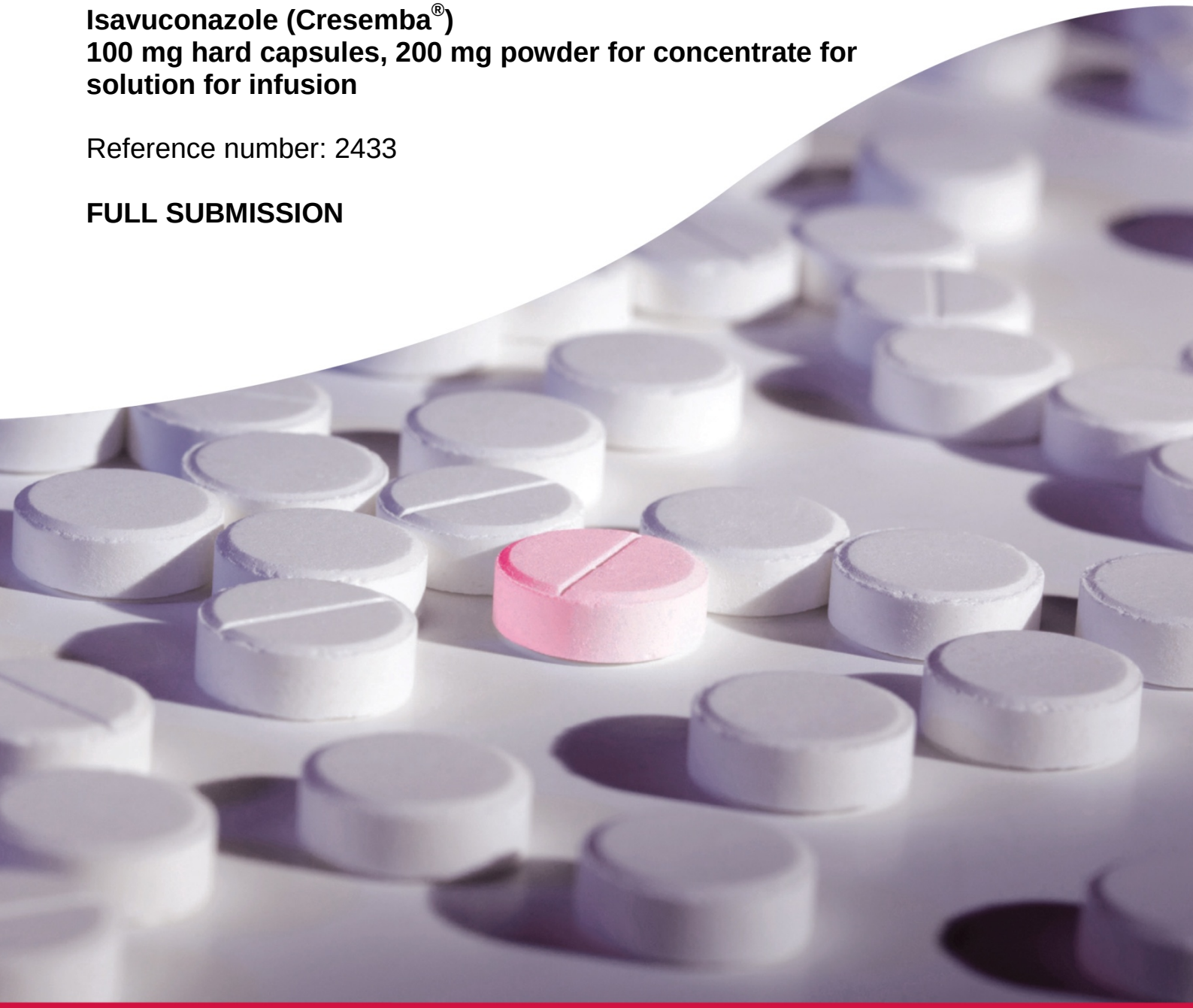
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Isavuconazole (Cresemba®)
100 mg hard capsules, 200 mg powder for concentrate for solution for infusion

Reference number: 2433

FULL SUBMISSION



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AWMSG Secretariat Assessment Report
Isavuconazole (Cresemba®▼) 100 mg hard capsules, 200 mg powder for concentrate for solution for infusion

This assessment report is based on evidence submitted by Basilea Pharmaceutica International Ltd[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Isavuconazole (Cresemba®▼) for the treatment of invasive aspergillosis in adults and the treatment of mucormycosis in adult patients for whom amphotericin B is inappropriate. Consideration should be given to official guidance on the appropriate use of antifungal agents[2,3]. ▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reaction[2,3].
Dosing	The recommended loading dose is 200 mg every 8 hours for the first 48 hours either orally (two capsules swallowed whole) or by intravenous infusion (one vial after reconstitution and dilution given over at least one hour). The recommended maintenance dose is 200 mg once daily starting 12 to 24 hours after the last loading dose[2,3]. Due to the high oral bioavailability, switching between intravenous and oral administration is appropriate when clinically indicated[2,3]. Duration of therapy is determined by the clinical response. Refer to the Summary of Product Characteristics for further information regarding dosing[2,3].
Marketing authorisation date	15 October 2015[2]
UK launch date	9 December 2015[1]

2.0 DECISION CONTEXT

2.1 Background

Invasive aspergillosis and mucormycosis are rare life-threatening fungal infections that may affect people who are critically ill or immunosuppressed[4]. Both infections have high mortality rates[5]. Invasive aspergillosis is caused by *Aspergillus* fungi and typically occurs in people who are immunocompromised, such as those with prolonged neutropenia, advanced HIV infection or inherited immunodeficiency, or who have had allogeneic haematopoietic stem cell transplants and/or lung transplants[6]. Mucormycosis is caused by infection with Mucorales fungi, most commonly *Rhizopus* and *Mucor* genera[7]. The most prevalent predisposing conditions are granulocytopenia, immunosuppression, diabetes and penetrating trauma[7].

