Drug Coverage Decision for B.C. PharmaCare

About PharmaCare B.C. PharmaCare is a government-funded drug plan. It helps British Columbians with the cost of eligible prescription drugs and specific medical supplies.

Details of Drug Reviewed

Drug	**isavuconazole**
Brand Name	Cresemba™
Dosage Forms	100 mg capsule and 200 mg/ ml powder for intravenous solution
Manufacturer	AVIR Pharma Inc.
Submission Type	**New Submission**
Use Reviewed	Invasive aspergillosis (IA) and invasive mucormycosis (IM)
Common Drug Review (CDR)	Yes, CDR recommended: **to Reimburse with clinical criteria and/or conditions**. Visit the CDR website for more details: www.cadth.ca/sites/default/files/cdr/complete/SR0586%20Cresemba%20-%20CDEC%20Final%20Recommendation%20May%2017%2C%202019_for%20posting.pdf .
Drug Benefit Council (DBC)	DBC met on June 3, 2019. The DBC considered the following: the final reviews completed by the CDR on May 15, 2019, which included clinical and pharmacoeconomic evidence review material and the recommendations from the Canadian Drug Expert Committee (CDEC). The DBC also considered patient input received by the CDR, Clinical Practice Reviews from two specialists, an Other Drug Agencies Review Recommendations document from the Canadian Agency for Drugs and Technologies in Health (CADTH), and two Budget Impact Assessments. The DBC received no Patient Input Questionnaire responses from patients, caregivers, or Patient Groups.
Drug Coverage Decision	**Limited Coverage Benefit for isavuconazole capsules for the treatment of IM.** Access the isavuconazole capsule criteria from: **www.gov.bc.ca/pharmacarespecialauthority** **The IV formulation and IA indication is a non-benefit.**
Date	February 23, 2021

Reasons	**Drug coverage decision is consistent with the DBC recommendation** • Isavuconazole is the only oral antifungal with a Health Canada indication for the treatment of invasive mucormycosis. • The all-cause mortality rate in IM patients treated with isavuconazole was similar to that observed in a historical cohort of patients receiving amphotericin B for the treatment of; 33% versus 39%, respectively (P=0.775). • The Ministry participated in the pan-Canadian Pharmaceutical Alliance negotiations with the manufacturer which were able to address the concerns identified by the CDEC to some extent, with respect to the cost-effectiveness and value for money for IM indication, however, not for IA indication were more cost-effective options are available.
Other Information	None

The Drug Review Process in B.C.

A manufacturer submits a request to the Ministry of Health (Ministry).

An independent group called the Drug Benefit Council (DBC) gives advice to the Ministry. The DBC looks at:

- whether the drug is safe and effective
- advice from a national group called the Common Drug Review (CDR)
- what the drug costs and whether it is a good value for the people of B.C.
- ethical considerations involved with covering or not covering the drug
- input from physicians, patients, caregivers, patient groups and drug submission sponsors

The Ministry makes PharmaCare coverage decisions by taking into account:

- the existing PharmaCare policies, programs and resources
- the evidence-informed advice of the DBC
- the drugs already covered by PharmaCare that are used to treat similar medical conditions
- the overall cost of covering the drug

Visit The Drug Review Process in B.C. - Overview and Ministry of Health - PharmaCare for more information.

This document is intended for information only.
It does not take the place of advice from a physician or other qualified health care provider.

Drug Benefit Council (DBC) Recommendation and Reasons for Recommendation

FINAL

Isavuconazole (Cresemba™)

AVIR Pharma Inc.

Description:

Drug review of **isavuconazole (Cresemba™)** for the following Health Canada approved indications:

For the treatment of invasive aspergillosis and invasive mucormycosis.

In their review, the DBC considered the following: the final reviews completed by the Common Drug Review (CDR) on May 15, 2019, which included clinical and pharmacoeconomic evidence review material and the recommendations from the Canadian Drug Expert Committee (CDEC). The DBC also considered patient input received by the CDR, Clinical Practice Reviews from two specialists, an Other Drug Agencies Review Recommendations document from the Canadian Agency for Drugs and Technologies in Health (CADTH), and two Budget Impact Assessments. The DBC received no Patient Input Questionnaire responses from patients, caregivers, or Patient Groups.

Dosage Forms:

Cresemba™ is available as isavuconazole 100 mg capsules and 200 mg/vial for intravenous injection.

