CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

ISAVUCONAZOLE (CRESEMBA)

(AVIR Pharma Inc.)

Indication: Invasive aspergillosis and invasive mucormycosis.

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CADTH

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Table of Contents

Tables

Figures

Abbreviations

AE	adverse event
AmB	amphotericin B
AML	acute myeloid leukemia
CDR	CADTH Common Drug Review
CML	chronic myeloid leukemia
IA	invasive aspergillosis
ICUR	incremental cost-utility ratio
IFD	invasive fungal disease
IM	invasive mucormycosis
IV	intravenous
L-AmB	liposomal amphotericin B
QALY	quality-adjusted life-year
SE	standard error

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Isavuconazole (Cresemba)
Study Question	What is the cost-effectiveness of isavuconazole compared with voriconazole for the treatment of IA and IM?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Patients with suspected IA, including some patients for whom IA was initially suspected but an IM infection was subsequently confirmed
Treatment	Loading dose: 200 mg three times daily for two days Maintenance dose: 200 mg once daily
Outcome	QALYs
Comparator	Voriconazole
Perspective	Canadian public health care payer
Time Horizon	17 years (assumed to be lifetime)
Results for Base Case	ICUR of $10,696 per QALY for isavuconazole compared with voriconazole
Key Limitations	• The manufacturer's model inappropriately assumed that patients who were alive at the end of trial follow-up (i.e., day 84) would survive until the end of the model time horizon (i.e., 17 years). This assumption is unrealistic because not all patients in the clinical trials had recovered from the infection by day 84 and also because of existing malignancies in these patients. This assumption favours isavuconazole, as the relative survival benefit is assumed to continue for 17 years. • The treatment pathway in the model is not consistent with clinical practice, as it does not reflect that patients who are clinically more likely to have IM may start on liposomal amphotericin B (rather than voriconazole, as in the model). Also, surgical management of patients is not included in the model pathway. • Information on the efficacy and safety for isavuconazole in patients with IM (with diagnosis established based on histopathology or culture) is based on a subset of patients (n = 21) from a single-arm study, thus limiting the quality of the evidence. • The model uses a baseline utility of 0.82 which is likely to be high, given the presence of malignancies in these patients; while a disutility of −0.11 is used for invasive fungal disease (IFD) for the duration of the infection, which likely underestimates the impact.
CADTH Common Drug Review Estimate(s)	• CADTH could not address the limitations related to the quality of the evidence in the IM population and the failure to include surgical management in the model. • CADTH reanalysis included: Using a more realistic approach to estimate survival (based on fitting the Weibull distribution to the trial data); using appropriate values for base utility (0.72) and disutility (−0.20); including medication wastage; adjusting treatment duration in IM patients; and using a lower cost for managing cholestasis. • In the CADTH base case, isavuconazole compared with voriconazole was associated with an ICUR of $73,036 per QALY, requiring a price reduction of 20% to be considered cost-effective at a willingness to pay of $50,000 per QALY (although with significant uncertainty in the results). • Scenario analyses showed that the ICUR is most sensitive to the assumption related to long-term benefit, the type of infection (IA or IM), and the mortality rates.

Drug	Isavuconazole (Cresemba)
Indication	Cresemba (isavuconazole, as isavuconazonium sulfate) is an azole antifungal indicated for use in adults for the treatment of: • IA • IM
Reimbursement Request	Per Health Canada indication
Dosage Form(s)	Oral capsules, 100 mg IV infusion: Powder for solution for intravenous infusion, 200 mg
NOC Date	December 19, 2018
Manufacturer	AVIR Pharma Inc.

IA = invasive aspergillosis; ICUR = incremental cost-utility ratio; IM = invasive mucormycosis; QALY = quality-adjusted life-year.

Executive Summary

Background

Isavuconazole (Cresemba) is an azole antifungal drug indicated for the treatment of invasive aspergillosis (IA) and invasive mucormycosis (IM) in adults.[1] It is available in powder form for intravenous (IV) administration and in capsule form for oral use. A vial for IV administration contains 200 mg of isavuconazole, priced at $400, while an oral capsule contains 100 mg of isavuconazole, priced at $78.83. Treatment is initiated with a loading dose of 200 mg every eight hours for six doses (48 hours) followed by a maintenance dose of 200 mg daily. Clinical experts recommend a minimum of 6 to 12 weeks of treatment for IA, while achieving a favourable clinical response in IM will take several weeks.[2,3] At the manufacturer's submitted price, the daily cost for the loading dose is $472.98 for the oral formulation and $1,200 for the IV formulation. The daily cost for the maintenance dose is $157.66 for the oral formulation and $400 for the IV formulation. Based on CADTH's calculations, an eight-week treatment course will cost $9,460 using the oral formulation and $24,000 using the IV formulation.

The manufacturer submitted a cost-utility analysis comparing isavuconazole with voriconazole in patients with suspected IA.[4] A decision tree model was developed in Microsoft Excel using a Canadian public health care payer perspective and a lifetime horizon (assumed to be 17 years in this patient population). Patients enter the model with suspected IA; for 5.75% of these patients, an IM is later diagnosed (with or without pathogen identification). Patients received first-line treatment with either isavuconazole or voriconazole; in case of treatment discontinuation, patients would switch to a second-line treatment. In patients suspected to have IA, that second-line treatment was assumed to be liposomal amphotericin B (L-AmB) followed by posaconazole or voriconazole (50:50 ratio). In patients with suspected IM, the second-line treatment was L-AmB) followed by posaconazole. The duration of the second-line treatment (in patients with IA or IM) was assumed to be the same as the total treatment duration in patients who continued treatment with isavuconazole (77 days for IA and 216 days for IM). Patients who are alive at day 84 were assumed to remain alive until the end of the model time horizon (i.e., 17 years). Relative effectiveness, safety, and the probability of switching to second-line treatment was based on the SECURE trial in patients with IA, and on the VITAL trial in patients with IM.[4-6]

Cost data were based on Canadian sources such as the Ontario Case Costing Initiative (OCCI), the Canadian Institute for Health Information (CIHI), and various provincial drug formularies.[7,8] The manufacturer reported that the use of isavuconazole compared with voriconazole in patients with suspected IA was associated with an incremental cost of $4,868 and an incremental quality-adjusted life-year (QALY) gain of 0.479, resulting in an incremental cost-utility ratio (ICUR) of $10,154 per QALY. The ICUR was below $50,000 per QALY in 100% of the 5,000 iterations. CADTH identified a number of programming-related issues that affected the probabilistic analysis. In the manufacturer's corrected base case, isavuconazole was associated with an ICUR of $11,053 compared with voriconazole; the ICUR was below $50,000 per QALY in 68.8% of the iterations, while isavuconazole was dominated (i.e., less effective and more expensive than voriconazole) in 21.9% of the iterations. This reflects the significant uncertainty in the parameters used in the economic model.

Summary of Identified Limitations and Key Results

CADTH identified several limitations in the manufacturer's model that have notable implications on the results of the economic analysis. Firstly, the manufacturer's model inappropriately assumed that patients who were alive at the end of trial follow-up (day 84) would survive until the end of the model time horizon (17 years). This assumption is unrealistic because not all patients in the clinical trials had recovered from the infection by day 84 and because of existing malignancies in these patients. This assumption favours isavuconazole, as the survival benefit in the trial is extrapolated over the model's lifetime time horizon. Secondly, the treatment pathway is not consistent with clinical practice in a number of ways. For example, it does not reflect that patients who are clinically more likely to have IM may receive L-AmB (rather than voriconazole, as in the model). Surgical management of patients is not included in the model pathway. Thirdly, the evidence on efficacy and safety for isavuconazole in IM patients is based on a subset of 21 patients from a single-arm study. Several limitations of this study were identified by the CADTH clinical review (open-label, single-arm study design and small sample size). Fourthly, a baseline utility value of 0.82 is used in the model. This is likely to be high, given the existing malignancies in patients (based on the SECURE and VITAL trials), while the disutility of 0.11 used for the duration of the invasive fungal disease (IFD) is likely to be an underestimate. Further, it is unclear why specific adverse events were chosen for inclusion in the analysis. The cost of adverse events may be overestimated; for example, the cost of cholestasis was assumed to be $23,135, although patients in the SECURE and VITAL trials did not require hospitalization. Finally, parameter uncertainty is not correctly characterized for probabilistic analysis, i.e., ± 25% of the parameter's mean value instead of standard errors from the original studies. Many of these limitations are likely to have favoured isavuconazole.

The CADTH analyses could not address all identified limitations, in particular, those related to the quality of the evidence in patients with IM and limitations related to treatment pathway. The CADTH reanalysis included the following changes: basing long-term survival on a Weibull distribution fitted to the trial data; assuming that second-line treatment would start within six days for all patients with IM; assuming a baseline utility of 0.72 (based on the literature) to reflect quality of life in patients with existing malignant conditions; assuming a higher disutility of −0.20 associated with IFD; including the cost of wastage of medication (for voriconazole IV and L-AmB); reducing the L-AmB treatment period to 18 days (as per the literature); and changing the cost of cholestasis to the average of other hepatobiliary adverse events ($448.67).