Antifungal agents to treat aspergillosis include amphotericin B, triazoles (voriconazole, itraconazole and posaconazole) and echinocandins (caspofungin, micafungin and anidulafungin)[5]. Voriconazole is usually the treatment of choice, with liposomal amphotericin B as an alternative first-line treatment when voriconazole cannot be used[8], for example in people with significant liver dysfunction[9]. Caspofungin, itraconazole or posaconazole may be used if voriconazole or liposomal amphotericin B are ineffective or not tolerated[8]. Treatment options may also depend on the laboratory sensitivity of the confirmed causative agent. For treating mucormycosis, surgical debridement and antifungal therapy are recommended[7]. The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and European Confederation of Medical Mycology (ECMM) joint clinical guidelines state that the treatment of choice is liposomal amphotericin B at a dose of at least 5 mg/kg per day[7]. Other treatment options include posaconazole (off-label) and amphotericin B lipid complex[7].

Isavuconazole (Cresemba®) is the active moiety of isavuconazonium sulphate, a water-soluble triazole antifungal agent. Its fungicidal effect is to weaken the structure and function of the fungal cell membrane by blocking the synthesis of ergosterol, a key component of fungal cell membranes[5].

2.2 Comparators

The comparators included in the company's submission for the treatment of invasive aspergillosis were:

- voriconazole (VFEND®)
- liposomal amphotericin B (AmBisome®)
- posaconazole (Noxafil®)[1].

The comparators for the treatment of mucormycosis were:

- liposomal amphotericin B (AmBisome®)
- posaconazole (Noxafil®) (off-label)[1].

2.3 Guidance and related advice

- South Wales Cancer Network (2014) Investigation and management of invasive fungal infection (IFI) in haematological patients[10]
- ESCMID and ECMM (2013) Joint clinical guidelines for the diagnosis and management of mucormycosis[7]
- North Wales Cancer Network (2007) Guidelines for the use of antifungal drugs for haematology patients[11]

The All Wales Medicines Strategy Group (AWMSG) has previously issued a Statement of Advice for the use of posaconazole (Noxafil®) 300 mg concentrate for solution for infusion for the treatment of fungal infections in adults[12].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company's submission includes data from two phase III studies: SECURE and VITAL[1]. SECURE compared the efficacy and safety of isavuconazole with voriconazole in treating invasive aspergillosis. VITAL studied isavuconazole in rare invasive mycoses, including mucormycosis, and in invasive aspergillosis with renal impairment. The company additionally submitted a matched control analysis comparing patients with mucormycosis in the VITAL study with patients in a registry database (FungiScope) who had emerging fungal infections treated with amphotericin B formulations[1]. The company also conducted a mixed treatment comparison of isavuconazole, voriconazole and amphotericin B in invasive aspergillosis. The company provided details of a cross-study comparison of efficacy outcomes in patients with renal impairment in the SECURE and VITAL studies, and a meta-analysis of

overall response in historical mucormycosis control populations[1]; however, these are not discussed in this report.

3.1 Invasive aspergillosis

3.1.1 SECURE study

This randomised, double-blind, multicentre study compared isavuconazole to voriconazole in the primary treatment of invasive aspergillosis and other mycoses caused by filamentous fungi[13]. Patients aged ≥ 18 years were included if they had proven, probable or possible invasive fungal disease caused by *Aspergillus* species or other filamentous fungi[13] (refer to Glossary).

A total of 527 patients were randomised 1:1 to receive either:

- intravenous voriconazole 6 mg/kg every 12 hours for the first 24 hours followed by 4 mg/kg every 12 hours. From day 3 onwards maintenance voriconazole was given orally (200 mg twice daily) or intravenously (4 mg/kg twice daily)
- intravenous isavuconazole 200 mg three times a day for 2 days followed by 200 mg once daily either orally or intravenously.

Patients were treated until they reached a treatment endpoint or up to a maximum of 84 days. Placebo dosing was used to maintain blinding by matching the frequency of daily dosing[13].

The primary efficacy endpoint was all-cause mortality at day 42. The key secondary efficacy outcome was overall response at the end of treatment in the modified intention-to-treat population (patients with proven or probable invasive aspergillosis), assessed by a blinded, independent data review committee. In total, 400 patients (78%) switched from intravenous to oral dosing: 194 for isavuconazole and 206 for voriconazole. Results are shown in Table 1. The primary objective of demonstrating non-inferiority of isavuconazole to voriconazole was met: the upper limit of the 95% confidence interval was below the pre-specified 10% non-inferiority margin. A Kaplan-Meier analysis of survival up to day 84 showed that mortality was similar between treatment groups[13]. Subgroup analyses of overall response further supported non-inferiority of isavuconazole relative to voriconazole[1].

Table 1. SECURE study results: primary and key endpoints and treatment discontinuations[13]

	Isavuconazole	Voriconazole	Adjusted treatment difference (95% CI)*
Intention-to-treat population†	**n = 258**	**n = 258**	
All-cause mortality at day 42	48 (19%)	52 (20%)	−1.0% (−7.8 to 5.7%)
All cause mortality at day 84	75 (29%)	80 (31%)	−1.4% (−9.2 to 6.3)
Modified intention-to-treat population§	**n = 143**	**n = 129**	
All-cause mortality at day 42	28 (20%)	30 (23%)	−2.6% (−12.2 to 6.9%)

* isavuconazole minus voriconazole
† defined as all patients who received at least one dose of medication (11 patients did not receive either isavuconazole [n = 5] or voriconazole [n = 6])
§ defined as intention-to-treat patients with proven or probable invasive mycoses, as determined by the data review committee
CI: confidence interval

3.1.2 Mixed treatment comparison

A mixed treatment comparison between isavuconazole, voriconazole and amphotericin B in the treatment of invasive aspergillosis was conducted, using an indirect comparison of isavuconazole and amphotericin B, and fixed and random effects models[1]. Three studies of patients with proven, probable or possible invasive fungal infections caused by *Aspergillus* species or other filamentous fungi were compared: the SECURE study and 2 open-label studies. The company states that the

models and scenarios, including two sensitivity analyses, did not show any significant differences in all-cause mortality or overall response of isavuconazole treatment compared with either voriconazole or amphotericin B (liposomal and deoxycholate formulations)[1].

