SMC2659

rezafungin acetate powder for concentrate for solution for infusion (Rezzayo®)

Napp Pharmaceuticals Limited

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The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan medicine process

rezafungin acetate (Rezzayo®) is accepted for restricted use within NHSScotland.

Indication under review: for the treatment of invasive candidiasis in adults.

SMC restriction: use should be on the advice of local microbiologists or specialists in infectious disease.

In a randomised, double-blind, phase III study, rezafungin was non-inferior to another echinocandin for global cure at day 14 in patients with candidaemia and/or invasive candidiasis and one or more systemic signs attributable to these conditions.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Rezafungin, an echinocandin derived from anidulafungin, selectively inhibits fungal 1,3-beta-D-glucan synthase, thereby preventing the formation of 1,3-beta-D-glucan, an essential component of the fungal cell wall not found in mammalian cells. This inhibition leads to rapid and concentration-dependent fungicidal activity against *Candida* species. [1, 2]

Rezafungin is given as a single 400 mg loading dose by intravenous (IV) infusion on day 1, followed by 200 mg on day 8 and once weekly thereafter. The duration of treatment should be based on the patient's clinical and microbiological response. In general, antifungal therapy should continue for at least 14 days after the last positive culture. [1]

1.2. Disease background

Invasive candidiasis is a serious fungal infection, including both bloodstream infection (that is, candidemia) and/or deep-seated invasive infections (such as intra-abdominal abscess, or infection of the bones), that is caused by *Candida* species. The infection typically occurs in patients with weakened immune systems or when damage in body tissues allows the infection to spread, for example, after transplantation or surgery or other immunosuppressive conditions. Specific risk factors among hospitalised patients, especially for those in intensive care units (ICU), include the presence of an indwelling central venous catheter, recent major surgery and total parenteral nutrition. There are at least fifteen distinct *Candida* species that cause human disease, but most invasive disease (>90%) is caused by the five most common pathogens, *C. albicans*, *C.glabrata*, *C. tropicalis*, *C. parapsilosis* and *C. krusei*. Each of these organisms has unique virulence potential, antifungal susceptibility and epidemiology, although, grouped together, significant infections due to these organisms are generally referred to as invasive candidiasis. Invasive candidiasis is a life-threatening disease that can be fatal due to damage to vital organs, and delays in initiation of appropriate antifungal therapy is associated with increased morbidity and mortality. [2-6]

1.3. Treatment pathway and relevant comparators

Management of invasive candidiasis includes source control (such as with removal of contaminated intravascular catheters) and early effective systemic antifungal therapy. The selection of an antifungal drug for initial treatment should be based on the patient's antifungal exposure/intolerance, severity of illness, relevant comorbidities and involvement of the brain, cardiac valves and/or visceral organs. Local epidemiology and surveillance data should also be considered. Guidelines generally recommend daily echinocandins IV (anidulafungin, caspofungin or micafungin [less commonly used due to its hepatoxicity]) as first-line therapy for adult patients. Alternative agents used to treat *Candida* infections include azoles (such as fluconazole, itraconazole and voriconazole) and polyenes (amphotericin B products, generally only used in second or later lines of therapy in patients failing or refractory to echinocandins or azoles due to their potential toxicity, except in chronic disseminated [hepatosplenic] candidiasis). In Scotland, however, the Scottish Antimicrobial Prescribing Group (SAPG) recommends fluconazole IV as first-line therapy in patients who are not critically ill, not on vasopressors for resuscitation of septic shock and without evidence of sepsis-associated organ dysfunction. Guidance from SAPG noted that based on 2017 national surveillance candidaemia data, most (≥85%) *Candida* species tested

were fluconazole susceptible. Guidelines also recommend that oral stepdown therapy from an echinocandin to fluconazole can be used when the patient is clinically stable, tolerates the oral route and the isolate is susceptible. [2-5, 7-10]