In the CADTH base case, isavuconazole compared with voriconazole was associated with an additional benefit of 0.073 QALYs at an additional cost of $5,364, resulting in an ICUR of $73,036 per QALY. The price of isavuconazole would need to be reduced by 20% to be considered cost-effective if a decision-maker is willing to pay $50,000 per QALY.

Conclusions

The model submitted by the manufacturer had a number of limitations and data-related uncertainties, some of which could be addressed by CADTH. In the CADTH base case, the ICUR for isavuconazole compared with voriconazole is likely to be significantly higher ($73,036 per QALY) than estimated by the manufacturer ($10,154 per QALY). Isavuconazole is not cost-effective compared with voriconazole at a willingness to pay of $50,000 per QALY, unless the price of isavuconazole is reduced by at least 20%.

CADTH could not address some of the limitations identified, such as the quality of the evidence in the IM population and non-inclusion of surgical management in the treatment pathway; these limitations should be taken into consideration in the interpretation of the results.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's PE Submission

The manufacturer submitted a cost-utility analysis comparing isavuconazole with voriconazole in patients with suspected invasive aspergillosis (IA). A decision tree analysis was conducted in Microsoft Excel using a Canadian public health care payer perspective and a time horizon of 17 years, which was assumed to represent a lifetime horizon. Costs and clinical outcomes (i.e., quality-adjusted life-years [QALYs]) were discounted after the first year at a rate of 1.5%. Both deterministic and probabilistic analyses were conducted, with the probabilistic analysis based on 5,000 iterations. The structure of the decision model, reproduced from the manufacturer's submission, is shown in Appendix 5 (Figure 1).

Patients entered the model with suspected IA, with 5.75% of patients later diagnosed (with or without pathogen identification) with invasive mucormycosis (IM). The primary outcome of interest in the decision tree is all-cause mortality assessed at day 84 in the SECURE trial in patients with IA and in the VITAL trial in patients with IM.[4-6] Patients who were alive at day 84 were assumed to stay alive for the rest of the model period (17 years). A utility of 0.71 was used for the duration of the invasive fungal infection and a utility value of 0.82 was used for the rest of the modelling horizon.[4]

Patients initially started on isavuconazole or voriconazole as first-line treatment and, in case of treatment discontinuation, switched to a second-line treatment. In patients with IA infection, second-line treatment was assumed to be liposomal amphotericin B (L-AmB) followed by either posaconazole or voriconazole (50:50 ratio). In patients with suspected IM (with or without pathogen identification), a third of patients initially treated with isavuconazole would transition to amphotericin B (L-AmB) with oral posaconazole step-down while all patients initially treated with voriconazole would switch to L-AmB with oral posaconazole step-down. The number of patients switching to a second-line treatment was estimated from the SECURE and VITAL trials.[4] The duration of second-line treatment (for IA and IM patients) was assumed to be the same as the remaining treatment duration in patients who continued treatment with isavuconazole.

Risk of harms (i.e., adverse events: hyperbilirubinemia, abnormal hepatic function, jaundice, cholestasis, rash erythema, skin lesions, drug eruption, retinal hemorrhage) was based on the SECURE trial for IA patients and based on the VITAL trial for IM patients.[4-6] The efficacy and safety of L-AmB-based regimens was based on the medical literature.[9,10]

Costs included were those related to treatment acquisition, hospitalizations, and adverse events. Drug costs were obtained from various provincial drug formularies. Hospitalizations costs were derived from the Canadian Institute for Health Information (CIHI) database.[8] Costs for adverse events were obtained from the Ontario Case Costing Initiative (OCCI).[7]

Manufacturer's Base Case

The manufacturer reported that the use of isavuconazole compared with voriconazole in patients with suspected IA was associated with a $4,868 increase in cost and a 0.479 QALY gain, resulting in an incremental cost-utility ratio (ICUR) of $10,154 per QALY (Table 2). The ICUR was below $50,000 per QALY in 100% of the iterations.

CADTH identified a number of technical issues with the model. These relate to the programming of the probabilistic analysis, including the use of deterministic values instead of probabilistic for some model parameters, errors in formulas, use of probabilistic discount rates, and the use of triangular distributions for utility data (see Table 7 for details). These issues resulted in suboptimal convergence of the submitted model, i.e., more than a 10% difference between the probabilistic and deterministic ICUR values. CADTH corrected these programming issues; the updated results of the manufacturer's base-case analysis are presented in the bottom panel of Table 2. These results showed that isavuconazole was associated with an incremental cost of $4,425, a QALY gain of 0.400, and an ICUR of $11,053. The ICUR was below $50,000 per QALY in 68.8% of the iterations (including 6.4% of the iterations where isavuconazole was dominant, i.e., more effective and less expensive than voriconazole). However, isavuconazole was dominated (i.e., less effective and more expensive than voriconazole) in 21.9% of the iterations. In summary, while the updated mean ICUR was similar to the manufacturer's original submission, there is greater uncertainty in results after the technical issues were corrected by CADTH.

Table 2: Summary of Results of the Manufacturer's Base Case

	Total Costs ($)	Incremental Cost of Isavuconazole ($)	Total QALYs	Incremental QALYs of Isavuconazole	Incremental Cost per QALY
Manufacturer's Base Case as Originally Submitted					
Isavuconazole	49,946[a]	4,868[a]	10.613[a]	0.479[a]	$10,154[a]
Voriconazole	45,078[a]		10.133[a]		
Manufacturer's Base Case After Correction of Programming Errors					
Isavuconazole	50,005	4,425	9.256	0.400	$11,053
Voriconazole	45,580		8.856		

QALY = quality-adjusted life-year.

[a] CADTH reporting mean values rather than the median values reported in the manufacturer's submission.

Summary of Manufacturer's Sensitivity Analyses

The manufacturer conducted multiple one-way deterministic sensitivity analyses showing that the results were most sensitive to all-cause mortality risk (all treatment groups), the utility value associated with the underlying disease, and the discount rate.

The manufacturer reported a median ICUR of $10,131 per QALY for the probabilistic societal perspective. No other scenario analysis was performed.

Limitations of Manufacturer's Submission

CADTH has identified several key limitations to the manufacturer's analysis that have notable implications on the economic analysis:

- **Long-term benefit of isavuconazole is likely overestimated:** The manufacturer assumed that survivors of invasive fungal disease (IFD) would live up to 17 years, based on a study by Bower et al.[11] However, the survival time reported by Bower et al. was based on a cohort of chronic myeloid leukemia (CML) patients, a much less aggressive leukemia than acute myeloid leukemia (AML) (note: 44% of the SECURE patient population and 27% of the VITAL patient population had AML).[5,6] In comparison, a

publication by Ellison et al. found that the five-year survival in Canadian patients with AML or CML (aged 45 to 54 years) was, respectively, 25.6% and 77.1% of that of the general Canadian population (of similar age).[12] This shows that patients with AML have much shorter survival than patients with CML.

The manufacturer assumed that patients who were alive at day 84 would also be alive at day 365 and for the entire modelling time horizon (i.e., 17 years). This assumption is unrealistic because not all patients in the clinical trials had recovered from the infection by day 84 and because of existing malignancies in these patients (49% and 70% of patients with active malignancy in the VITAL and SECURE trials, respectively).[5,6] In addition, the model assumes that the survival benefit or treatment effect (and the QALYs) observed at day 84 will remain constant over 17 years; this is likely to overestimate the QALY gain associated with isavuconazole.

CADTH conducted analyses using extrapolated survival curves that showed the approach used by the manufacturer likely overestimates the long-term benefit (i.e., QALY gain) by four times in favour of isavuconazole (Appendix 5).

- **The treatment pathway is not consistent with clinical practice:** As per the clinical expert consulted by CADTH, treatment for IFD depends on patients' clinical presentation. While most patients are treated empirically with voriconazole when IA is suspected, if the clinical presentation (e.g., sinus and brain involvement) suggests a high probability of IM infection, then patients are started on L-AmB (rather than voriconazole). This pathway is not reflected in the decision model. Excluding this pathway in the model likely increases the cost in the voriconazole arm, in turn favouring isavuconazole.

  Furthermore, as per the clinical expert consulted for this review, it is unlikely that 14 days will elapse before response to treatment is assessed, IM is suspected, and treatment is changed to L-AmB. Change of treatment, if required, is likely to happen within five to six days of starting initial treatment. The assumption of longer initial treatment with voriconazole increases costs in the voriconazole arm and favours isavuconazole.

  The model assumes that treatment with L-AmB in IM patients would continue for 27 days. This is longer than the typical treatment duration in clinical practice (21 days) and longer than the median treatment duration in the matched-control part of the VITAL study (18 days).[13] Longer treatment with L-AmB increases costs in the voriconazole arm and favours isavuconazole.

  The model assumed that in the case of IA, 48% of patients on isavuconazole and 45% of patients on voriconazole will require a second-line therapy. However, in comparison, in the SECURE trial, 35.7% of patients on isavuconazole and 29.8% of patients on voriconazole received another antifungal agent during the follow-up period.[6] A similar proportion (36%) was reported in a study comparing voriconazole to AmB in IA.[14] This assumption, however, has a relatively small impact on the results.