3.2 Mucormycosis

3.2.1 VITAL study

This open-label, single-arm, multicentre study evaluated the efficacy and safety of isavuconazole for treating invasive fungal infections caused by rare fungi including Mucorales, and invasive aspergillosis in patients with renal impairment[14]. Patients aged ≥ 18 years with data review committee-assessed proven or probable invasive fungal infection caused by *Aspergillus* species, Mucorales or other rare fungi were eligible for enrolment[14].

All patients (n = 146) received isavuconazole 200 mg given intravenously or orally every 8 hours for two days followed by a maintenance dose of 200 mg isavuconazole once daily until a treatment endpoint was reached or up to a maximum of 84 days[14]. The primary endpoint was overall response at day 42, assessed by a data review committee[14].

Of 37 patients with mucormycosis only, 32 had proven and 5 had probable disease; 11 had refractory disease and 5 had received previous antifungal treatment[14]. Outcome results for these patients are shown in Table 2. The overall success rate was 11%[14]. Of 21 patients receiving isavuconazole as primary therapy, 3 (14%) had a partial response at day 42 and 10 of 20 (50%) were considered to have a successful clinical response (a subcomponent of overall response)[1,15]. All-cause mortality (excluding one patient for whom survival status was unknown) was 13 (35%) at day 42, with 8 deaths attributed to progressive invasive fungal disease[14].

Table 2. Efficacy outcomes in patients with mucormycosis treated with isavuconazole[14]

	Patients with mucormycosis (n = 37)					
	Complete response n	Partial response n	Stable disease n	Disease progression n	Death n	Missing data n
Overall response at day 42*	0	4 (11%)	16 (43%)	1 (3%)	13 (35%)	3 (8%)
Overall response at day 84*	2 (5%)	5 (14%)	11 (30%)	1 (3%)	15 (41%)	3 (8%)
*As assessed by data review committee						

3.2.2 Matched control analysis of VITAL study results

In the absence of comparative data, mortality outcomes with isavuconazole and amphotericin B were compared by a matched control analysis of data from the VITAL study and data from the European FungiScope registry[1]. Of 136 cases of mucormycosis with available survival data up to day 42 in FungiScope, 33 were matched with the 21 patients in the VITAL study who received primary therapy with isavuconazole. Of the 33 FungiScope controls, 22 (66.7%) had received treatment with liposomal amphotericin B, 7 (21.2%) with amphotericin B deoxycholate, and 4 (12.1%) with amphotericin B lipid complex.

The all-cause crude and weighted mortality rates at day 42 were reported to be similar between the VITAL study cases (33%) and the matched FungiScope controls (39%); refer to Table 3[1]. A Kaplan-Meier analysis of survival rates up to day 84 showed similar mortality between the cases and controls (57.1% and 49.7%, respectively)[1,14].

Table 3. Matched control analysis: day 42 all-cause mortality[14]

	VITAL study: isavuconazole n = 21	FungiScope: amphotericin B n = 33	p-value
Crude all-cause mortality (95% confidence interval)	7 (33%) (14.6 to 57.0)	13 (39%) (22.9 to 57.9)	p= 0.775*
Weighted all-cause mortality (95% confidence interval)	33% (13.2 to 53.5)	41% (20.2 to 62.3)	p = 0.595†
*Calculated from Fisher's exact test † Calculated from a X^2 test			

3.3 Comparative safety

The most common treatment-emergent adverse events in the SECURE study, occurring in at least 5% of patients in either treatment group, were: nausea, vomiting, diarrhoea, pyrexia and hyperkalaemia[13]. Serious adverse events were reported in 134 (52.1%) isavuconazole-treated patients and 149 (57.5%) voriconazole-treated patients. Medicine-related adverse events were reported in 109 patients (42%) receiving isavuconazole and 155 patients (60%) receiving voriconazole (p = 0.001)[13].

Differences between moderate and severe adverse events in specific therapeutic areas were also noted. A lower frequency of hepatobiliary disorders (23 [9%] versus 42 [16%] p = 0.016), eye disorders (39 [15%] versus 69 [27%] p = 0.002), and skin or subcutaneous tissue disorders (86 [33%] versus 110 [42%] p = 0.037) were observed for isavuconazole compared with voriconazole[13]. A higher proportion of isavuconazole-treated patients had febrile neutropenia (5.4% versus 1.9%, p = 0.037); septic shock (5.4% versus 3.9%) and dyspnoea (1.9% versus 0.4%) were also reported as serious treatment-emergent adverse events although these results were not statistically significant[16].

In the VITAL study, 35 patients (95%) had one or more adverse events during treatment; 28 (76%) had serious adverse events[14]. Adverse events were similar in distribution to those reported in the SECURE study; the most common adverse events, occurring in over 25% of patients, were: vomiting, diarrhoea, nausea and pyrexia[14].

The Committee for Medicinal Products for Human Use (CHMP) considered the observed safety profile of isavuconazole to be in accordance with that expected for an azole antifungal agent[5]. Isavuconazole shares the toxicity profile of other triazoles, including drug-induced liver toxicity, although it was generally associated with fewer marked laboratory abnormalities than voriconazole[5].

