CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

ISAVUCONAZOLE (CRESEMBA — AVIR PHARMA INC.)

Indication: For use in adults for the treatment of:

- invasive aspergillosis
- invasive mucormycosis.

RECOMMENDATION

The CADTH Canadian Drug Expert Committee (CDEC) recommends that isavuconazole (ISA) be reimbursed in adult patients for the treatment of invasive aspergillosis (IA) and invasive mucormycosis (IM) only if the following condition is met:

Condition for Reimbursement

Pricing Condition

1. Reduction in price.

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Reasons for the Recommendation

1. In one phase III, double-blind randomized controlled trial (RCT) in adults with invasive fungal disease (IFD) caused by aspergillus species or other filamentous fungi (the SECURE study, N = 527), ISA was statistically noninferior to voriconazole (VRC) with respect to all-cause mortality through day 42 and the two treatments resulted in similar overall treatment response at the end of treatment. Results for all-cause mortality in the per-protocol (PP) population, as well as the modified and mycological intention-to-treat (ITT) populations, through day 42 were consistent with the primary analysis, as were the results through day 84 in these four study populations.

2. In the SECURE study, the percentage of patients reporting treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) was similar for the ISA and VRC treatment groups. The percentage of patients who withdrew due to an adverse event (WDAE) was numerically lower in the ISA group compared with the VRC group.

3. ISA is not considered to be cost-effective for treating patients with suspected IA at the manufacturer's submitted price. Based on a CADTH Common Drug Review (CDR) reanalysis, ISA was associated with an incremental cost-utility ratio (ICUR) of $73,036 per quality-adjusted life-year (QALY) compared with VRC; however, there is considerable uncertainty in this estimate. A minimum 20% reduction in the price of ISA is required for ISA to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY.

Discussion Points

- IA is more commonly encountered in clinical practice than IM. VRC remains an appropriate choice for initial treatment of IFD in many situations.
- The evidence available for the use of ISA for the treatment of IM is limited to a small subgroup of patients (N = 37) from the single-arm VITAL study. Among a smaller subgroup of patients in the VITAL study who received ISA as primary therapy for IM (N = 21), the all-cause mortality rate was similar to that observed in a historical cohort of patients receiving amphotericin B (AmB) for the treatment of IM; 33% versus 39%, respectively. It was noted that untreated IM is associated with a high mortality rate.
- ISA is the only oral antifungal with a Health Canada indication for the treatment of IM, although the committee noted that posaconazole is used for the treatment of IM in clinical practice.

Background

ISA has a Health Canada indication for use in adult patients for the treatment of IA and IM. ISA is an azole antifungal agent. It is available as an oral dosage form (capsules, 100 mg) and IV dosage form (powder for solution for IV infusion, 200 mg). The Health Canada–recommended dosage for the treatment of IA or IM is 200 mg (IV or oral) every eight hours for 48 hours (six doses) followed by a maintenance dose of 200 mg (IV or oral) once daily.

Summary of Evidence Considered by CDEC

The committee considered the following information prepared by CDR: a systematic review of ISA that included phase III and IV RCTs and pivotal trials provided in the manufacturer's submission to CDR and Health Canada, an indirect treatment comparison (network meta-analysis [NMA]), and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from a clinical expert with experience in treating patients with IA and IM.

Summary of Patient Input

No patient input was received for this submission.

Clinical Trials

The systematic review included two clinical trials. The SECURE study was a double-blind, multi-centre, noninferiority RCT, while the VITAL study was a single-arm trial. Both trials were conducted in multiple nations, including Canada, North and South America, Europe, Africa, Asia, and Pacific regions. The SECURE study (N = 527) enrolled adults with proven, probable, or possible IFDs caused by aspergillus species or other filamentous fungi. Patients were randomized (1:1) to ISA (200 mg IV three times a day on days 1 and 2, then either IV or orally once daily) or VRC (6 mg/kg IV twice daily on day 1, 4 mg/kg IV twice daily on day 2, then 4 mg/kg IV twice daily or 200 mg orally twice daily from day 3 onward). The maximum treatment duration was 84 days. The overall withdrawal was 54% in the SECURE study.

In the SECURE study, the following population analysis sets were used:

- The ITT population consisted of all randomized patients who received at least one dose of the study drug.
- The modified ITT population consisted of ITT patients who had proven or probable IFD.
- The mycological ITT population consisted of modified ITT patients with proven or probable IA based on cytology, histology, culture, or Galactomannan criteria.
- The PP population was a subset of ITT patients who did not deviate from the protocol.

The VITAL study (N = 146) assessed the efficacy and safety of IV and oral formulations of ISA (the same dosage used as in the SECURE study) in the treatment of proven or probable IM (n = 37) or proven, probable, or possible IA (n = 24). The maximum treatment duration was 180 days. The overall withdrawal was 64.9% in the IM group and 58.3% in the IA group, respectively, in the VITAL study.