  Lastly, surgical debridement is often used to manage patients with IA[2] and IM;[3] however, this was not included in the economic model. For example, in the case-control part of the VITAL study, 9 out of 21 patients (43%) in the isavuconazole group and 13 out of 33 patients (39%) in the AmB group received surgical treatment. Mortality in the surgically treated isavuconazole patients was 44% as compared with 25% in the non-surgically treated patients. Similarly, mortality in the surgically treated AmB patients was 23% compared with 50% in the non-surgically treated patients.[13] Excluding surgery in the treatment pathway may have favoured isavuconazole by excluding additional costs in patients who have a higher risk of mortality.

- **The quality of the clinical evidence, in particular in IM:** The efficacy and safety evidence of isavuconazole is based on 21 patients who received isavuconazole as primary treatment for IM (a subset of the VITAL study).[4] CADTH clinical review identified a number of limitations of the VITAL study, including open-label single-arm nature of the study design and small sample size.[15]

- **Utility and disutility values are likely over or underestimated:** The manufacturer uses a utility value of 0.82 as baseline value for patients without IFD.[4] However, this appears high given that in the SECURE and VITAL studies, 70% and 49% of patients, respectively, had an uncontrolled malignancy at baseline.[5,6] In fact, this is very close to the utility value of 0.83 estimated in the general population of healthy Canadians in Alberta aged 50 to 59 years.[16] In comparison, two recent papers estimated that the utility values in relapsing patients with AML or those receiving induction or consolidation treatment ranged from 0.10 to 0.57, while utilities in remission or cured patients ranged from 0.62 to 0.76.[17,18] This suggests the baseline utility value is incorrectly assumed to be high, which favours isavuconazole.

  The manufacturer used a disutility value of 0.11 for the duration of the IFD.[4] This value is based on a health-state valuation study for chronic lymphocytic leukemia using a sample of the UK general population.[19] The value of 0.11 was associated with grade 3 or 4 pyrexia in this study. This is likely a conservative estimate. In comparison, the disutility of grade 3 or 4 pneumonia was found to be 0.20 in the same study.[19] This latter value is close to the value of 0.218 associated with serious infection in patients with AML.[20]

- **Probabilistic analysis is based on inappropriately defined uncertainty intervals:** In addition to the programming issues identified earlier and summarized in Table 7, the manufacturer used ± 25% of the parameters' base value as an estimate of parameter uncertainty in the probabilistic analysis. For most parameters in the manufacturer's model, standard errors, standard deviations, or 95% confidence intervals were available from the primary data sources and should have been used in the probabilistic analysis, in line with CADTH guidelines.[21]

- **Cost of adverse events (AEs) likely overestimated:** The manufacturer selected AEs from the SECURE trial based on statistically significant differences between groups.[4] These were related to three body systems: hepatobiliary, cutaneous/subcutaneous tissues, and visual. From each body system, a small list of AEs was selected and costed. It is unclear how the AEs were chosen within each body system. Moreover, a cost of $23,135 was used for the treatment of cholestasis, which appears to be high, given that none of the cholestasis events in the SECURE trial were reported as serious AEs requiring hospitalization.[6] This overestimation of AE costs favours isavuconazole.

- **Intravenous (IV) medication costs are likely underestimated:** Wastage of IV medications has not been considered, therefore underestimating IV medication costs. Furthermore, patient weight is not included in the probabilistic analysis.

CADTH Common Drug Review Reanalyses

Before undertaking any reanalyses, CADTH corrected programming and other errors (e.g., typographical error in body weight) in the model and also used appropriate sources for parameter uncertainty (i.e., standard errors, where available). These changes, together with data sources, are listed in Appendix 5 (Table 12).

Subsequently, CADTH conducted the following reanalyses:

A: Long-term survival (beyond day 84) based on a Weibull distribution fitted to the trial data (see Appendix 5 for details).

B: Assuming that all patients in the voriconazole arm who have not recovered by day 6 switch to L-AmB and posaconazole (instead of assuming that only 50% switch at day 6 and the rest at day 14). This is based on the advice of the clinical expert consulted by CADTH for this review.

C: Assuming a baseline utility value of 0.72 to reflect that a large part of the target population has an ongoing malignancy (see details in Appendix 5).

D: Assuming that IFD is associated with a disutility of −0.20 instead of −0.11.[19] This reflects the quality-of-life impact of IFD.

E: Incorporating the cost of medication wastage for voriconazole IV and L-AmB.

F: Reducing L-AmB treatment duration in IM patients to 18 days. This is based on the matched-control portion of the VITAL trial.[13]

G: Replacing the cholestasis cost in the model with the average cost of all hepatobiliary AEs, i.e., $448.67.

CADTH base case: A to G (all of the previously described modifications combined).

In the CADTH base case, the use of isavuconazole compared with voriconazole in adult patients with suspected IA was associated with an additional benefit of 0.073 QALY at an additional cost of $5,364, resulting in an ICUR of $73,036 per QALY (Table 3). The probability of the isavuconazole ICUR being below $50,000 per QALY is 39%. Isavuconazole is dominated (i.e., less effective and more expensive than voriconazole) in 28.0% of the iterations. The highest impact of the changes on the manufacturer's base case was the use of a more realistic assumption for long-term survival. CADTH could not address the limitations pertaining to the quality of evidence in IM patients and the absence of consideration of surgical management in the treatment pathway.

Table 3: Results From CADTH Reanalyses

Scenarios			Total Costs ($)	Total QALY	ICUR ($)
	Base case submitted by manufacturer	Isavuconazole	49,946	10.613	10,154
		Voriconazole	45,078	10.133	
		Incremental	4,868	0.479	
	Corrected manufacturer's base case	Isavuconazole	50,005	9.256	11,053
		Voriconazole	45,580	8.856	
		Incremental	4,425	0.400	
A	Reduced long-term benefit	Isavuconazole	49,808	2.828	37,600
		Voriconazole	45,269	2.707	
		Incremental	4,539	0.121	
B	100% switch to L-AmB-based regimen after 6 days	Isavuconazole	49,722	9.286	15,820
		Voriconazole	45,189	9.000	
		Incremental	4,533	0.287	
C	Base utility value: 0.7239 (SE: 0.01968)	Isavuconazole	49,745	8.184	12,579
		Voriconazole	45,263	7.828	
		Incremental	4,482	0.356	
D	Disutility for IFD: −0.20 (SD: 0.02; n: 89)	Isavuconazole	49,896	9.264	10,997
		Voriconazole	45,393	8.855	
		Incremental	4,504	0.410	
E	Medication wastage	Isavuconazole	49,844	9.282	10,399
		Voriconazole	45,592	8.873	
		Incremental	4,252	0.409	
F	L-AmB treatment duration: 18 days	Isavuconazole	49,568	9.285	12,187
		Voriconazole	44,508	8.870	
		Incremental	5,060	0.415	
G	Cholestasis costs: $448.67 (SE: 21.737)	Isavuconazole	49,617	9.287	11,789
		Voriconazole	44,718	8.871	
		Incremental	4,899	0.416	
CADTH base case (A + B + C + D + E + F + G)		Isavuconazole	49,488	2.463	73,036
		Voriconazole	44,124	2.390	
		Incremental	5,364	0.073	

ICUR = incremental cost-utility ratio; IFD = invasive fungal disease; L-AmB = liposomal amphotericin B; QALY = quality-adjusted life-year; SD = standard deviation; SE = standard error.

Note: These results are based on probabilistic analyses; hence, minor variations between model runs are expected.

For the CADTH base case, the price of isavuconazole would need to be reduced by at least 20% to be considered cost-effective at a willingness to pay of $50,000 per QALY (Table 4). However, there is significant uncertainty in the ICUR estimate, given the limited comparative evidence available in IM patients. Based on an additional subgroup analysis on the CADTH base case, the economic results were found to be highly sensitive to the type of infection modelled (scenario analysis 4, Appendix 5). In the patient subgroup with IA infection, the ICUR increased to $88,226 per QALY; whereas, in the patient subgroup with IM infection, isavuconazole was dominant (i.e., more effective and less costly compared with voriconazole). There remains uncertainty regarding the true rates of IM infection, although it

is expected to be low. At price reductions of 60% and 70% for isavuconazole, the probability of isavuconazole being the most likely cost-effective intervention at $50,000 per QALY increased to 74% and 80%, respectively, in the CADTH base case.

Table 4: CADTH Reanalysis Price-Reduction Scenarios

Incremental Cost-Utility Ratios of Submitted Drug Versus Comparator		
Price	**Base-Case Analysis Submitted by Manufacturer**	**CADTH Reanalysis**
Submitted	$11,016	$73,036
10% reduction	$8,486	$58,172
20% reduction	$6,099	$47,295
30% reduction	$3,741	$32,771
40% reduction	$1,219	$20,179
50% reduction	Dominant	$7,506
60% reduction	Dominant	Dominant
70% reduction	Dominant	Dominant

In addition, the following scenario analyses were performed on the CADTH base case.

