



CDEC FINAL RECOMMENDATION

IVACAFTOR

(Kalydeco — Vertex Pharmaceuticals Inc.)

Indication: Cystic fibrosis with G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or G970R mutation

Note: The Canadian Drug Expert Committee (CDEC) previously reviewed ivacaftor for the treatment of cystic fibrosis (CF) with G551D mutation (see [CDEC Final Recommendation](#), March 22, 2013). The current CDEC recommendation is for the new treatment indication of CF in patients age six years and older who have one of the following mutations in the CF transmembrane conductance regulator (CFTR) gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or G970R.

Recommendation:

CDEC recommends that ivacaftor be listed 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, if the following condition is met:

Condition

- Substantial reduction in price: ivacaftor will not be considered cost-effective without a substantial reduction in the submitted price.

Reasons for the Recommendation:

1. In two double-blind randomized controlled trials (RCTs) (ENVISION and STRIVE) and one double-blind randomized crossover trial (KONNECTION), ivacaftor was superior to placebo for improvement in per cent predicted forced expiratory volume in one second (FEV₁) as well as multiple secondary outcomes including health-related quality of life, body mass index, weight gain, and sweat chloride levels. 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 CADTH Common Drug Review (CDR) estimated that the incremental cost per quality-adjusted life-year (QALY) for ivacaftor is approximately \$850,932, and could be as high as \$1.2 million per QALY; therefore, ivacaftor is not considered to be cost-effective at the submitted price.
3. Patient groups identified an unmet need in the treatment of CF that CDEC concluded could potentially be met by ivacaftor.

Of Note:

1. CDEC 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, CDEC concluded that it is important to develop appropriate discontinuation criteria for non-responders. CDEC noted that discontinuation criteria based on sweat chloride levels are currently being used by the CDR-participating drug plans and the National Institute for Health and Care Excellence in the United Kingdom; however, the clinical expert consulted by CDR indicated that there is uncertainty regarding the utility and validity of these criteria.
2. CDEC 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, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or G970R mutation in the CFTR gene.

Ivacaftor is available as 150 mg oral tablets and the recommended dose for adults and children six years of age and older is 150 mg every 12 hours with fat-containing food. The product monograph states that the efficacy and safety of ivacaftor have not been evaluated in patients younger than six years of age. The dose should be reduced to 150 mg once daily for patients with moderate hepatic impairment. Ivacaftor should be used with caution in patients with severe hepatic impairment at a starting dose of 150 mg every other day and modified according to tolerability and clinical response. The dose of ivacaftor should be reduced to 150 mg twice per week when co-administered with strong CYP3A inhibitors and 150 mg once daily when co-administered with moderate CYP3A inhibitors.

Summary of CDEC Considerations:

CDEC 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 individuals living with CF and their caregivers.

Patient Input Information

The following is a summary of information provided by one patient group that responded to the CDR call for patient input for this review.

- Currently, there is no cure for CF. A considerable amount of time (two to seven hours per day) is spent on airway clearance activities to maintain lung health in a CF patient. In some situations when a patient's condition worsens, usually as a result of an infection, he or she may be required to stay in hospital for at least two weeks.
- Patients with CF and their caregivers can experience a substantial impact emotionally, psychologically, physically, and financially as a result of the disease.
- Ivacaftor is an oral targeted therapy that treats the underlying cause of CF. A number of patients with CF and their caregivers expect that ivacaftor will improve lung function and

weight gain, decrease time spent for treatment and, in many cases, help avoid the need for lung transplantation.

Clinical Trials

The CDR systematic review included three double-blind RCTs (STRIVE, ENVISION, and KONNECTION). STRIVE (N = 167) and ENVISION (N = 52) were similar 48-week, parallel-group, placebo-controlled RCTs comparing ivacaftor 150 mg every 12 hours with placebo added to a stable regimen of CF background therapies in patients with a G551D mutation on at least one allele. Patients receiving inhaled hypertonic saline (a mucolytic drug) had to discontinue that treatment before study enrolment. In STRIVE adolescent and adult patients with CF who were at least 12 years old and had an FEV₁ score of 40% to 70% (inclusive) of the predicted normal were studied; while within the ENVISION trial pediatric patients with CF who were 6 to 11 years old and had an FEV₁ score of 40% to 105% (inclusive) of the predicted normal were studied. KONNECTION (N = 39) was a two-period crossover trial of 20 to 24 weeks duration. Participants were randomized to receive ivacaftor or placebo for a period of 8 weeks, then underwent a 4 to 8 week washout period, before crossing over to receive the other treatment. The study enrolled CF patients aged six years or older without a G551D mutation and with one of the following mutations in at least one allele: G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or G970R. In all three double-blind RCTs, patients were recommended to continue with their stable medications for CF, with the exception of hypertonic saline, which was not permitted during the trials.