3.4 AWTTC critique

- Isavuconazole is licensed for treating invasive aspergillosis and for treating mucormycosis in patients for whom amphotericin B therapy is inappropriate[2]. Both infections are rare, life-threatening conditions for which there are few treatment options available and mortality rates are high; CHMP acknowledged that there is an urgent medical need for new, effective antifungal medicines[5].
- For invasive aspergillosis, Welsh guidelines suggest that licensed first-line treatment options include: voriconazole, liposomal amphotericin B or caspofungin[10,11]. In their submission, the company did not consider caspofungin to be a relevant comparator as it is only indicated for second-line treatment of invasive aspergillosis in people for whom amphotericin B is inappropriate. In the absence of direct studies comparing isavuconazole to liposomal amphotericin B, the company conducted a systematic review and mixed treatment comparison, the results of which showed no significant differences. However, results should be interpreted with caution because of the heterogeneity of the studies and definition of overall response.
- No direct or indirect safety data for isavuconazole compared with amphotericin B, posaconazole or caspofungin was provided.

- For mucormycosis, the company included amphotericin B as a comparator; however, isavuconazole is only indicated for use in patients for whom liposomal amphotericin B is inappropriate, therefore, amphotericin B followed by a step down to posaconazole as the comparator treatment may not be the most appropriate comparison. There are currently no other licensed treatments for mucormycosis available other than amphotericin B. Clinical expert opinion sought by AWTTC suggests that posaconazole is used off-label for mucormycosis when amphotericin B is inappropriate, however no comparative evidence of isavuconazole versus posaconazole has been provided.
- No randomised studies of treatments for mucormycosis have been conducted and only limited data are available. In the absence of randomised controlled trials, the company carried out a matched control analysis using data from the VITAL study and data from European FungiScope registry. Although this approach has limitations, CHMP concluded that the analysis demonstrated that the treatment effect with isavuconazole in respect to improving survival of patients seems comparable to that of amphotericin B[5].
- Unlike some of the comparators, no routine monitoring of hepatic or renal function is needed during isavuconazole treatment and no dose adjustments are necessary in people with renal or mild to moderate hepatic impairment. Intravenous isavuconazole can be used in patients with moderate to severe renal impairment whereas intravenous voriconazole cannot be used in these patients[2,3,9]. In addition, isavuconazole also has a fixed, oral, once-daily maintenance dosing regimen without the need for therapeutic drug monitoring.

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes two separate cost-minimisation analyses (CMA) of isavuconazole as a treatment option for two separate indications:

- the first-line treatment of invasive aspergillosis
- the treatment of mucormycosis in patients for whom amphotericin B is inappropriate[1].

Isavuconazole is administered by intravenous infusion at a dose of 600 mg for the first 2 days (200 mg x 3), followed by a daily maintenance dose of 200 mg (intravenous followed by oral therapy), for both indications. For treating invasive aspergillosis, the comparator is a weighted basket of 75% voriconazole (intravenous followed by oral therapy); and 25% intravenous liposomal amphotericin B (AmBisome®) followed by step-down to oral posaconazole. For treating mucormycosis in people for whom amphotericin B is inappropriate, the comparator for isavuconazole is intravenous liposomal amphotericin B (AmBisome®) followed by step-down to oral posaconazole.

A simple model is used to calculate the difference in:

- total cost per patient of isavuconazole versus a weighted average total cost per patient of voriconazole and liposomal amphotericin B followed by step-down to oral posaconazole, for invasive aspergillosis; and,
- total cost per patient of isavuconazole versus total cost per patient of liposomal amphotericin B followed by step-down to oral posaconazole, for mucormycosis.

The model adopts an NHS perspective and a time horizon corresponding to the treatment duration, taken from published studies and judged to reflect time until resolution of the fungal infection, or death. The mean treatment duration for invasive aspergillosis is 46.7 days, based on the SECURE study[13]; and the mean treatment duration for mucormycosis is 136.5 days, based on the VITAL study[15]. No discounting is applied because the time horizon does not exceed one year. The model estimates

weight-based dosing for the comparators for both indications using data from the SECURE study[13] of isavuconazole for invasive aspergillosis. The company justifies this on the basis of the sample size of the SECURE study (n = 527 intent-to-treat) compared with the VITAL study[15] (n = 146 intent-to-treat). The analyses do not take into account clinical outcome data, mortality or patient quality of life because these parameters are assumed to be equal for isavuconazole and its comparators.

Costs considered by the calculations include: drug acquisition, hospitalisation, monitoring, intravenous drug preparation and administration, and treatment of adverse events. The dosing and schedules of isavuconazole[3] and voriconazole[9] treatments (for invasive aspergillosis only) were taken from the Summary of Product Characteristics (SPC) and all patients are assumed to start on intravenous treatment and are then switched to oral treatment based on the SECURE study[13]. Patients on voriconazole below 40 kg in body weight receive half doses. Patients on intravenous AmBisome® receive 3 mg/kg (50%) or 5 mg/kg (50%)[17] doses for invasive aspergillosis, or 5 mg/kg for mucormycosis, and are then switched to oral posaconazole as per its SPC[18].

Treatment durations were assumed to be equal for isavuconazole and voriconazole. AmBisome® treatment duration was taken from published evidence for invasive aspergillosis[19] and from matched patients in the FungiScope database for mucormycosis[14]. The treatment duration of posaconazole as a step down from AmBisome® was calculated based on the total treatment duration as observed in the SECURE study minus treatment duration of AmBisome®.

The number of vials used was calculated based on the patient weight distribution observed in the SECURE study. Length of hospital stay was assumed equal for all comparators for invasive aspergillosis and set to the mean length of stay of all patients in the SECURE study. Length of hospital stay for mucormycosis was taken from the VITAL study for isavuconazole and the FungiScope database for AmBisome®[14].