Limitations of the SECURE study include the high discontinuation rate in the ISA and VRC groups (54.3% and 53.5%, respectively). It was uncertain how the high discontinuation rate affects the validity of the outcomes reported in the SECURE study. In addition, no comparative efficacy data were available for patients with prior treatment failure. Whether the comparative efficacy of ISA versus VRC observed in the SECURE study can be generalized to those patients with prior treatment failure is uncertain. The generalizability of the findings from the SECURE study could be also limited because of the exclusion of patients with AIDS, abnormal liver function, and those receiving antifungal prophylaxis with a mould-active azole. Limitations of the VITAL study include the single-arm design (lack of a comparator group) and the small sample size for the IM and IA subpopulations (n = 37 and n = 24, respectively).

Outcomes

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

- survival status (i.e., all-cause mortality)
- overall response (a composite of the clinical, mycological, and radiological responses)
- health care resource utilization (days in hospital)
- TEAEs, SAEs, notable adverse events (AEs), and WDAEs.

The primary outcome in the SECURE study was all-cause mortality through day 42 for the ITT population. The primary outcome in the VITAL study was overall response at day 42.

Efficacy

For Invasive Fungal Disease or Invasive Aspergillosis

For patients with proven, probably, or possible IFD: All-cause mortality through day 42 was reported in 18.6% of patients in the ISA group and 20.2% in the VRC group. The results demonstrated that ISA was noninferior to VRC in terms of all-cause mortality based on a ≤ 10% pre-specified noninferior margin (adjusted between treatment group difference: –1.0%; 95% confidence interval [CI], –7.8 to 5.7). Results for the PP population through day 42 were consistent with the primary analysis. All-cause mortality through day 84 was reported in 29.1% and 31.0% of patients in the ISA and VRC treatment groups, respectively (adjusted between-group difference: –1.4%; 95% CI, –9.2 to 6.3).

The overall treatment response (a composite of clinical, mycological, and radiological response) at the end of treatment in the ISA group was similar to that observed in the VRC group, despite numerically more patients in the VRC group reporting treatment response than in the ISA group (39% in the ISA group versus 41% in the VRC group).

For patients with proven, probable IFDs: All-cause mortality through day 42 was reported in 19.6% of patients in the ISA group and 23.3% in the VRC group (adjusted between group treatment difference, −2.6; 95% CI, −12.2 to 6.9). The overall treatment response at the end of treatment in the ISA group was similar to that observed in the VRC group, despite numerically more patients experiencing overall treatment response in the VRC group than in the ISA group (35.0% for ISA versus 36.4% for VRC) (adjusted between treatment group difference, 1.6; 95% CI, –9.4 to 12.6).

For patients with proven, probable IA: All-cause mortality through day 42 was reported in 18.7% of patients in the ISA group and 22.2% of patients in the VRC group (adjusted between group treatment difference, –2.7; 95% CI, –12.9 to 7.5). It also demonstrated a similar overall treatment response at the end of treatment in the ISA group compared with that reported in the VRC group, although numerically more patients in the VRC group reported treatment response than in the ISA group (35% for ISA versus 38.9% for VRC, respectively).

For patients with proven, probable, or possible IFDs, days in hospital was reportedly similar in both ISA and VRC treatment groups.

For Invasive Mucormycosis

For patients with proven or probable IM: In the VITAL study, the overall all-cause mortality through day 42 and day 84 were 37.8% and 43.2%, respectively. The all-cause mortality was higher than that observed for the IA population in both the VITAL and SECURE studies. Based on the manufacturer's additional analysis, which compared the all-cause mortality of the ISA treatment as the primary therapy for IM in the VITAL study (7/21, 33%) with that of AmB therapy for IM reported in the FungiScope registry database (13/33, 39%), no statistically significant difference was identified between the two groups (*P* = 0.775).

Harms (Safety)