Outcomes

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

- Per cent predicted FEV₁ — the maximal amount of air forcefully exhaled in one second. The measured volume is converted to a percentage of predicted normal value.
- 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 (CFQ-R) — a 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 from baseline in body weight.
- Changes from baseline sweat chloride levels.
- Total adverse events, serious adverse events, and withdrawals due to adverse events.

Absolute change from baseline in per cent predicted FEV₁ was the primary end point in all three trials.

Efficacy

- Ivacaftor was statistically superior to placebo for change from baseline in per cent predicted FEV₁ in all three studies:
 - KONNECTION: 10.67 (95% CI, 7.26 to 14.10) at 8 weeks ($P < 0.0001$).
 - STRIVE: 10.58 (95% CI, 8.57 to 12.59) at 24 weeks ($P < 0.0001$) and 10.50 (95% CI, 8.50 to 12.50) at 48 weeks ($P < 0.0001$).
 - ENVISION: 12.45 (95% CI, 6.56 to 18.34) at 24 weeks ($P < 0.0001$) and 9.99 (95% CI, 4.52 to 15.46) at 48 weeks ($P = 0.0006$).

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- The between-treatment differences were also statistically significant for subgroups based on FEV₁ status and age in KONNECTION and STRIVE, [REDACTED].
- Compared with placebo, the rate of pulmonary exacerbations was statistically significantly lower for ivacaftor-treated patients at 24 weeks (rate ratio 0.38 [95% CI, 0.22 to 0.64]) and at 48 weeks (rate ratio 0.43 [95% CI, 0.27 to 0.68]) in STRIVE. [REDACTED].
- The improvements in CFQ-R respiratory domain were statistically significant in KONNECTION and STRIVE; however, only the parent/caregiver response at 24 weeks was statistically significant in ENVISION. The mean differences were reported as follows:
 - KONNECTION: 9.63 (95% CI, 4.53 to 14.73) at 8 weeks ($P = 0.0004$).
 - STRIVE: 8.08 (95% CI, 4.73 to 11.42) at 24 weeks ($P < 0.0001$) and 8.60 (95% CI, 5.32 to 11.87) at 48 weeks ($P < 0.0001$).
 - ENVISION: 6.06 (95% CI, -1.41 to 13.53) at 24 weeks ($P = 0.1092$) and 5.06 (95% CI, -1.64 to 11.76) at 48 weeks ($P = 0.1354$) for patient responses, and 5.93 (95% CI, 0.50 to 11.36) at 24 weeks ($P = 0.0330$) and 4.88 (95% CI, -0.44 to 10.20) at 48 weeks ($P = 0.0713$) for parent/caregiver responses.
- Compared with placebo, ivacaftor produced statistically significantly greater gains in body weight in all three trials. Mean differences were reported as follows:
 - KONNECTION: 1.67 kg (95% CI, 0.71 to 2.63)
 - STRIVE: 2.71 kg (95% CI, 1.33 to 4.03)
 - ENVISION: 2.77 kg (95% CI, 1.31 to 4.23).
- Compared with placebo, ivacaftor produced a statistically significant greater decrease in sweat chloride levels in all three trials. Mean differences were reported as follows:
 - KONNECTION: -49.15 mmol/L (95% CI, -56.86 to -41.43)
 - STRIVE: -48.07 mmol/L (95% CI, -51.47 to -44.68)
 - ENVISION: -53.47 mmol/L (95% CI, -60.92 to -46.02).