Cost per bed day was taken from published literature[20]. Cost of fortnightly monitoring for isavuconazole and weekly monitoring for the comparators included serum creatinine, urinalysis and liver function tests and was based on Scottish published unit costs[21]. Intravenous administration costs were based on interviews with nurses[22] and costed using published unit costs[23]. Number of cardiac and hepatobiliary adverse events were taken from the SECURE study and micro-costed using published costs[24-26]. Cost of nephrotoxicity of AmBisome® was estimated using published evidence[27,28].

No deterministic or probabilistic sensitivity analyses are presented to assess parameter uncertainty. Scenario analyses are used to explore the effect of changes on the results.

4.1.2 Results

The medicine acquisition cost for isavuconazole is based on a confidential discount offered to all patients in Wales via a Wales Patient Access Scheme (WPAS). The results of the base case analysis for invasive aspergillosis are presented in Table 4. [Commercial in confidence information removed].

Table 4. Results of the base case analysis for treatment of invasive aspergillosis

Base case analysis – invasive aspergillosis	Isavuconazole	Weighted average of comparator*	Voriconazole	AmBisome® → posaconazole
Medicine costs				
IV medicines	¶¶	£3,710	£2,580	£7,101
Oral medicines	¶¶	£2,876	£3,009	£2,477
Total medicine costs	¶¶	£6,586	£5,589	£9,578
Hospitalisation costs	£9,379	£9,379	£9,379	£9,379
Monitoring costs	£3	£18	£18	£18
Administration costs	£49	£64	£66	£57
Adverse event costs	£63	£138	£114	£212
Total costs	¶¶	**£16,185**	£15,165	£19,244
Cost difference	-	¶¶	¶¶	¶¶

*The weighted comparator was assumed to consist of 75% voriconazole and 25% AmBisome®/posaconazole in the base case.
¶¶ Commercial in confidence figure removed
IV: intravenous

The results of the base case analysis for invasive mucormycosis are presented in Table 5. [Commercial in confidence information removed].

Table 5. Results of the base case analysis for treatment of mucormycosis

Base case analysis – mucormycosis	Isavuconazole	AmBisome® → posaconazole
Medicine costs	¶¶	£16,355
IV medicines **Oral medicines**	¶¶	£7,932
Total medicine costs	¶¶	£24,287
Hospitalisation costs	£10,169	£13,427
Monitoring costs	£9	£38
Administration costs	£69	£106
Adverse event costs	£63	£212
Total costs	¶¶	**£38,070**
Cost difference		¶¶

¶¶ Commercial in confidence figure removed
IV: intravenous

Table 6 summarises the scenarios provided by the company to address uncertainty around the key input parameters. [Commercial in confidence information removed].

[Commercial in confidence information removed].

Table 6. Results of the scenario analyses

Scenario	Cost difference	Plausibility
Invasive aspergillosis		
Scenario 1: Observed treatment and hospitalisation durations for isavuconazole and voriconazole from the SECURE study instead of mean values for all patients	¶¶	This scenario is plausible. While the differences in treatment duration and length of hospital stay in the SECURE study were not statistically significant, they could have an effect on the cost.
Scenario 2: Treatment duration was doubled for all treatments (equally for intravenous and oral)	¶¶	This scenario is plausible because duration of treatment can be highly variable in practice, and may be higher than that evaluated in the SECURE study.
Scenario 3: Patient shares of voriconazole and AmBisome® altered to 40% voriconazole and 60% AmBisome® based on research on invasive fungal infection treatment practice in the UK commissioned by the company, which showed that the split was 61.5% AmBisome® versus 38.5% voriconazole.	¶¶	This scenario is plausible because treatment can be highly variable in practice, and may differ from the values used in the base case.
Scenario 4: 25% of isavuconazole and voriconazole patients start on oral therapy	¶¶	This scenario is plausible because 25% of patients in the VITAL study did not receive intravenous treatment.
Scenario 5: Treatment duration of AmBisome® set to 19 days[29]	¶¶	This scenario is plausible considering that alternative published sources suggest 19 days instead of the 14.5 days used in the base case.
Scenario 6: Twice daily dose of 300 mg assumed for voriconazole	¶¶	In the case of inadequate response, the voriconazole SPC allows for an increase in the maintenance dose up to 300 mg twice daily. It is unclear how many patients would have inadequate response: increasing the dose for all patients appears implausible.
Mucormycosis		
Scenario 8: Alternative comparator: oral posaconazole 300 mg once daily, as 3 x 100 mg tablets	¶¶	This scenario may be less plausible because posaconazole is not licensed for mucormycosis and the company state that no prospective studies, comparable with the VITAL study for isavuconazole, have been conducted to support such an indication. As such, the company suggest that posaconazole is likely to only be used as a step-down or second-line option following amphotericin B formulations. However, posaconazole is included in some clinical guidelines for the treatment of mucormycosis (off-label use).
Scenario 9: Alternative comparator: oral posaconazole, suspension of 200 mg in 5 ml, four times daily	¶¶	This scenario is implausible because the company states that posaconazole is not indicated or licensed for mucormycosis, nor have any prospective studies, comparable with the VITAL study for isavuconazole, been conducted to support such an indication.
¶¶ Commercial in confidence figure removed		

No deterministic or probabilistic sensitivity analyses are provided by the company.

4.1.3 AWTTC critique

The reliability of the CMA presented depends on the extent to which isavuconazole is considered to be therapeutically equivalent to the comparators. The company justifies this approach with the non-inferiority of isavuconazole compared with voriconazole in the SECURE study[13] and the fact that in its indirect comparison differences in mortality and response to treatment with isavuconazole were not statistically significant compared with AmBisome® for the treatment of invasive aspergillosis. The company also states that the results of the VITAL study[15] compared with data from a retrospective matched control population[14] demonstrated isavuconazole to provide similar survival benefits.