Voriconazole (SMC 194/05), for treatment of candidaemia in non-neutropenic patients, and caspofungin (SMC 74/03), for treatment of invasive candidiasis, are accepted for restricted use by SMC for patients with fluconazole-resistant *Candida* infection who do not respond to, or cannot tolerate amphotericin B therapy or who are at an increased risk of serious side effects with amphotericin. Anidulafungin (SMC 465/08) is accepted for restricted use for the treatment of invasive candidiasis in adult non-neutropenic patients who are unable to tolerate fluconazole or have invasive candidiasis that is resistant to fluconazole. Micafungin (SMC 497/08) is accepted for restricted use for the treatment of invasive candidiasis in adults, elderly and children (including neonates). Caspofungin (SMC 147/04) is also accepted for restricted use for the empirical therapy for presumed fungal infections (such as *Candida* or *Aspergillus*) in febrile, neutropenic adult patients under the care of specialists experienced in the management of fungal disease.

1.4. Category for decision-making process

Eligibility for a PACE meeting
Rezafungin meets SMC orphan criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of rezafungin for the indication under review comes from the ReSTORE study. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant study[1, 2, 11]

Criteria	ReSTORE
Study design	Phase III, multicentre, randomised, double-blind, study.
Eligible patients	• ≥18 years of age • Established mycological diagnosis of candidaemia and/or invasive candidiasis from a sample taken ≤4 days (96 hours) before randomisation. • Presence of one or more systemic signs attributable to candidaemia or invasive candidiasis (such as fever, hypothermia, hypotension, tachycardia, tachypnea, local signs of inflammation) appearing from ≤12 hours prior to the qualifying positive culture through time of randomisation.
Treatments	Using a double-dummy method: • Rezafungin (n=100) 400 mg IV loading dose on day 1, followed by 200 mg IV on day 8 and once weekly thereafter, for a total of two to four doses, with oral placebo step-down from day 4 if eligibility criteria were met, or • Caspofungin (n=99) 70 mg IV loading dose on day 1, followed by 50 mg IV once daily for ≥14 days up to 28 days, with optional step-down to oral fluconazole (depending on eligibility criteria) 6 mg/kg administered once daily (maximum daily dose of 800 mg) from day 4 plus IV placebo.
Randomisation	Equal randomisation stratified by diagnosis (candidaemia only or invasive candidiasis) and by APACHE II score/ANC (APACHE II score ≥20 OR ANC <500 cells/microlitre versus APACHE II score <20 AND ANC ≥500 cells/microlitre) at screening.
Primary outcome	Global cure confirmed by an independent DRC at day 14 (determined from clinical cure as assessed by the investigator, mycological eradication, and radiological

	cure [for qualifying patients with invasive candidiasis]). Non-inferiority was to be concluded if the lower bound of the 95% confidence interval for the difference in day 14 cure rates (rezafungin – caspofungin) was >-20%.
Secondary outcomes	• All-cause mortality at day 30 (FDA primary outcome, using a 20% non-inferiority margin) • Global cure by visit (at day 5, day 30, end-of-treatment and follow-up visits) • Mycological eradication by visit • Clinical cure by visit • Radiological cure by visit.
Statistical analysis	Efficacy analyses were performed in the mITT population, which included all patients who had a documented *Candida* infection based on central laboratory evaluation of a blood culture or a culture from a normally sterile site obtained ≤4 days (96 hours) before randomisation and received at least one dose of study drug. The study was powered only for the primary efficacy analyses for both the FDA and EMA/MHRA in the mITT population.
Abbreviations: ANC: absolute neutrophil count; APACHE: Acute Physiology and Chronic Health Evaluation; DRC: Data Review Committee; EMA: European Medicines Agency; FDA: U.S. Food and Drugs Administration; IV: intravenous; mITT: modified intent-to-treat; MHRA: Medicines and Healthcare products Regulatory Agency.	

