CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

IVACAFTOR
(Kalydeco — Vertex Pharmaceuticals Inc.)
Indication: Cystic Fibrosis With R117H Mutation

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that ivacaftor be listed for the treatment of cystic fibrosis (CF) in patients aged 18 and older with the R117H mutation, if the following clinical criteria and condition are met:

Clinical criteria
- Confirmed diagnosis of CF with chronic sinopulmonary disease
- Discontinuation criteria should be developed for non-responders in consultation with physicians who have expertise in the treatment of CF.

Condition
- Substantial reduction in price.

Reasons for the Recommendation:
1. In one double-blind randomized controlled trial (RCT) (KONDUCT; N = 69), ivacaftor was superior to placebo for improvement in per cent predicted forced expiratory volume in one second ($ppFEV_1$), as well as secondary outcomes such as respiratory symptoms and sweat chloride levels.
2. At the submitted price of $306,600 per year, the incremental cost per quality-adjusted life-year (QALY) for ivacaftor is approximately $926,776 and could be as high as $4.6 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 could potentially be met by ivacaftor.

Of Note:
- The clinical expert consulted by the CADTH Common Drug Review (CDR) noted that chronic sinopulmonary disease should include the following: chronic cough and sputum production; persistent chest radiograph abnormalities (e.g., bronchiectasis); and persistent infection with CF pathogens (e.g., *Staphylococcus aureus, Haemophilus influenzae*, and *Pseudomonas aeruginosa*).

- The clinical course for individuals with the R117H mutation is highly variable; thus, it is difficult to identify which patients will develop progressive pulmonary disease and benefit most from treatment with ivacaftor.

Background:
Ivacaftor is a cystic fibrosis transmembrane conductance regulator (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 aged 18 years and older who have a R117H mutation in the CFTR gene.

Ivacaftor is available as 150 mg oral tablets and the recommended dose in adults is 150 mg every 12 hours with fat-containing food. 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 and pivotal studies of ivacaftor in patients with the R117H mutation, 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
One patient group, Cystic Fibrosis Canada, responded to the CDR call for patient input. Information was gathered through feedback from CF patients and their families with the assistance of CF clinics and through social media. The following is a summary of information that was provided:

- 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 requires hospitalization.
- 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 orally administered therapy that treats the underlying cause of CF. All of the patients with CF and the caregivers who contributed to the submission expect that ivacaftor will improve lung function and weight gain and, in many cases, help avoid or delay the need for lung transplantation.

Clinical Trials
The CDR systematic review included one double-blind RCT (KONDUCT). The trial compared 24 weeks of ivacaftor (150 mg every 12 hours) versus placebo (added to a stable regimen of CF background therapies) in patients aged six years or older with confirmed CF and the R117H mutation on at least one CFTR allele (N = 69, including 50 adults). For patients aged six to 11 years, the study enrolled those with a baseline ppFEV$_1$ ≥ 40 to ≤ 105, and for those aged ≥ 12 years, ppFEV$_1$ ≥ 40 to ≤ 90 was required.

The Committee focused on the data from the adult subgroup, given that the Health Canada indication is for use in adults.

Outcomes

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

- $ppFEV_1$ — the maximal amount of air forcefully exhaled in one second. The measured volume is converted to a percentage of predicted normal value. The minimal clinically important difference (MCID) for change in FEV_1 in CF patients is unknown
- Pulmonary exacerbations — defined as treatment with new or changed antibiotic therapy for any of four or more sinopulmonary signs and symptoms
- Respiratory symptom domain of the 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. The respiratory domain yields a standardized score from 0 to 100, with higher scores indicating better quality of life. The MCID is considered to be 4.0 points for patients with stable disease and 8.5 points for patients with an exacerbation
- Changes from baseline in body mass index
- Changes from baseline sweat chloride levels
- Total adverse events, serious adverse events, and withdrawals due to adverse events.

The absolute change from baseline in $ppFEV_1$ was the primary end point in the RCT.

Efficacy

- Ivacaftor was statistically superior to placebo for change from baseline in $ppFEV_1$ in the adult subgroup of patients. The mean differences for ivacaftor versus placebo were:
  - Adult subgroup: 5.0% (95% confidence interval [CI], 1.1 to 8.8); $P = 0.01$
  - Full population: 2.1% (95% CI, −1.1 to 5.4); $P = 0.20$.
- The improvements in the CFQ-R respiratory domain were statistically and clinically significant for ivacaftor versus placebo in both the full population and the subgroup of adult patients. The mean differences for ivacaftor versus placebo were:
  - Adult subgroup: 12.6 (95% CI, 5.0 to 20.3); $P = 0.002$
  - Full population: 8.4 (95% CI, 2.2 to 14.6); $P = 0.0091$.
- Compared with placebo, ivacaftor produced a statistically significantly greater decrease in sweat chloride levels in both the full population and the subgroup of adult patients. The mean differences for ivacaftor versus placebo were:
  - Adult subgroup: −21.9 mmol/L (95% CI, −26.5 to −17.3); $P < 0.0001$
  - Full population: −24.0 mmol/L (95% CI, −28.0 to −19.9); $P < 0.0001$.
- There were no statistically significant differences between ivacaftor and placebo for change from baseline in body mass index:
  - Adult subgroup: 0.3 kg/m^2 (95% CI, −1.9 to 2.5); $P = 0.78$
  - Full population: 0.3 kg/m^2 (95% CI, −1.6 to 2.1); $P = 0.78$.
- There were no statistically significant differences between ivacaftor and placebo for time to first exacerbation or the incidence of exacerbations.