Scenario 1 explores the uncertainty in the day 84 mortality rates by using extreme values from the 95% confidence intervals. For IA, scenario 1A uses the upper limit of the mortality rate for isavuconazole and the lower limit for voriconazole. Scenario 1B for IA uses the lower limit of mortality rate for isavuconazole and the upper limit for voriconazole. For IM, scenario 1C uses the upper limit of mortality rate for isavuconazole and the lower limit for voriconazole (L-AmB). Scenario 1D for IM uses the lower limit of mortality rate for isavuconazole and the upper limit for voriconazole (L-AmB). Scenario 2 assessed the impact of using a baseline utility value of 0.59 instead of 0.72 in the CADTH base case (see Appendix 5 for details).[17] Scenario 3 assessed the impact of using a disutility value of −0.218 for IFD instead of 0.20, as in the CADTH base case (see Appendix 5 for details).[20] Scenario 4 assessed the impact of the type of infection, i.e., the analysis is performed for IA only (scenario 4A) or IM only (scenario 4B), in view of the quality of evidence in IM. Scenario 5 explores the impact of the percentage of patients receiving a second-line antifungal therapy by reducing this percentage to 10.8% in the isavuconazole treatment arm for IM, based on the VITAL trial[5] (scenario 5A), and by reducing it to 35.7% for isavuconazole and 29.8% for voriconazole for IA based on the SECURE trial.[6] Scenario 7A uses a more optimistic value for the long-term benefit, i.e., about twice that of the CADTH base case.

The results of the CADTH scenario analyses are presented in Appendix 5 (Table 13). The results are most sensitive to the assumption on the long-term benefit, the type of infection (i.e., IA versus IM) and mortality risks. The ICUR with a more optimistic long-term benefit is $33,163 per QALY. The ICUR is $88,226 per QALY when the analysis is performed for IA patients only (scenario 4A), while isavuconazole is dominant when considering IM patients only (scenario 4B). When changing the mortality risk under scenario 1A, isavuconazole is dominated by voriconazole (i.e., isavuconazole is less effective and more expensive). Under scenario 1C for mortality analysis, the ICUR for isavuconazole is more than $26 million per QALY.

Issues for Consideration

Isavuconazole is a substrate of CYP3A4 and CYP3A5. Co-administration of medications that are inhibitors or inducers of CYP3A4 and/or CYP3A5 may increase or decrease isavuconazole plasma concentrations and may also affect the plasma levels of the other medication. Appropriate drug monitoring and dose adjustments of products such as immunosuppressants and medications with a narrow therapeutic window may be necessary. This was not considered in the economic evaluation.

Patient Input

No patient input was received.

Conclusions

The model submitted by the manufacturer had a number of limitations and data-related uncertainties, some of which were addressed in the CADTH reanalysis. In the CADTH base case (assuming long-term survival based on a more realistic scenario, an alternate treatment duration for L-AmB, and using appropriate values for baseline utility and disutility and appropriate drug use and cost of AEs), the ICUR for isavuconazole compared with voriconazole is likely to be significantly higher ($73,036) than estimated by the manufacturer. Isavuconazole is not cost-effective compared with voriconazole at a willingness to pay of $50,000 per QALY, unless the price of isavuconazole is reduced by at least 20%. CADTH could not address some of the limitations identified, such as the quality of the evidence in the IM population and non-inclusion of surgical management in the treatment pathway; these limitations should be taken into consideration in the interpretation of the results.

Appendix 1: Cost Comparison

The comparators presented in the following table have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice, versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and, as such, may not represent the actual costs to public drug plans.

Table 5: The CADTH Common Drug Review Cost Comparison Table for the Treatment of Invasive Aspergillosis and Invasive Mucormycosis

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Daily Drug Cost ($)	Duration of Therapy	Cost Per Treatment Course ($)
Isavuconazole (Cresemba)	100 mg	Capsule	78.83[a]	**Loading dose:** 200 mg three times daily for two days **Maintenance dose:** 200 mg once daily	**Loading dose:** 472.98 **Maintenance dose:** 157.66	Treatment duration determined by clinical response. Minimum of 6 to 12 weeks in IA;[b] longer in IM[c] 8 weeks used for comparison	9,459.60
	200 mg	Vial	400.00[a]	**Loading dose:** 200 mg three times daily for two days **Maintenance dose:** 200 mg once daily	**Loading dose:** 1,200.00 **Maintenance dose:** 400.00		24,000.00
Other Azoles							
Voriconazole (generics)[h]	200 mg	Tablet	12.9808	**Loading dose:** 400 mg (200 mg if < 40 kg) twice daily for one day **Maintenance dose:** 200 mg (100 mg if < 40 kg) twice daily	**Loading dose:** 51.92 **Maintenance dose:** 25.96	8 weeks	1,479.81
	50 mg	Tablet	3.2465	**Loading dose:** 400 mg (200 mg if < 40 kg) twice daily for one day **Maintenance dose:** 200 mg (100 mg if < 40 kg) twice daily	**Loading dose:** 51.94 **Maintenance dose:** 25.97	8 weeks	1,480.40

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Daily Drug Cost ($)	Duration of Therapy	Cost Per Treatment Course ($)
	200 mg	Vial	136.5800[e]	**Loading dose:** 6 mg/kg twice daily for one day **Maintenance dose:** 4 mg/kg twice daily	**Loading dose:** 819.48 **Maintenance dose:** 546.32	8 weeks	30,867.08
Voriconazole (VFEND)[h]	200 mg	Vial	156.2700[d]	**Loading dose:** 6 mg/kg twice daily for one day **Maintenance dose:** 4 mg/kg twice daily	**Loading dose:** 937.62 **Maintenance dose:** 625.08	8 weeks	35,317.02
	3 g (40 mg/mL)	Powder for oral suspension	10.2850[d] (per mL)	**Loading dose:** 10 mL (5 mL if < 40 kg) twice daily for one day **Maintenance dose:** 5 mL (2.5 mL if < 40 kg) twice daily	**Loading dose:** 205.70 **Maintenance dose:** 102.85	8 weeks	5,862.45
Posaconazole (Posanol)	40 mg/mL	Oral suspension	9.7031[e] (per mL)	400 mg (10 mL) twice daily **or** 200 mg (5 mL) four times daily	194.06	8 weeks	10,867.47
	100 mg	Delayed-release tablet	48.5152[e]	**Loading dose:** 300 mg twice daily for one day **Maintenance dose:** 300 mg once a day	**Loading dose:** 291.09 **Maintenance dose:** 145.54	8 weeks	8,296.10
	300 mg (18 mg/mL)	Vial	407.8900[e]	**Loading dose:** 300 mg twice daily for one day **Maintenance dose:** 300 mg once a day	**Loading dose:** 815.78 **Maintenance dose:** 407.89	8 weeks	23,249.73
Itraconazole (Mint-itraconazole)[h]	100 mg	Capsule	4.2412	200 mg twice daily	16.96	8 weeks	950.03
Caspofungin (Generics)[h]	50 mg 70 mg	Vial	188.7000[i]	**Loading dose:** 70 mg once daily for one day **Maintenance dose:** 50 mg daily	**Loading dose:** 188.70 **Maintenance dose:** 188.70	8 weeks	10,567.20

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Daily Drug Cost ($)	Duration of Therapy	Cost Per Treatment Course ($)
Polyene							
Liposomal amphotericin B (AmBisome)	50 mg	Vial	130.6800[f]	3 to 5 mg/kg/day	653.40 to 914.76	8 weeks	36,590.40 to 51,226.56
Amphotericin B (Fungizone)[g]	50 mg	Vial	88.7500	**Starting dose:** 0.25 mg/kg/day to 0.3 mg/kg/day **Target dose:** Dose may be increased by 5 mg to 10 mg per day to a final daily dosage of 0.5 mg/kg/day to 1.0 mg/kg/day (maximum 1.5 mg/kg daily)	**Starting dose:** 88.75 **Target dose:** 88.75 to 177.50 **Maximum dose:** 266.25	8 weeks	4,970.00 to 14,910.00 (target dose: 9,940.00)
Amphotericin B lipid complex (Abelcet)[g]	100 mg (5 mg/mL)	Vial	193.5100[e]	5 mg/kg/day	774.04	8 weeks	43,346.24

CDR = CADTH Common Drug Review; IA = invasive aspergillosis; IM = invasive mucormycosis.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed November 2018), unless otherwise indicated, and do not include dispensing fees.[22] Daily drug costs are based on an assumed patient weight of 70.0 kg and wastage of excess medication in vials, if applicable. Treatment course for all indications and drugs was assumed to be eight weeks.

[a] Manufacturer submitted price.

[b] UpToDate: Treatment and prevention of IA.[2]

[c] UpToDate: Mucormycosis (zygomycosis).[3]

[d] Alberta Drug Benefit List (accessed November 2018).[23]

[e] IQVIA database (accessed November 2018).[24]

[f] British Columbia Pharmacare Formulary (accessed November 2018).[25]

[g] According to CADTH clinical expert guidance, the primary amphotericin B option used in practice is AmBisome.

[h] Product not active in IM.

[i] The 50 mg vial price is from the Ontario Drug Benefit Formulary (accessed November 2018) (Ontario Ministry of Health Long-Term Care, 2018 No. 1). The 70 mg vial price is from the Alberta Drug Benefit List (accessed November 2018) (Alberta Health, 2018 No. 4).