The results of the base case CMA indicate that the use of isavuconazole is generally cost-saving compared with the weighted comparator in invasive aspergillosis, cost-saving compared with AmBisome® followed by posaconazole, but more costly than voriconazole. For the treatment of mucormycosis, isavuconazole is cost-saving compared with AmBisome® followed by posaconazole but more costly than posaconazole alone.

Strengths of the economic analysis:

- The comparators used in the analysis appear to be in line with clinical guidelines for treating invasive aspergillosis. Although the North Wales Cancer Network recommends AmBisome® for patients with a proven fungal infection that is not sensitive to caspofungin, the company suggests that caspofungin is only indicated for second-line treatment of invasive aspergillosis in patients for whom amphotericin B is not suitable or whose disease is refractory to amphotericin B and is therefore not considered a relevant comparator.
- The company provides an appropriate account of all methods and results.
- The company uses amphotericin B as a comparator for the treatment of patients with mucormycosis in this analysis. Amphotericin B is the only other licensed medicine for the treatment of mucormycosis and clinical evidence to support the use of posaconazole off-label as a comparator in practice in Wales has not been provided. Other comparators used for the treatment of proven fungal infections have been excluded from the analysis because of their toxicity and inactivity against Mucorales fungi.

Limitations of the economic analysis:

- The phase III SECURE study evaluating efficacy and safety in invasive aspergillosis found isavuconazole to be non-inferior to voriconazole and the indirect and matched comparisons with AmBisome® for mucormycosis showed no significant differences between outcomes. However, no bioequivalence studies were conducted and although isavuconazole achieves similar outcomes to the comparators, its safety profile and mortality results appear favourable. A CMA may therefore underestimate the cost-effectiveness of isavuconazole.
- The company states that there was a statistically significant difference in moderate and severe cardiac and hepatobiliary adverse events in the SECURE study. Although this difference is reflected in the costs in the model, it would also have an effect on patients' quality of life. Therefore, a cost-utility analysis would have given a more appropriate comparison.
- The model used to calculate the cost-effectiveness of isavuconazole compared with the other treatment options is not a conventional health economic model and resembles a budget impact analysis. No model cycles are considered and all probabilities (e.g. hospitalisation, adverse events) are based on the mean values of the SECURE and VITAL studies and are assumed equal for all comparators. This severely limits the usefulness and accuracy of the model and the results it produces. No simulated patient cohort is included in the model but total cost per patient is calculated for the patients of the SECURE study specifically. This approach will affect the generalisability of the results.

- Patient characteristics for both analyses were taken from the SECURE study in invasive aspergillosis; this could introduce bias in the analysis of patients with mucormycosis if baseline characteristics were to differ between the two patient groups.
- The company states that the doses of AmBisome® used in the FungiScope analysis were higher than those recommended by the North and South Wales Cancer Networks (mean 428 mg, equivalent to 5.7 mg/kg versus 3 mg/kg). This might underestimate the efficacy of isavuconazole relative to AmBisome®, although it will also overestimate the cost of AmBisome®, both of which will cause bias. The company states that increased doses will be used in practice for mucormycosis and that the doses in the analysis are likely to be a good representation of clinical practice in Europe. However, this is an assumption.
- Data from the VITAL study were compared directly with outcome data from a database[14] registering patients with mucormycosis treated with AmBisome® by case-matching. Sample sizes were small (21 isavuconazole compared with 33 matched controls) and the patient characteristics were heterogeneous (e.g. variations in doses of AmBisome® received by patients, management techniques, geographical distribution, diagnostic approach, duration of treatment, and assessment of outcomes). In addition 36.4% of patients registered on the database switched from AmBisome® to posaconazole during the observed period of 42 days (whereas all patients in the model are assumed to switch) and the overall baseline mortality risk was higher in the more severely ill VITAL population. These inconsistencies and methodological limitations (no indirect comparison) will introduce considerable uncertainty. However, a more robust indirect treatment comparison might be impossible because of the rarity of the disease.
- Mean treatment durations and lengths of hospital stay for invasive aspergillosis were taken from the SECURE study and were assumed to be equal for isavuconazole and voriconazole. Although the differences in treatment duration and length of hospital stay for the two options were not statistically significant, they were not equal, which will introduce bias. Furthermore, treatment duration for AmBisome® is based on the median reported in published literature[19] and length of stay was assumed to be equal to the other comparators which will bias the comparison.
- The company did not use the most recent published unit costs and inflated some unit costs and published study costs to 2015 but not others. These inaccuracies will introduce bias.
- The company assumes a share of 75% voriconazole and 25% AmBisome® for the mixed comparator based on conflicting evidence. The company's own research on treatment practice in the UK shows a split of 61.5% AmBisome® and 38.5% voriconazole. These discrepancies will introduce bias. However, the base case approach can be considered conservative as it lowers the cost of the comparator and might underestimate the cost savings of isavuconazole which is shown in scenario analysis 3.
- The base case assumes that all patients start on intravenous isavuconazole while the company's own research suggests that a proportion of patients will only receive oral treatment. This will underestimate the cost savings with isavuconazole as explored in scenario 4 of the sensitivity analysis.
- In the SECURE study, 41.1% of patients were from Western Europe, Australia or New Zealand; 11.6% of patients were from Western Europe in the VITAL study (13.5% of patients with Mucorales infections). The company suggests that these patients are broadly representative of those treated in Welsh practice. However, it is unknown how many patients (if any) were recruited in the UK and it is therefore unclear how generalisable the results of the study are to the UK (and specifically to the Welsh population of patients with invasive fungal infections).

