STRIVE and ENVISION were headache (22.9% versus 16.7% in STRIVE; 26.9% versus 15.4% in ENVISION) and upper respiratory tract infection (22.9% versus 15.4% in STRIVE; 23.1% versus 7.7% in ENVISION).
- Serious adverse events were reported less frequently in the ivacaftor group compared with the placebo group in STRIVE (24.1% versus 42.3%). The proportion of patients with at least one serious adverse event was similar for both groups in ENVISION (19.2% versus 23.1%). Pulmonary exacerbations were the most commonly reported serious adverse event in either trial.
- Withdrawals due to adverse events were infrequent in the included trials. The proportion of patients who withdrew as a result of adverse events was numerically lower in the ivacaftor treatment group compared with the placebo groups (1.2% versus 5.1% in STRIVE and 0% versus 3.8% in ENVISION).

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing ivacaftor plus standard of care (SoC) with SoC alone – where SoC could consist of tobramycin, pancrelipase, dornase alfa, azithromycin, or salbutamol. The economic submission was based on an individual patient model where patients are followed during their lifetime (up to age 80). Survival was assumed to be a function of age, gender, percent predicted FEV₁, pancreatic sufficiency, weight-for-age, exacerbations, whether the patient had diabetes, and whether the patient was infected with *Staphylococcus aureus* or *Burkholderia cepacia*. Treatment with ivacaftor was assumed to impact the percent predicted FEV₁, weight-for-age, and exacerbations. The manufacturer assumed ivacaftor was associated with a ~10% improvement in FEV₁ and this improvement would be maintained during the patient's lifetime. For patients not receiving ivacaftor, the percent predicted FEV₁ was assumed to decrease by either 1% or 2% per year. In addition, patients receiving ivacaftor were assumed to gain weight and experience a reduced number of exacerbations. The manufacturer reported that ivacaftor plus SoC led to an increase of 4.6 life-years and 4.6 QALYs at an incremental cost of \$3.2 million, when compared with standard care, for incremental cost per life-year gained and QALY gained were both ~ \$700,000.

A number of limitations with the economic evaluation were noted:

- Results were based on median rather than mean values.
- The assumption that the percent predicted FEV₁ beyond 48 weeks is maintained with ivacaftor may bias the results in favour ivacaftor.
- No justification was provided for assumptions relating to patient's decline in FEV₁ and weight.
- The assumption that the cost of ivacaftor will be reduced by 90% in 2026 is not appropriate.

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- A lack of transparency regarding the derivation of costs and utilities used in the model was noted.

CDR re-analysis based on alternate assumptions (use of means rather than medians; same annual decline in the percent predicted FEV₁ for ivacaftor and SoC; more conservative cost estimates; no reduced price of ivacaftor after 2026; and, a decline in utility of 0.001 per year) resulted in an incremental cost per QALY of ~\$2 million for ivacaftor plus SoC compared with SoC alone. Cost per QALY estimate could exceed \$9 million, using all the above revised assumptions, with a waning of treatment effects during a 10-year time horizon.

The daily cost of ivacaftor is \$840 (150 mg twice daily) or \$306,600 annually.

Other Discussion Points:

The Committee noted the following:

- STRIVE and ENVISION restricted enrolment to patients with mild to moderate CF; however, the Health Canada indication does not restrict the use of ivacaftor by individuals with mild to moderate severity CF. Comparative clinical trials evaluating the effectiveness of ivacaftor in individuals with severe CF have not been reported.
- The increase in body weight reported in STRIVE and ENVISION likely represents a clinically significant improvement for many CF patients.
- Extension trials suggest that the benefits and safety of ivacaftor are maintained for at least 96 weeks; however, controlled efficacy studies are only available for up to 48 weeks.
- Patient groups indicated that a substantial amount of time is spent on activities related to airway clearance to maintain lung health in individuals with CF. Patients enrolled in STRIVE and ENVISION continued their existing physiotherapy during the studies; therefore, it is unclear if ivacaftor has the potential to reduce the need for other CF therapies.
- Patients with CF in Canada are routinely tested for the G551D mutation; therefore, the availability of ivacaftor should not result in additional testing or re-testing for patients.
- Inhaled hypertonic saline use was not permitted in the STRIVE and ENVISION trials. Although this therapy is not used in all patients, its exclusion from the trials limits the generalizability of findings to all relevant CF patients.
- In STRIVE, the difference between ivacaftor and placebo for the respiratory domain of the Cystic Fibrosis Questionnaire – Revised exceeded the minimal clinically important difference for patients with stable disease.

Research Gaps:

The Committee noted that there is an absence of evidence regarding the following:

- There were no RCTs that evaluated the efficacy of ivacaftor in patients with severe CF or patients with CF who are younger than six years of age.
- There were no RCTs that were designed to examine the effect of ivacaftor treatment on any of the following end points: long-term disease progression (e.g., rate of decline in lung function); the need for lung transplantation; ability to discontinue existing therapies; or mortality.

CDEC Members:

Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Julia Lowe, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

February 20, 2013 Meeting**Regrets:**

Two CDEC members did not attend.

Conflicts of Interest:

One CDEC member did not participate in the vote due to a conflict of interest.

About this Document:

CDEC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC made its recommendation. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The Final CDEC Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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