Appendix 2: Summary of Key Outcomes

Table 6: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive Is Isavuconazole Relative to Voriconazole?

Isavuconazole Versus Voriconazole	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)				X		
Drug treatment costs alone				X		
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation (CADTH base case)	$73,036 per QALY					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year.

Appendix 3: Additional Information

Table 7: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?			X
Comments Reviewer to provide comments if checking "no"	Several programming errors were found in the model: • In the sheet "SA Parameters," the formula in cells T19 to T52 contained a #REF! error code, causing the choice of value to be inadequate, depending on the type of analysis being run. • Several cells in the model's decision tree referred to the static base values rather than probabilistic values therefore, these parameters were not varied in the probabilistic analysis, contrary to what the manufacturer was saying. Specifically, in the sheet "Decision Tree," cells L20, L36, L52, L68, and 062 referred to static rather than probabilistic values. • The utility values used to calculate total QALYs in the Decision Tree sheet referred to static, not probabilistic, values. • The discount rate was included in the probabilistic sensitivity analysis. • The formula for beta distribution used in the probabilistic analysis included lower and upper bounds. This skewed the probabilistic analysis and caused a lack of convergence between the probabilistic and deterministic analyses. • The formula for the beta and gamma distributions used in the probabilistic analysis used a value of zero in case of error, rather than the average, again skewing the probabilistic analysis results and causing lack of convergence. • A triangular distribution was used for utility and disutility values, skewing the probabilistic results and causing lack of convergence. • The percentage of erythema was computed from the number of rash cases ("inputs" in cells G193 and G205). Furthermore, parameter uncertainty as reported in the various sources of evidence was not used in the probabilistic analysis; rather, an arbitrary ± 25% of the base value was used.		
Was the material included (content) sufficient?	X		
Comments Reviewer to provide comments if checking "poor"	None		
Was the submission well organized and was information easy to locate?	X		
Comments Reviewer to provide comments if checking "poor"	None		

SA = sensitivity analysis.

Table 8: Authors Information

Authors of the Pharmacoeconomic Evaluation Submitted to CDR			
☐ Adaptation of global model/Canadian model done by the manufacturer ☒ Adaptation of global model/Canadian model done by a private consultant contracted by the manufacturer ☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the manufacturer ☐ Other (please specify)			
	Yes	**No**	**Uncertain**
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis			X

CDR = CADTH Common Drug Review.

Appendix 4: Summary of Other HTA Reviews of Drug

Isavuconazole has been reviewed and recommended by the Scottish Medicines Consortium (SMC), by France's Haute Autorité de la Santé (HAS), and by the All Wales Medicines Strategy Group (AWMSG). Details can be found in Table 9.

Table 9: Other Health Technology Assessment Findings

	SMC (March 4, 2016)[26]	HAS (March 16, 2016)[27]	AWMSG (November 2016)[28]
Treatment	In adults for the treatment of invasive aspergillosis (IA) and invasive mucormycosis (IM) in patients for whom amphotericin B is inappropriate		
Price	Not reported		28-day treatment course: • intravenous: £9,531 • oral: £2,397
Similarities with CDR submission	Same clinical evidence (SECURE and VITAL trials)		
Differences with CDR submission	• CMA rather than CUA • Use of an ITC for the comparison with amphotericin B	No economic analysis submitted	Two separate CMAs: • first-line IA treatment • IM patients for whom amphotericin B is inappropriate
Manufacturer's results	• Savings: £102 per patient (adverse events: £75) over a weighted average of the two comparators in IA • Savings: £11,272 per patient (drug costs: £8,000; hospitalization: £3,000) for IM	Not applicable	Extent of savings not reported because the price of isavuconazole was based on a confidential rebate provided through the WPAS
Issues noted by the review group	• The manufacturer used a weighted average of comparators; changing the proportion of each product affects savings • Use of 5 mg/kg dose for amphotericin B • For IM, the manufacturer results were not cost saving when posaconazole was the comparator	• No demonstration of an added clinical benefit compared with voriconazole in terms of efficacy in the treatment of IA • Limited data available in the treatment of IM	• A CUA would have been preferable (i.e., isavuconazole favourable safety profile on severe cardiac and hepatobiliary events) • Dose of 5 mg/kg for amphotericin B • Use of an external control in IM • Weighted average of comparator prices
Results of reanalyses by the review group (if any)	• If voriconazole is the only comparator, there is an incremental cost of £1,322 rather than savings • If a dose of 3 mg/kg is used for amphotericin B, there is an incremental cost of £700 rather than savings	Not applicable	Not applicable

	SMC (March 4, 2016)[26]	HAS (March 16, 2016)[27]	AWMSG (November 2016)[28]
Recommendation	Accepted for use within NHS Scotland	• Substantial actual benefit but no clinical added value • Inclusion into the list of reimbursable products for hospital use	Recommended only in circumstances where the approved WPAS is utilized or where the list/contract price is equivalent to or lower than the WPAS price

AWMSG = All Wales Medicines Strategy Group; CMA = cost-minimization analysis; CUA = cost-utility analysis; HAS = Haute Autorité de la Santé; IA = invasive aspergillosis; IM = invasive mucormycosis; ITC = indirect treatment comparison; NHS = National Health Services; SMC = Scottish Medicines Consortium; WPAS = Wales Patient Access Scheme.

Appendix 5: Reviewer Worksheets

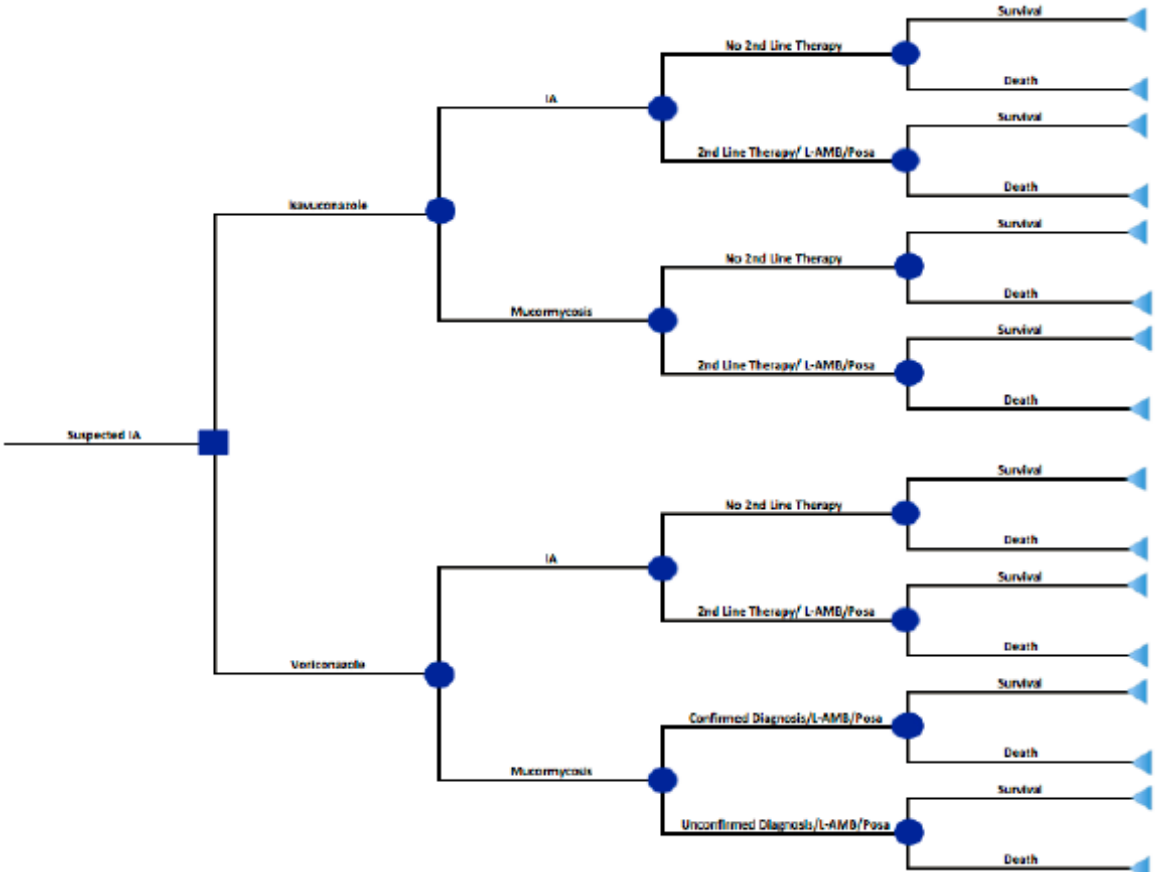
Manufacturer's Model Structure and Data Inputs

Model Structure

The manufacturer developed a decision tree to assess the cost-effectiveness of isavuconazole compared with voriconazole in treating both invasive aspergillosis (IA) and invasive mucormycosis (IM). Patients entered the model with an invasive fungal disease (IFD) that was suspected to be IA. However, some patients were subsequently found to have IM. After receiving an initial treatment with either isavuconazole or voriconazole, a certain proportion of patients receive second-line treatment (presumably due to suboptimal response or intolerance to initial treatment). A graphical representation of the model structure taken from the manufacturer's submission is given in Figure 1.