- The trial duration was a maximum of 84 days for the SECURE study and a maximum 180 days for the VITAL study. The harm outcomes were reported at the end of treatment plus four weeks after the last dose treatment.
- SAEs: In the SECURE study, a numerically smaller proportion of patients reported SAEs in the ISA group compared with the VRC group (52.1% versus 57.5%). SAEs that occurred in 5% or more of either of the respective ISA or VRC treatment groups were respiratory failure (5.4% versus 4.6%), septic shock (5.4% versus 3.9%), and febrile neutropenia (5.4% versus 1.9%). In the VITAL study, a total of 61.1% patients reported one or more SAEs. The most common serious TEAE was acute renal failure (5.5%).
- AEs: In the SECURE study, a similar proportion of patients reported overall AEs in the ISA and VRC groups (96.1% versus 98.5%) The most common TEAEs in the respective ISA or VRC treatment groups were nausea (27.6% versus 30.1%), vomiting (24.9% versus 28.2%), diarrhea (23.7% versus 23.2%), pyrexia (22.2% versus 30.1%), constipation (14.0% versus 20.8%), and hypokalemia (17.5% versus 21.6%). In the VITAL study, safety outcomes was reported for all patients (N = 146). One or more AEs were reported by 95.2% patients. The most common AEs were vomiting (24.7%) and nausea (23.3%).
- AEs of special interest: In the SECURE study, ISA demonstrated a numerically better safety profile than VRC in terms of the AEs of special interest, including hepatic impairment (1.6% versus 3.5%, respectively), cardiovascular harms (tachycardia, 4.7% versus 8.7%, respectively), and visual disturbances (1.6% versus 7.3%, respectively).
- WDAEs: In the SECURE study, 14.4% in the ISA group and 22.8% in the VRC group discontinued from the study drug due to AEs.

Indirect Treatment Comparisons

An NMA that assessed the comparative efficacy of ISA versus AmB formulations or VRC in the treatment of patients with IA was identified in the literature by CADTH. The NMA found that the efficacy of ISA in terms of all-cause mortality and overall response in the treatment of patients with IA is similar to VRC or liposomal AmB. However, due to various limitations, particularly the potential methodological and clinical heterogeneity and sparsity of trials, no conclusion on the comparative efficacy of ISA and other available therapies could be credibly drawn.

No NMA evidence was identified to compare ISA with posaconazole, itraconazole, and caspofungin in the treatment of IA. No NMA was identified for the treatment of IM.

Cost and Cost-Effectiveness

ISA can be administered orally or intravenously with a loading dose of 200 mg three times daily for the first two days, followed by a maintenance dose of 200 mg daily. At the manufacturer's submitted price of $400 for a 200 mg vial for IV administration and $78.83 per 100 mg capsule, an eight-week treatment course will cost $24,000 for the IV formulation or $9,640 for the oral capsule. In practice, treatment course length will depend on clinical response, and a combination of IV and oral treatment will likely be used.

The manufacturer submitted a cost-utility analysis comparing ISA with VRC in patients with suspected IA, in which 5.75% had IM. A decision tree analysis was conducted from a Canadian public health care payer perspective over a lifetime horizon (i.e., 17 years). Patients entered the model with suspected IA and initially started on ISA or VRC as first-line treatment. If first-line treatment was discontinued, patients would switch to a second-line treatment. In patients with IA infections, second-line treatment was assumed to be liposomal AmB followed by either oral posaconazole or VRC (50:50 ratio). In patients with suspected IM infections, the second-line treatment was liposomal AmB followed by oral posaconazole. The main clinical inputs to the economic model were all-cause mortality assessed at day 84 and the probability of switching to second-line treatment, informed by or estimated from the SECURE trial for patients with IA and the VITAL trial for patients with IM. Patients who remained alive at day 84 were assumed to stay alive for the rest of the model period (17 years). In the manufacturer's base-case, ISA compared with VRC was associated with an ICUR of $10,154 per QALY gained in treating patients with suspected IA.

CADTH identified several key limitations:

- Those alive at the end of the trial (day 84) were assumed to survive until the end of the model time horizon (17 years), resulting in an overestimation of the survival benefit for ISA.
- The treatment pathway was not consistent with clinical practice. For example, initial treatment for IFDs depends on patient clinical presentation, such that when patients present with symptoms suggestive of an IM infection, they would be initiated on liposomal AmB rather than VRC.
- Clinical evidence for IM was based on a single-arm study (the VITAL trial).
- The baseline utility value for patients without IFD was likely overestimated, while the disutility for IFD (0.11) was likely underestimated.
- The cost of some AEs was likely overestimated, increasing the expected costs associated with VRC.
- Wastage of IV medications was not accounted for, underestimating IV medication costs.

CADTH reanalyses accounted for some of the identified limitations (i.e., survival benefit, utility estimates, cost of AEs, and IV medication wastages) and this resulted in an ICUR of $73,036 per QALY for ISA compared with VRC. Based on a CDR reanalysis, a price reduction of 20% for ISA is required for ISA to achieve an ICUR of $50,000 per QALY. However, there is significant uncertainty associated with the economic results given the limited comparative evidence available for patients with IM and the sensitivity of the results by type of infection. To achieve an 80% probability that ISA would be cost-effective at a willingness-to-pay threshold of $50,000 per QALY, a price reduction of 70% would be required.

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

April 10, 2019 Meeting

Regrets

One CDEC member did not attend.

Conflicts of Interest

None.