Harms (Safety and Tolerability)

- Most patients in the included trials, whether randomized to ivacaftor or placebo, experienced at least one adverse event
 - KONNECTION: 73.7% in the ivacaftor group and 83.8% in the placebo group.
 - STRIVE: 98.8% in the ivacaftor group and 100.0% in the placebo group.
 - ENVISION: 100.0% in the ivacaftor group and 96.2% in the placebo group.
- In all three trials, serious adverse events were numerically less frequent for ivacaftor compared with placebo
 - KONNECTION: 10.5% in the ivacaftor group and 21.6% in the placebo group.
 - STRIVE: 24.1% versus 42.3% in the placebo group.
 - ENVISION: 19.2% versus 23.1% in the placebo group.
- CF lung exacerbation was the most commonly encountered serious adverse event.
- Withdrawals due to adverse events were infrequent in all three included trials
 - KONNECTION: 0% in both ivacaftor and placebo groups.
 - STRIVE: 1.2% in the ivacaftor group and 5.1% in the placebo group.
 - ENVISION: 0% in the ivacaftor group and 3.8% in the placebo group.
- In all three trials, the number of adverse events that could signal possible hepatic harms was small overall, with no clear pattern emerging between ivacaftor and placebo groups.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing ivacaftor plus standard of care (SoC) with SoC alone for the treatment of CF. SoC consisted of, but was not limited to, respiratory, nutritional, and rehabilitative support such as mucolytic drugs, osmotic drugs, antibiotics, bronchodilators, pancreatic enzymes, dietetic therapy, and chest physiotherapy.

The analysis was based on patient level simulation where patients are followed during their lifetime (up to age 80), with four health states based on patients' lung function, and one absorbing state (death). Efficacy and transition probabilities were derived from patient level data from clinical trials (KONNECTION, STRIVE, ENVISION, and PERSIST). 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 QALYs for each individual patient were estimated based on assumptions relating to the relationship with FEV₁. The manufacturer reported that the incremental cost per QALY for ivacaftor plus SoC was \$356,349 compared with SoC alone.

CDR identified the following key limitations with the manufacturer's economic submission:

- 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. 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 uncertain. In a conservative analysis, where CDR assumed that the same decline in FEV₁ for ivacaftor and SoC would occur over time, the incremental cost-utility ratio was \$1.2 million per QALY.
- The model estimated utilities based on a small sample of directors of CF centres (N = 7) in Australia.
- The manufacturer assumed that the cost of ivacaftor would be reduced by 82% after 12.5 years (patent expiry). It is uncertain whether a generic alternative will be available following the expiry of the patent.

CDR re-analysis considering: trial-based utility measures; no price reduction after anticipated patent expiry for ivacaftor; CF costs not being a function of FEV₁; and patients consuming 93% of the full dose of ivacaftor on an annual basis instead of █%, resulted in an incremental cost-utility ratio for ivacaftor compared with SoC of \$850,932 per QALY gained.

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

Other Discussion Points:

- Ivacaftor is approved for use in the treatment of nine non-G551D mutations; however, there are limited data regarding any one of those multiple mutations.
- Patients with severe or very severe CF (based on FEV₁ < 40% predicted normal) were not enrolled in STRIVE, ENVISION, or KONNECTION; however, it is likely that such patients would receive treatment with ivacaftor in clinical practice.
- STRIVE, ENVISION, and KONNECTION were insufficient in size and duration to examine survival as an end point.

- The generalizability of study results is limited to patients with mild-to-moderately severe CF who are at least six years old. It is unknown to what extent these findings apply to younger patients or to those with CF that is more severe.
- There is no published information regarding the minimal clinically important difference in FEV₁ in CF; however, the clinical expert consulted for this review indicated that the magnitude of improvement reported in the included studies should be considered clinically meaningful.
- The improvements in patient-reported respiratory symptoms achieved with ivacaftor, as measured by the CFQ-R in KONNECTION and STRIVE, exceeded the minimal clinically important difference, which is considered to be 4 points for patients with stable disease and 8.5 points for patients with exacerbation.
- Patients with CF in the included clinical trials demonstrated gains in body weight that are likely clinically significant.

Research Gaps:

- There are no data regarding the use of ivacaftor in children with CF who are younger than six years of age.
- All three studies excluded patients with abnormal liver function, abnormal renal function, or those using inhaled hypertonic saline.

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

November 19, 2014 Meeting

Regrets:

None

Conflicts of Interest:

None

About This Document:

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The manufacturer has reviewed this document and has requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

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