Parameter uncertainty was addressed by varying most model parameters by ± 25% of the base value in a probabilistic analysis. A scenario analysis was performed with a societal perspective. Multiple one-way (varying one parameter at a time) deterministic analyses were performed using the same lower- and upper-parameter boundaries as for the probabilistic analysis. Discounting (1.5%; lower boundary: 0%; upper boundary: 5%) was applied probabilistically to both costs and quality-adjusted life-years (QALYs) in the manufacturer's base case.

Figure 1: Model Structure



IA = invasive aspergillosis; L-AmB = liposomal amphotericin B; Posa = posaconazole.

Source: Manufacturer's pharmacoeconomic submission.[4]

Data Inputs

Model parameters such as all-cause mortality risks, patient need for second-line treatment, adverse events, and duration of the hospital stay are informed by the SECURE trial (for IA) and the VITAL trial (for IM). Utilities and long-term survival are based on the medical literature. Costs are taken from official sources such as provincial drug formularies, the Canadian Institute for Health Information (CIHI) database, and the Ontario Case Costing Initiative (OCCI). Critical appraisal of data inputs and manufacturer's assumptions can be found in Table 10 and in Table 11.

Table 10: Data Sources

Data Input	Description of Data Source	Comments
Baseline characteristics	According to the manufacturer, the following parameters are based on the SECURE trial: • patient weight: 71.4 kg • patient age: 51 years old.[6]	Body weight is not accurately reported by the manufacturer. Average body weight in the SECURE and VITAL trials was 68.64 kg and 70.13 kg, respectively.[6,5]
Efficacy	**For IA:** All-cause mortality at day 84 from the ITT population: isavuconazole: 29%; voriconazole: 31%.[6]	The primary end point in the SECURE trial was all-cause mortality at day 42 (19% and 20%).[6] Mortality risk is applied to patients regardless of second-line therapy.
	For IM: Isavuconazole: All-cause mortality at day 84 from the ITT population (primary therapy subgroup; n = 27): 43%.[5] Voriconazole: 12-week all-cause mortality from Chamilos et al.:[9] • L-AmB started in fewer than 6 days: 42.86% • L-AmB started in greater than 6 days: 82.90%.	The primary end point in the VITAL trial was overall response at day 42. Both all-cause mortality at day 42 and day 84 were secondary end points. Similar to IA, mortality risk is applied to all patients irrespective of second-line treatment. The clinical expert consulted by CADTH reported that patients with suspected IA who actually have IM will not respond to voriconazole and are likely to be switched to L-AmB within 5 to 6 days due to the rapid deterioration of their condition.
	Percentage of patients not responding to therapy and requiring second-line treatment: **For IA:** • isavuconazole = 47.67%[4] • voriconazole = 45.35%.[4] **For IM:** • isavuconazole = 33.33%[4] • voriconazole = 100%.	The value was based on the assumption that all patients who discontinued treatment and were alive were eligible for second-line treatment. This is a conservative approach, as 40% of the discontinuations were due to reasons other than lack of efficacy or AEs. According to the SECURE trial (Table 48), 35.7% of isavuconazole patients and 29.8% of voriconazole patients received another mould-active antifungal drug up to day 84.[6] In the VITAL trial (Table 12.3.12.2.1), 10.8% of patients received another antifungal drug after end of treatment and up to day 84.[5]
Natural history	**Life expectancy**: Assumed to be 17 years based on a study of patients with CML in Sweden.[11]	The manufacturer wrongly reported that the study was done on patients with AML.[4] In the SECURE trial, the underlying disease for most (44%) patients was AML.[6] CML is a less aggressive disease than AML; hence, using survival from patients with CML to estimate life expectancy likely overestimates survival.[12]
Utilities	Base utility: From a study of patients with AML (0.82).[29]	This study used the EQ-5D to estimate utility in AML patients who were, on average, diagnosed 5.9 years prior.[29] The majority of SECURE and VITAL patients had uncontrolled malignancy at baseline, indicating that the patients in the study by Leunis were likely healthier than those in the trial population.[5,6]
	Disutility associated with IFD: 0.11.[19]	This study estimates health states in CLL.[19] The manufacturer took a more conservative approach by using the disutility associated with pyrexia (0.11; SD = 0.02).[4,19]
AEs (Indicate which specific AEs were considered in the model)	Only AEs where a statistically significant difference between SECURE trial groups was observed were selected.[4] These were: hepatobiliary, cutaneous/subcutaneous tissues, and visual system organ classes (Table 55 SECURE trial report).[6]	AEs were frequent in the SECURE patient population with nearly all patients reporting at least one. In general, the proportions were slightly lower in the isavuconazole group. The largest exception was nervous system disorders (isavuconazole: 37%; voriconazole: 34%). Further details can be found in the CADTH clinical report.[15]

Data Input	Description of Data Source	Comments
	L-AmB nephrotoxicity: 11.5%.[10]	Sourced from a study comparing caspofungin to L-AmB.[10]
Mortality	See efficacy (row 2).	See efficacy (row 2).
Resource Use and Costs		
Drug	• Isavuconazole: From AVIR Pharma Inc.[4] • Voriconazole IV: Alberta Drug Benefit List.[23] • Voriconazole oral: Ontario Drug Benefit.[22] • L-AmB: British Columbia Pharmacare Formulary.[25] • Posaconazole oral: RAMQ.[30]	Medication costs should preferably be sourced from jurisdictions representative of participating drug programs. The RAMQ is not part of these. All doses were consistent with respective product monographs. Lack of dose escalation for L-AmB may overestimate costs.
Administration	Treatment duration for all these medications is dependent on patient status, extent of infection, and pathogen response. In general, a minimum of 6 to 12 weeks is recommended for IA, longer for IM.[2,3]	
	IA: Treatment duration assumed to be equal for all patients and equal to that of isavuconazole (77.1 days) and voriconazole (74.4) in the SECURE trial, regardless of the use of second-line therapy.[6] Patients receiving second-line therapy switched after 14 days of initial therapy.[4]	**IA**: As per SECURE study: 46.9 days for isavuconazole and 46.5 days for voriconazole (Table 22).[6] To account for model structure, the manufacturer had to estimate treatment duration in responders and non-responders to initial treatment.
	IM: Based on the VITAL trial, treatment duration with isavuconazole or voriconazole is 216.5 days, regardless of initial therapy or transition to second-line therapy.[5] Patients starting on isavuconazole and requiring second-line therapy switch after 14 days (according to manufacturer's clinical expert).[4] IM patients starting on voriconazole will transition to second-line therapy after 6 or 14 days depending on whether the pathogen is identified or not.[9] It was assumed the pathogen would be identified for 50% of patients (according to manufacturer's clinical expert).[4]	**IM**: Same method as for IA, but using the isavuconazole treatment duration (i.e., 149 days) from VITAL trial (Table 27).[5]
	According to the manufacturer's clinical expert, it was assumed that 75% of patients would start on IV therapy and 25% would receive oral therapy only.	The clinical expert consulted by CADTH for this review felt that the manufacturer's assumption was reasonable.
	No IV administration costs were included.	Acceptable, as patients are hospitalized while receiving IV medications.
Event	**Hospitalization LoS** **IA**: Mean LoS from SECURE trial (Table 75): 18.6 days.[6] **IM**: LoS 19.3 days (VITAL clinical study report, Table 80).[5] LoS for patients switching to L- AmB: 27.2 days.[5]	**IA**: Value is from initial hospital stay. Patients switching to L-AmB do not stay longer in hospital before switching to oral therapy. **IM**: Value based on the initial hospital stay for those receiving isavuconazole. Patients receiving L-AmB stay longer in hospital. CADTH was unable to validate source of LoS for patients switching to L-AmB.
	Hospitalization costs $1,261.63 per day.	Value from CIHI database (code 637: blood and lymphatic disorder in individuals aged 18 to 59 years).[8]
AEs	**AE costs** from OCCI database:[7] • hepatobiliary disorders: hyperbilirubinemia (E806: $487), abnormal liver function (R945:	All AEs assumed to be treated as ambulatory care. It is unclear how the manufacturer chose diagnosis codes. For example, for eye disorders, retinal hemorrhage was

Data Input	Description of Data Source	Comments
	$410), jaundice (R17: $449) and cholestasis (K710: $23,125). • skin and subcutaneous disorders: skin rash (R21: $129), erythema (L538: $139), skin lesions (B09: $124), drug eruption (L270 and L271: $167). • eyes: retinal hemorrhage (H356: $201). • nephrotoxicity (N19: $6,373).	observed in only 1.9% and 0% of voriconazole and isavuconazole patients, respectively, while other eye disorders occurred more frequently (e.g., diplopia, vision blurred, visual impairment; isavuconazole: 3.5%; voriconazole: 10.4%).[6] Cholestasis costs were based on the acute inpatient costs of cholestasis treatment, despite none of the patients with cholestasis being hospitalized.[6]
Health state	• Base utility value: 0.82.[29] • Disutility for IFD: 0.11.[19]	The base value is from an AML study, the most common underlying condition in the SECURE trial.[6,29] For patients on treatment, the base value is reduced by the disutility for IFD (assumed to be equivalent to that of pyrexia).[19]

AE = adverse event; ALL = acute lymphocytic leukemia; AML = acute myeloid leukemia; CIHI = Canadian Institute for Health Information; CLL = chronic lymphocytic leukemia; CML = chronic myeloid leukemia; EQ-5D = EuroQol 5-dimensions questionnaire; IA = invasive aspergillosis; IFD = invasive fungal disease; IM = invasive mucormycosis; ITT = intention-to-treat; IV = intravenous; L-AmB = liposomal amphotericin B; LoS = length of stay; NHL = non-Hodgkin's lymphoma; OCCI = Ontario Case Costing Initiative; RAMQ: Régie de l'assurance maladie du Québec; SD = standard deviation.