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any published evidence on the cost-effectiveness of isavuconazole for the treatment of people with invasive aspergillosis or mucormycosis.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The total number of people with invasive aspergillosis and mucormycosis in Wales was assumed to be equal to the incidence because people are expected to have died or had resolution of fungal infection within a year. Based on a retrospective French study of invasive fungal infections[30], the incidence was estimated to be 1.8 in 100,000 for invasive aspergillosis and 0.12 in 100,000 for mucormycosis. Considering a Welsh total adult population of 2,527,100 people[31], this would equate to 46 adults with invasive aspergillosis and 3 adults with mucormycosis per year in Wales. The incidences of invasive aspergillosis and mucormycosis are estimated to increase by 4.4% and 7.3% per year[30], respectively. This would result in 46 people with invasive aspergillosis in year 1 increasing to 54 people in year 5 and 3 people with mucormycosis in year 1 increasing to 4 in year 5. In total, it is expected that 49 people with invasive fungal infections will need treatment in year 1 increasing to 58 in year 5. [Commercial in confidence information removed]. The cost of a course of voriconazole was calculated at £5,589, AmBisome® followed by posaconazole was costed at £9,578 per course for invasive aspergillosis and £24,287 for mucormycosis. Medicine costs for adverse events were included but hospitalisation, monitoring and administration costs were excluded from the analysis.

The company provides the same series of scenario analyses as described in the cost-effectiveness evidence.

5.1.2 Results

The estimated net budget impact as presented by the company is shown in Table 7. The company estimates that the use of isavuconazole will save £3,401 in year 1, increasing to £22,095 in year 5 with a total cost saving over 5 years of £72,581.

Table 7: Company-reported costs associated with use of isavuconazole

	2017	2018	2019	2020	2021
Number of eligible patients*	49	51	53	56	58
Uptake (%)	¶¶	¶¶	¶¶	¶¶	¶¶
Estimated number of treated patients	¶¶	¶¶	¶¶	¶¶	¶¶
Medicine expenditure (£)	¶¶	¶¶	¶¶	¶¶	¶¶
Savings from displaced medicines (£)	−37,471	−118,003	−165,181	−216,795	−227,659
Secondary & tertiary care costs or savings (£) (adverse event medicine costs only)	−7	−23	−31	−41	−42
Net financial costs or savings (£)	−£3,401	−£10,891	−£15,503	−£20,691	−£22,095

*Total number of invasive fungal infections (including invasive aspergillosis and mucormycosis)
¶¶ Commercial in confidence figure removed

The estimated budget impact was most sensitive to changes in treatment duration and proportion of patients receiving AmBisome® followed by posaconazole in the weighted comparator for invasive aspergillosis, with cost savings increasing with longer

treatment duration and a higher proportion of patients receiving AmBisome® followed by posaconazole. [Commercial in confidence information removed].

5.1.3 AWTTC critique

Strengths of the budget impact analysis:

- The company presents a range of scenario analyses to account for uncertainty in the estimated budget impact.

Limitations of the budget impact analysis:

- The company uses population estimates from 2014 to calculate the incidence of invasive aspergillosis and mucormycosis despite there being more recent data available. This will introduce bias, although the effect on the budget impact is likely to be small.
- The incidence figures for invasive fungal infections are based on a single retrospective study which analysed the discharge database of the French hospital system from 2001-2010[30]. This study was considered to be appropriate to the Welsh context because of its large size, recent publication and the expected similarity of patient characteristics across Europe. However, the incidence figures reported by the European Medicines Agency[32] differ significantly especially for invasive aspergillosis (2 in 10,000 instead of 1.8 in 100,000) which will introduce bias. The company argues that the EMA figures reflect maximum rather than mean and that their average value is likely to be a better estimate of the actual incidence of invasive aspergillosis and mucormycosis in Wales.
- Uptake rates are estimates by the company and changes in uptake will affect the budget impact. However, the company has not provided sensitivity analyses for this parameter.
- The budget impact analysis does not include costs of monitoring, intravenous infusion administration or hospitalisation which will introduce bias and likely underestimate the cost savings of isavuconazole due to its lower toxicity.
- The budget impact analysis assumes a weighted comparator for the treatment of invasive aspergillosis of 75% voriconazole and 25% AmBisome® followed by posaconazole. It is unclear whether this assumption is realistic. Higher percentage of voriconazole use will decrease the cost savings made with isavuconazole; higher use of AmBisome® followed by posaconazole will increase potential cost savings.

5.2 Comparative unit costs

The costs of the different treatment options for invasive aspergillosis and mucormycosis are described in Table 8. Costs are based on patient weight and treatment duration as reported in the SECURE study.

Table 8. Examples of acquisition costs of treatments for invasive aspergillosis and mucormycosis

Regimen	Example dose	Approximate cost per 28-day treatment*
Isavuconazole (Cresemba®) 200 mg vial for intravenous infusion	600 mg once-daily for first 2 days, then 200 mg once-daily	£9,531
Isavuconazole (Cresemba®) 100 mg capsules, 14-pack	200 mg once-daily	£2,397
Voriconazole (Vfend®) 200 mg tablets, 28-pack	Body weight over 40 kg: 400 mg every 12 hours for 2 doses then 200 mg every 12 hours, increased if necessary to 300 mg every 12 hours Body weight under 40 kg: 200 mg every 12 hours for 2 doses then 100 mg every 12 hours, increased if necessary to 150 mg every 12 hours	£2,205 to £3,229 (> 40 kg) £1,103 to £1,615 (< 40 kg)
Voriconazole (Vfend®) 200 mg vial for intravenous infusion	6 mg/kg every 12 hours for 2 doses, then 4 mg/kg every 12 hours (reduced to 3 mg/kg every 12 hours if not tolerated) for maximum 6 months	£8,640 to £8,794
Amphotericin B encapsulated in liposomes (AmBisome®) 50 mg vial for intravenous infusion	3 mg/kg once daily	£11,506 to £16,109
Caspofungin (Cancidas®) 50 or 70 mg vial for intravenous infusion	70 mg on first day then 50 mg once daily (70 mg once daily if body-weight over 80 kg)	£9,264 to £11,670
Posaconazole (Noxafil®) 100 mg tablets, 24-pack	300 mg twice daily on first day, then 300 mg once daily	£2,164
Posaconazole (Noxafil®) 200 mg/5 ml oral suspension†	300 mg twice daily on first day, then 300 mg once daily	£1,018

* Based on the list price
† Where possible, Noxafil® tablets should be used in preference to the suspension because the tablets have a higher bioavailability; the suspension is not interchangeable with the tablets on a milligram-for-milligram basis

Not all regimens may be licensed for use in this patient population. See relevant SPCs for full licensed indications and dosing details[2,3,9,17,18,33,34].
Costs are based on British National Formulary list prices as of 10 August 2016, assuming wastage[24].
Costs of administration are not included.
This table does not imply therapeutic equivalence of medicines or the stated doses.