Harms (Safety and Tolerability)

- The majority of patients in the KONDUCT trial experienced at least one adverse event. Infective pulmonary exacerbations and cough were the most frequently reported events in

both treatment groups for the overall study population. Numerically more patients who received ivacaftor reported oropharyngeal pain (15% versus 6%), nasal congestion (15% versus 6%), wheezing (12% versus 3%), or abdominal pain (12% versus 0%) compared with placebo. The proportions of patients who experienced at least one adverse event were:
    - Full population: ivacaftor (94%) and placebo (100%)
    - Adult subgroup: ivacaftor (96%) and placebo (100%).
- Serious adverse events were numerically less frequent for ivacaftor than for placebo, although the number of patients was low in both groups. Infective lung exacerbation was the most common serious adverse event. The proportions of patients who experienced at least one serious adverse event were:
    - Full population: ivacaftor (12%) and placebo (17%)
    - Adult subgroup: ivacaftor (8%) and placebo (23%).
- No patients in the KONDUCT trial discontinued treatment due to adverse events.
- There was no clear pattern of elevated liver function tests or other liver-related adverse events noted in the KONDUCT trial.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis from a Canadian public payer perspective, comparing ivacaftor plus standard of care (SOC) (defined as, but not limited to, respiratory, nutritional, and rehabilitative support such as mucolytics, osmotic agents, antibiotics, bronchodilation, pancreatic enzymes, diet therapy, and chest physiotherapy) with SOC alone for the treatment of patients with CF, over a lifetime time horizon (80 years). The analysis was based on a Markov model and patient-level simulations. Patient profiles were used based on 50 patients from the KONDUCT trial aged 18 or older. Patient characteristics that were considered included age, gender, FEV_1, pancreatic insufficiency, and weight-for-age. These were combined with population data on the age-specific proportion of patients who have diabetes and are *Staphylococcus aureus*–infected or *Burkholderia cenocepacia* complex–infected. FEV_1 was modelled based on treatment and time. These data, derived from the use of a published survival model, were then used to predict the exacerbation rates with and without ivacaftor and the proportion of patients who were alive or dead. Results were reported in terms of the total cost, QALYs, and life expectancy. No probabilistic analyses were conducted.

CDR noted the following limitations with the manufacturer's economic evaluation:

- The long-term comparative efficacy of ivacaftor plus SOC versus SOC alone is uncertain. The manufacturer assumed that patients on SOC alone would have a continuous annual decline in lung function. This is in contrast with the assumptions that patients receiving ivacaftor plus SOC would have an immediate improvement in FEV_1 and the difference between ivacaftor plus and SOC alone would be exacerbated over time due to an assumed reduced annual decline in lung function with ivacaftor.
- There is uncertainty regarding the utility estimates. The manufacturer assumed a relationship between utility values, FEV_1, and the number of exacerbations based on information extracted from an abstract.
- Inappropriate estimates regarding the cost of ivacaftor were used in the model. 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 reduced the cost of treatment, although no related reduction in efficacy was assumed.

- The effect of ivacaftor plus SOC on health care costs has not been validated. 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.

The manufacturer reported in the base case that the incremental cost per QALY for ivacaftor plus SOC compared with SOC is $926,776 and the incremental cost per life-year gained is $1.4 million. CDR reanalysis accounting for different assumptions regarding the decline in FEV_1, price reduction after patent expiry, full adherence, independent utility effect from ivacaftor, and different CF costs resulted in an incremental cost of $4.6 million per QALY gained for ivacaftor plus SOC compared with SOC.

At the submitted list price of $420 per 150 mg tablet, the daily cost of ivacaftor is $840 or $306,600 annually.

Other Discussion Points:
CDEC noted the following:

- The clinical course for individuals with the R117H mutation is highly variable. Thus, it is difficult to identify which patients will develop progressive pulmonary disease and benefit most from treatment with ivacaftor.
- There is no published information regarding the MCID in FEV_1 in CF; however, the clinical expert consulted for this review indicated that the magnitude of improvement reported in the adult subgroup of the KONDUCT trial can be considered clinically meaningful.
- Ivacaftor was studied as an add-on to a stable regimen of CF medications and there is no evidence to suggest that ivacaftor may reduce the overall burden of treatment, which patients reported as an important consideration.
- The Health Canada–approved indication for the R117H mutation is limited to patients aged 18 and older. It is likely that there will be interest from physicians, patients, and caregivers in accessing treatment with ivacaftor for those who are younger than 18 years.

Research Gaps:
CDEC noted that there is insufficient evidence regarding the following:

- 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); need for lung transplantation; ability to discontinue existing therapies; or mortality.
- The treatment effects observed in the KONDUCT trial may be generalizable only to adult CF patients with moderately severe pulmonary disease. It is unclear whether ivacaftor would benefit adult patients with preserved pulmonary function, as no data were available for those with a $ppFEV_1$ >90%.
- Patients with severe pulmonary disease at baseline ($ppFEV_1$ < 40%) were excluded from the KONDUCT trial.

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, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

October 21, 2015 Meeting
Regrets:

None.

Conflicts of Interest:

None.

About This Document:

CDEC provides formulary listing recommendations or advice to CDR-participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

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