Table 11: Manufacturer's Key Assumptions

Assumption	Comment
Treatment compliance is 100% for both groups.	Acceptable, considering this is a life-threatening disease.
All patients with an IFD are initially treated at the hospital.	Acceptable, considering this is a life-threatening disease.
No wastage of medication is considered.	Several mediation forms will require a degree of wastage. This assumption likely underestimates medication costs.
Assumed that those who survive their IFD will have an average life expectancy of 17 years.	This is based on the assumption that the survival of an IFD is equivalent to the survival of a patient with CML. This is unlikely to be the case (see comments in Table 10 under efficacy).
Half (50%) of patients with IM will receive confirmation of their diagnosis and 50% will never receive confirmation.	This information is unknown. However, according to the clinical expert consulted by CADTH for this review, due to the rapid evolution of this disease, it is likely that most IM patients will be switched to second-line therapy within 5 to 6 days when the response to initial therapy is suboptimal.
A total of 75% of patients will start on IV treatment and switch to oral therapy, while 25% will receive oral therapy only.	Although different from the data from the SECURE and VITAL trials, this assumption was felt to be reasonable by the clinical expert consulted by CADTH for this review.
Patients with IM showing no clinical improvement after 14 days will receive second-line therapy with L-AmB.	As per clinical expert consulted by CADTH for this review, due to the rapid evolution of this disease, it is likely that most IM patients will be switched to second-line therapy within 5 to 6 days when the response to initial therapy is suboptimal.
Pathogen identification takes 6 days.	According to the CADTH clinical expert consulted for this review, if a patient has IM it is unlikely that more than 5 to 6 days will pass before second-line treatment is started due to the rapid evolution of this infection. Therefore, the time at which the pathogen is identified may not be a relevant pathway for IM patients.
Patients with IM started on voriconazole who receive pathogen identification will start second-line treatment after 6 days.	As per the clinical expert consulted by CADTH for this review, it is likely that, due to the rapid evolution of this disease, most IM patients will be switched to second-line therapy within 5 to 6 days when response to initial therapy is suboptimal.
A total of 5.75% of patients with suspected IA will have IM.	According to the CADTH clinical expert consulted for this review, this proportion is unknown. A proportion of 5.75% was considered reasonable, but it could also be as high as 10%.
Total duration of second-line therapy is equal	The information is unknown, but this assumption is considered reasonable.

Assumption	Comment
to the total duration of first-line therapy.	
The most common underlying condition in patients with IFD is AML.	In the SECURE trial, 44% of patients had AML. Other important underlying conditions were ALL (in 10% of patients); lymphoma (in 5 to 9% of patients); and CLL (in 5% of patients). In the VITAL study, 27% of patients had AML; 8% had ALL; 5% had CLL; 5% had multiple myeloma; and 35% had a bone marrow transplant.

ALL = acute lymphocytic leukemia; AML = acute myeloid leukemia; CLL = chronic lymphocytic leukemia; CML = chronic myeloid leukemia; IA = invasive aspergillosis; IFD = invasive fungal disease; IM = invasive mucormycosis; IV = intravenous.

Manufacturer's Results

CADTH reviewers found multiple programming errors that had an impact on the results. These have been listed in Table 7. In view of this, CADTH corrected the programming errors and reran the manufacturer's base case. The updated analysis showed that the incremental cost-utility ratio (ICUR) was $11,053 and that the ICUR was below $50,000 per QALY in 68.8% of the iterations (including 6.4% of the iterations where isavuconazole was dominant, i.e., more effective and less expensive). However, in 21.9% of the iterations, isavuconazole was dominated, i.e., less effective and more expensive.

CADTH Common Drug Review Reanalyses

In addition to the programming errors, CADTH reviewers noted that in the probabilistic analysis, arbitrary values (± 25% of the base value) were used to estimate the standard error (SE) in lieu of published parameter-uncertainty values such as SE, standard deviation, or 95% confidence interval. Therefore, prior to undertaking any reanalysis, CADTH replaced these arbitrary values by observed values when these were available. The updated values are listed in Table 12. In addition, a typographical error on body weight was corrected.

Table 12: Parameter-Uncertainty Values Used in the Probabilistic Analysis

Line[a]	Parameter	Mean Value[b]	SE	SD	n	95% CI LL	95% CI UL	Distribution[c]	Source
16	IV treatment duration — isavuconazole in IA	8.1		8.53	257	7.0571	9.1429	Gamma	SECURE study, Table 22[6]
17	IV treatment duration — voriconazole in IA	8.9		9.57	259	7.7345	10.0655	Gamma	
18	IV treatment duration — isavuconazole in IM	15.5		14.46	18	8.8198	22.1802	Gamma	VITAL study, Table 27[6]
21	All-cause mortality — isavuconazole in IA	0.2907				0.2360	0.3502		SECURE trial, Table 12.3.1.6[6]
22	All-cause mortality — voriconazole in IA	0.3101				0.2542	0.3704		
23	All-cause mortality — L-AmB-based regimens post isavuconazole in IA	0.2907				0.2360	0.3502		Assumed by the manufacturer to be the same as for isavuconazole

Line[a]	Parameter	Mean Value[b]	SE	SD	n	95% CI LL	95% CI UL	Distribution[c]	Source
									in IA
24	All-cause mortality — isavuconazole in IM	0.4286	0.1080		21	0.2169	0.6402		Estimated from SE formula for a proportion
25	All-cause mortality — voriconazole in IM	0.4860	0.0845		35	0.3204	0.6516		
26	All-cause mortality — L-AmB-based regimens in IM	0.8290	0.0636		35	0.7043	0.9537		
27	Percentage of patients receiving second-line therapy — isavuconazole in IA	0.4767	0.0311		258	0.4158	0.5377		
28	Percentage of patients receiving second-line therapy — voriconazole in IA	0.4535	0.0310		258	0.3927	0.5142		
29	Percentage of patients receiving second-line therapy — isavuconazole in IM	0.3333	0.1029		21	0.1317	0.5350		
31	Hospital LoS — isavuconazole in IA	18.6		18.27	245	16.3122	20.8878		SECURE trial, Table 75[6]
32	Hospital LoS — voriconazole in IA	18.6		18.27	245	16.3122	20.8878		Assumed by the manufacturer to be the same as for isavuconazole
33	Hospital LoS — L-AmB-based regimens in IA	18.6		18.27	245	16.3122	20.8878		
34	Hospital LoS — isavuconazole in IM	19.3		25.81	20	7.9883	30.6117		VITAL study Table 80[6]
39	Base utility	0.82		0.17	88	0.7845	0.8555	Beta	Leunis et al., Table 2[29]
40	Disutility IFD	0.11		0.02	89	0.1058	0.1142	Gamma	Beusterien et al., Table 1[19]
41	Cost of rash	129.0		175	15,917	126.28	131.72		OCCI R21 all ages ambulatory care[7]
42	Cost of erythema	139.0		101	56	112.55	165.45		OCCI L538 all ages ambulatory care[7]
43	Cost of skin lesion	124.0		102	2,391	119.91	128.09		OCCI B09 all ages ambulatory care[7]
44	Cost of drug eruption	157.0		150	140	132.15	181.85		OCCI L271 all ages ambulatory care

Line[a]	Parameter	Mean Value[b]	SE	SD	n	95% CI LL	95% CI UL	Distribution[c]	Source
									(typo on base value corrected[7])
45	Retinal hemorrhage	201.0		140	90	172.07	229.92		OCCI H356 all ages ambulatory care[7]
46	Cost of hyperbilirubinemia	487.0		321	77	415.30	558.70		OCCI E806 all ages ambulatory care[7]
47	Cost of abnormal hepatic function	410.0		309	328	376.56	443.44		OCCI R945 all ages ambulatory care[7]
48	Cost of jaundice	449.0		347	900	426.33	471.67		OCCI R17 all ages ambulatory care
49	Cost of cholestasis	23,135.0		23,376.33	8	1,713	141,971		OCCI K710 all ages acute inpatient. SE computed from minimum and maximum values (assuming equivalent to 99.7% CI)[7]
50	Cost of per day of hospitalization for nephrotoxicity	1,158.73		1,010.55	42	853.10	1,464.35		OCCI N19 all ages acute inpatient[7]
51	Prevalence of mucormycosis	0.0575			9,093	0.0527	0.0623		Bitar 2014[31]

95% CI LL = lower limit of the 95% confidence interval; 95% CI UL: upper limit of the 95% confidence interval; CI = confidence interval; IA = invasive aspergillosis; IFD = invasive fungal disease; IM = invasive mucormycosis; IV = intravenous; L-AmB = liposomal amphotericin B; LoS: length of stay; n: sample size; OCCI = Ontario Case Costing Initiative; SD: standard deviation; SE: standard error.