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, isavuconazole (Cresemba®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company does not anticipate that isavuconazole (Cresemba®) will be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 13 July 2016
Date range of evidence search: No date limits were applied to database searches.

6.5 Consideration of AWMSG policy relating to ultra-orphan medicines

The applicant company suggests that isavuconazole (Cresemba®) in the given population meets the AWMSG criteria for an orphan medicine in its invasive aspergillosis indication and an ultra-orphan medicine in its mucormycosis indication. AWMSG defines an orphan medicine as a medicine that has been granted EMA-designated orphan status and is used to treat a condition with a prevalence of no more than 5 in 10,000 patients in the UK (or 1,500 patients in Wales). An ultra-orphan medicine is defined by a prevalence of less than 1 in 50,000 in the UK equivalent to 60 patients or less in Wales. The definitions apply to the full population of the licensed indication[35].

Isavuconazole (Cresemba®) has been designated as an orphan medicine by the EMA for the treatment of invasive aspergillosis[32] and mucormycosis[36]. The PEDW statistics presented by the company suggest 9 finished consultant episodes of invasive pulmonary aspergillosis in adults, 14 cases of other pulmonary aspergillosis, 4 cases of other forms of aspergillosis, and 10 cases of unspecified aspergillosis (37 in total) in Wales in 2014/15 and no recorded cases of mucormycosis[37]. The EMA reports that invasive aspergillosis affected approximately 2 in 10,000 people and mucormycosis affected 0.06 in 10,000 people in the European Union in 2014. Applying these prevalences to the Welsh adult population of 2,543,797[38], AWTTC estimates that 509 people per year in Wales could develop invasive aspergillosis and 15 could develop mucormycosis and would therefore be eligible for isavuconazole. This would suggest that the total number of eligible patients meets the criteria for considering isavuconazole (Cresemba®) as an orphan medicine. AWTTC does not consider isavuconazole (Cresemba®) to be eligible as an ultra-orphan medicine because the full population of the licensed indication exceeds the 1 in 50,000 threshold.

For medicines designated orphan status, NMG/AWMSG will consider evidence on the following to inform its decisions (see Table 9).

Table 9. Orphan and ultra-orphan medicines and medicines specifically developed for rare diseases, considerations for NMG/AWMSG.

NMG/AWMSG considerations	AWTTC comments
The degree of severity of the disease as presently managed, in terms of quality of life and survival.	Invasive aspergillosis and mucormycosis are very rare, life-threatening fungal infections which can cause rapid deterioration in the condition of already critically ill and/or immunosuppressed people. Other licensed medicines are available for the treatment of invasive aspergillosis. There are currently no other licensed treatments for mucormycosis when amphotericin B is considered inappropriate. Treatment options may be limited by drug-drug interactions[39], tolerability and resistance, hence there is an urgent medical need for new, effective antifungal medicines, as acknowledged by CHMP. Mortality rates for both infections are high: invasive aspergillosis has reported mortality rates of 30-40% for treated patients; mucormycosis has a mortality rate of 50-85%, with a rate approaching 100% for disseminated disease[5].
Whether the medicine addresses an unmet need (e.g. no other licensed medicines).	It is widely accepted that there is an unmet need for the indication under consideration. For patients with mucormycosis infections for whom amphotericin B is inappropriate, there is no other licensed treatment. Isavuconazole provides an alternative licensed treatment option for invasive aspergillosis and mucormycosis infection, which is available in intravenous and oral forms[2,3].
Whether the medicine can reverse,	The SECURE study results showed non-inferiority of

NMG/AWMSG considerations	AWTTC comments
rather than stabilise the condition.	isavuconazole compared with voriconazole for the primary endpoint of all-cause mortality at day 42 and the key secondary efficacy outcome of overall response at the end of treatment in the modified intention-to-treat population.
Whether the medicine may bridge a gap to a "definitive" therapy (e.g. gene therapy), and that this "definitive" therapy is currently in development.	Isavuconazole does not bridge a gap to a definitive therapy.
The innovative nature of the medicine.	The company suggests that due to its small molecular size isavuconazole is the only azole with activity against Mucorales fungi and penetrates the blood-brain barrier, therefore offering advantages relative to other azoles for infections with CNS involvement[1]. However, specific comparative evidence demonstrating innovation has not been presented[5].
Added value to the patient which may not adequately be captured in the QALY (e.g. impact on quality of life such as ability to work or continue in education/function, symptoms such as fatigue, pain, psychological distress, convenience of treatment, ability to maintain independence and dignity).	No specific evidence of the added value relating to added value to the patient has been presented.
Added value to the patient's family (e.g. impact on a carer or family life).	Specific evidence has not been provided.

GLOSSARY

Proven, probably or possible invasive fungal disease

The European Organization for Research and Treatment of Cancer and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) defines three types of invasive fungal disease:

- 'proven' requires demonstration of fungal elements in diseased tissue (based on histology or culture) for most conditions;
- 'probable' requires host factors, clinical features and mycological evidence;
- 'possible' requires host factors and clinical evidence of invasive fungal disease only[40,41].

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