Recommendations:

1. The Drug Benefit Council (DBC) recommends that isavuconazole (Cresemba) not be listed at the submitted price.
2. If a significant price reduction is achieved (i.e. a price similar or lower than the current first line treatment for invasive aspergillosis), then isavuconazole may be listed with the following criteria: confirmed invasive aspergillosis or invasive mucormycosis; and if a patient is established on isavuconazole in hospital, on discharge they should continue isavuconazole.

Of Note:

- The DBC recognizes that the choice of initial antifungal treatment and subsequent stepdown are typically made in the hospital setting. On transition to community, the DBC expects most patients would continue on the same antifungal treatment that the patient is on at the time of hospital discharge.

Reasons for the Recommendation:

1. Summary

- In one double-blind, multi-centre, noninferiority randomized controlled trial (RCT) which enrolled adults with proven, probable, or possible invasive fungal diseases (e.g. invasive aspergillosis and invasive mucormycosis) caused by aspergillus species or other filamentous fungi, isavuconazole was statistically noninferior to voriconazole with respect to all-cause mortality through day 42 and the two treatments resulted in similar overall treatment response at the end of treatment.
- The percentage of patients reporting treatment-emergent adverse events and serious adverse events was similar between the isavuconazole and voriconazole treatment groups.
- At the manufacturer's submitted price, isavuconazole is not considered to be cost-effective for treating patients with suspected invasive aspergillosis.
- Isavuconazole is the only oral antifungal with a Health Canada indication for the treatment of invasive mucormycosis, although in clinical practice posaconazole is also used. The DBC noted that untreated invasive mucormycosis is associated with a high mortality rate.

2. Clinical Efficacy

- The DBC considered the CDR systematic review, which included two clinical trials, SECURE and VITAL. SECURE was a double-blind, multi-centre, noninferiority RCT which enrolled adults with proven, probable, or possible invasive fungal diseases caused by aspergillus species or other filamentous fungi. Patients were randomized to isavuconazole (200 mg IV three times a day on days 1 and 2, then either IV or orally once daily) or voriconazole (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 rate was 54% in the SECURE study.
- In SECURE, isavuconazole was statistically noninferior to voriconazole with respect to all-cause mortality through day 42. Results for all-cause mortality in the per-protocol population, as well as the modified and mycological intention-to-treat populations, through day 42 were consistent with the primary analysis, as were the results through day 84.
- VITAL was a single-arm trial that assessed the efficacy and safety of IV and oral formulations of isavuconazole in the treatment of proven or probable invasive mucormycosis or proven, probable, or possible invasive aspergillosis. The maximum treatment duration was 180 days. The overall withdrawal rate was 64.9% in the invasive mucormycosis group and 58.3% in the invasive aspergillosis group.
- The evidence available for the use of isavuconazole for the treatment of invasive mucormycosis 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 isavuconazole as primary therapy for invasive mucormycosis (N = 21), the all-cause mortality rate was similar to that observed in a historical cohort of patients receiving amphotericin B for the treatment of invasive mucormycosis; 33% versus 39%, respectively.
- For detailed information on the systematic review of isavuconazole please see the CDEC Final Recommendation at: https://www.cadth.ca/isavuconazole.

3. Safety

- In the SECURE study, the percentage of patients reporting treatment-emergent adverse events and serious adverse events was similar for the isavuconazole and voriconazole treatment groups. The percentage of patients who withdrew due to an adverse event was numerically lower in the isavuconazole group compared with the voriconazole group.
- For detailed information on the safety and tolerability of isavuconazole, please see the CDEC Final Recommendations in the link above.

4. Economic Considerations

- At the manufacturer's submitted price, isavuconazole is not considered to be cost-effective for treating patients with suspected invasive aspergillosis.
- The CDR reanalysis of the manufacturer's pharmacoeconomic submission found that isavuconazole was associated with an incremental cost-utility ratio (ICUR) of $73,036 per quality-adjusted life-year (QALY) compared with voriconazole; however, there is considerable uncertainty in this estimate.
- The CDR estimated a minimum 20% reduction in the price of isavuconazole would be required for isavuconazole to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY.

5. Of Note

- The DBC received no Patient Input Questionnaire responses from patients, caregivers, or patient groups.
- Isavuconazole is the only oral antifungal with a Health Canada indication for the treatment of invasive mucormycosis, although in clinical practice posaconazole is used. The DBC noted that untreated invasive mucormycosis is associated with a high mortality rate.
- invasive aspergillosis is more commonly encountered in clinical practice than invasive mucormycosis. The DBC noted that voriconazole remains an appropriate choice for initial treatment of invasive fungal diseases in many situations.