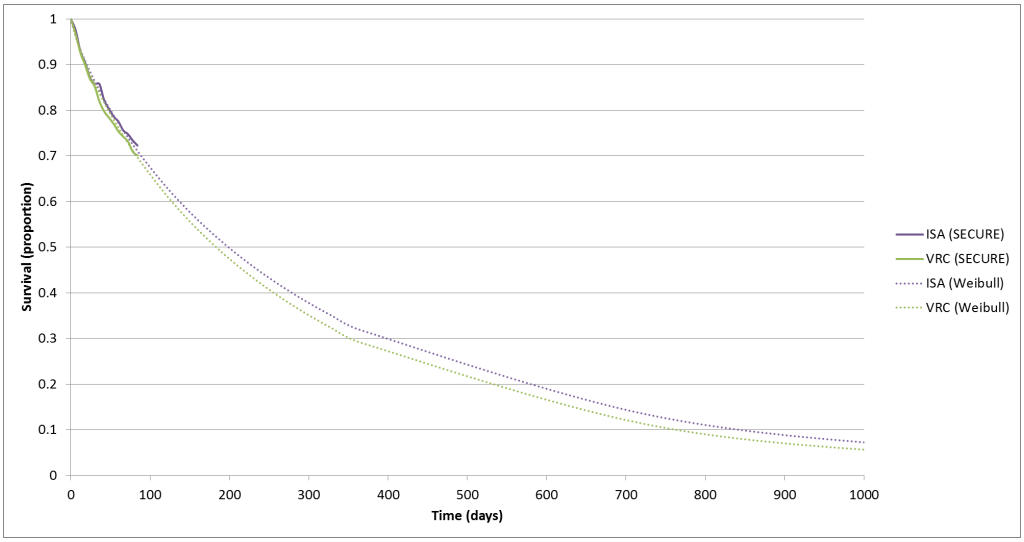
[a] Line: Corresponding line in the model sheet sensitivity-analysis parameters.

[b] Base values added for reference.

[c] Only distributions that were changed are listed here.

Furthermore, the method used by the manufacturer to estimate the long-term benefit of isavuconazole is likely overestimating the long-term benefit, as all patients alive on day 84 were assumed to be alive for 17 years (see Figure 2: ISA [Weibull]) and VRC [Weibull])). To rectify this, CADTH used survival curves from the SECURE trial paper (see Figure 2: ISA [SECURE] and VRC [SECURE]).[32] After testing for several statistical models, the Weibull distribution was found to provide the best fit for both isavuconazole and voriconazole and was used to project survival curves beyond the study period (see Figure 2: ISA [Weibull] and VRC [Weibull]). Utilities were applied to each curve and the incremental benefit was estimated by subtracting the total QALYs in the voriconazole group from the total QALYs in the isavuconazole group. These estimations showed that the manufacturer had overestimated the long-term benefit by about four times.

Figure 2 Estimations of Long-Term Survival From SECURE Trial



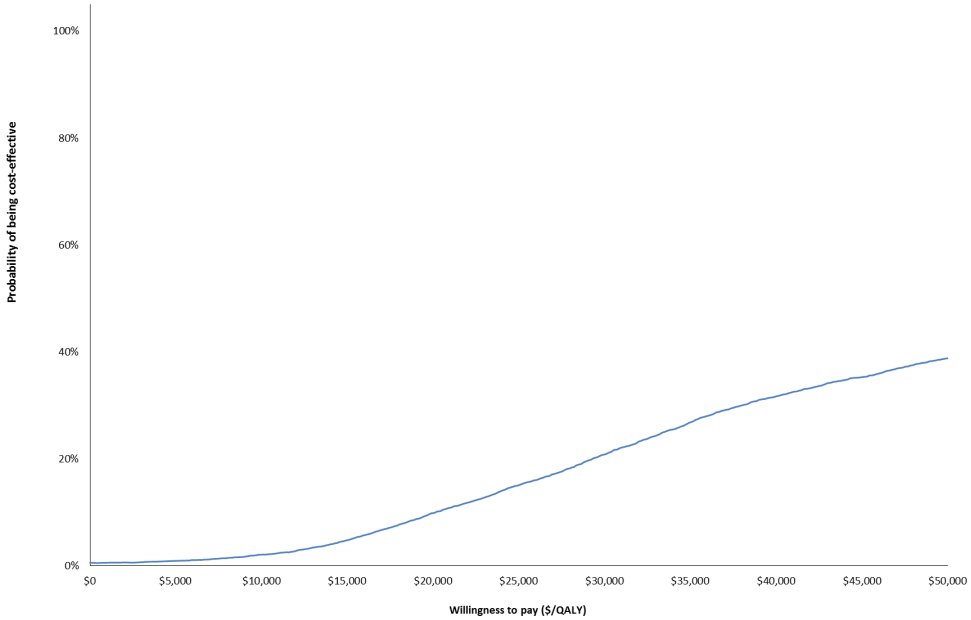
ISA = isavuconazole; VRC = voriconazole.

Note: ISA (Weibull) and VRC (Weibull) = Manufacturer's survival projections using study data only.

ISA (SECURE) and VRC (SECURE) = Digitalized survival curve from Maertens et al.[32]

Given that a large proportion of patients in the manufacturer trials had malignancies, it is inappropriate to assume that their baseline utility would be as high as 0.82 (as used in the model). Therefore, a recently published study assessing health-state preferences for acute myeloid leukemia (the most common malignancy in the trial populations) was used in the CADTH base case.[17] A weighted average of four health states in this study was used, based on the time typically spent in each health state.[12] This resulted in a utility value of 0.7239 (SE: 0.01968). Alternatively, in a scenario analysis, the value for the functionally cured state was replaced by the value for the remission state (0.62), giving a weighted average of 0.59393 (SE: 0.02678).

Figure 3: Cost-Acceptability Curve (CADTH Base Case)



QALY = quality-adjusted life-year.

Table 13: Results From CADTH Scenario Analyses

Scenarios			Total Costs ($)	Total QALYs	ICUR
Scenario 1: Testing Day 84 Mortality Rates					
1A	IA patients: Upper limit of mortality rate for isavuconazole and lower limit for voriconazole	Isavuconazole	49,249	2.362	Dominated
		Voriconazole	44,459	2.572	
		Incremental	4,789	−0.210	
1B	IA patients: Lower limit of mortality rate for isavuconazole and upper limit for voriconazole	Isavuconazole	49,676	2.556	$16,343
		Voriconazole	43,752	2.194	
		Incremental	5,925	0.363	
1C	IM patients: Upper limit of mortality rate for isavuconazole and lower limit for voriconazole (L-AmB)	Isavuconazole	49,151	2.424	$26,162,347
		Voriconazole	44,324	2.424	
		Incremental	4,826	0.000	
1D	IM patients: Lower limit of mortality rate for isavuconazole and upper limit for voriconazole (L-AmB)	Isavuconazole	49,598	2.506	$39,959
		Voriconazole	43,794	2.361	
		Incremental	5,805	0.145	

Scenarios			Total Costs ($)	Total QALYs	ICUR
Scenario 2: Testing Base Utility					
2	Base utility: 0.59393 (SE: 0.02678)	Isavuconazole	49,528	2.024	$90,890
		Voriconazole	44,161	1.965	
		Incremental	5,366	0.059	
Scenario 3: Testing Disutility for Infection					
3	Disutility: 0.218 (SE: 0.00212)	Isavuconazole	49,472	2.460	$75,313
		Voriconazole	44,146	2.389	
		Incremental	5,326	0.071	
Scenario 4: Testing the Type of Infection					
4A	IA patients only	Isavuconazole	49,614	2.495	$88,226
		Voriconazole	42,762	2.429	
		Incremental	5,852	0.066	
4B	IM patients only	Isavuconazole	63,204	1.975	Dominant
		Voriconazole	66,371	1.783	
		Incremental	−3,167	0.191	
Scenario 5: Percentage Use of Second-Line Antifungal Therapy					
5A	10.8% with isavuconazole in IM	Isavuconazole	48,725	2.465	$66,825
		Voriconazole	43,816	2.392	
		Incremental	4,909	0.073	
5B	35.7% with isavuconazole and 29.8% with voriconazole in IA	Isavuconazole	45,425	2.469	$93,220
		Voriconazole	38,947	2.400	
		Incremental	6,479	0.069	
Scenario 6: Long-Term Benefit					
6A	Optimistic benefit	Isavuconazole	49,516	5.213	$33,162
		Voriconazole	44,157	5.052	
		Incremental	5,359	0.162	

IA = invasive aspergillosis; ICUR = incremental cost-utility ratio; IM = invasive mucormycosis; L-AmB = liposomal amphotericin B; QALY = quality-adjusted life-year; SE = standard error.

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