Rezafungin was demonstrated to be non-inferior to caspofungin for global cure as assessed by the Data Review Committee (DRC) at day 14 in the mITT population. Results for the primary and secondary outcomes are summarised in Table 2.2. [1, 2, 11]

Table 2.2: Primary and selected secondary outcome results (mITT population) [1, 2, 11, 12]

	Rezafungin (N=93)	**Caspofungin (N=94)**	**Difference, % (95% CI)**
Global cure at day 14			
Cure, %	59	61	-1.1 (-14.9 to 12.7)
Failure or indeterminate, %	41	39	-
Failure, %	30	31	-
Indeterminate, %	11	8.5	-
All-cause mortality			
All-cause mortality at day 30, %	24	21	2.4 (−9.7 to 14.4)
Global cure by visit			
Global cure at day 5, %	56	52	3.8 (−10.5 to 17.9)
Global cure at day 30, %	50	49	0.5 (−13.7 to 14.7)
Clinical cure by visit			
Clinical cure at day 5, %	63	74	-11 (−24.0 to 2.3)
Clinical cure at day 14, %	67	67	-0.4 (−13.8 to 13.1)
Clinical cure at day 30, %	55	55	-0.5 (−14.6 to 13.7)

Mycological eradication by visit			
Mycological eradication at day 5, %	69	62	7.1 (−6.6 to 20.6)
Mycological eradication at day 14, %	68	66	1.8 (−11.7 to 15.2)
Mycological eradication at day 30, %	60	56	3.8 (−10.3 to 17.8)
Radiological cure by visit [a]			
Radiological cure at day 5, % (n/N)	27 (4/15)	35 (6/17)	-8.6 (-39.0 to 24.1)
Radiological cure at day 14, % (n/N)	65 (11/17)	59 (10/17)	5.9 (-26.3 to 37.0)
Radiological cure at day 30, % (n/N)	59 (10/17)	65 (11/17)	-5.9 (-37.0 to 26.3)
Abbreviations: CI = confidence interval; mITT = modified intent-to-treat. [a] Of patients with invasive candidiasis documented by radiologic/imaging evidence at baseline			

In the ReSTORE study, the median duration of IV and oral treatment combined in the rezafungin group and in the caspofungin group was 14 days. In the rezafungin group, 25% (25/98) patients switched to oral stepdown for a median duration of 10 days (range: 7 to 11 days), whereas in the caspofungin group 36% (35/98) patients switched to oral therapy for a median duration of 10 days (range: 5 to 12 days).[11]

2.2. Health-related quality of life outcomes

No Health-Related Quality of Life (HRQoL) outcomes were assessed in this study. [11]

2.3. Supportive studies

STRIVE was a multicentre, randomised, double-blind, phase II study, which assessed the efficacy and safety of rezafungin compared with caspofungin for the treatment of candidaemia and/or invasive candidiasis. Eligibility criteria were similar to the ReSTORE study except patients with neutropenia were excluded. The study consisted of two parts. In part A, patients were randomised equally to receive rezafungin 400 mg IV once weekly (n=81), or 400 mg IV on day 1, followed by 200 mg IV on day 8 and once weekly thereafter (n=57) for a total of two to four doses, or caspofungin once daily (n=69) (70 mg IV followed by 50 mg IV daily for up to 28 days with an optional oral fluconazole stepdown after day 3). In part B, patients were randomised in a 2:1 ratio to receive rezafungin IV once weekly (initially 400 mg once weekly, modified to 400 mg on week 1 followed by 200 mg once weekly thereafter, to align with the dosing regimen selected for the phase III study) or caspofungin IV once daily with an optional oral fluconazole stepdown after day 3. The primary outcome was overall response (defined as resolution of signs of candidaemia or invasive candidiasis plus mycological eradication) at day 14, assessed in the microbiological intention-to-treat population. The study was not powered for inferential analysis hence all analyses were exploratory. In parts A and B combined, overall response rates in the rezafungin 400 mg, rezafungin 400 mg then 200 mg, and caspofungin groups respectively were 60% (46/76), 76% (35/46) and 67% (41/61). All-cause mortality at day 30 was 16%, 4.4% and 13%, respectively. [13, 14]

A pooled analysis of the ReSTORE and STRIVE studies was performed, which was used in the economic analysis. Data from groups using licensed doses of rezafungin (400 mg in week 1 then 200 mg once weekly) and caspofungin (70 mg loading dose then 50 mg once daily) were included

in the analysis. The primary outcome was all-cause mortality at day 30 (tested for non-inferiority with a prespecified margin of 20%), assessed in a pooled mITT population. Mycological response was assessed as a secondary outcome. All-cause mortality at day 30 was similar between groups (19% [26/139]) for the rezafungin group and 19% [30/155] for the caspofungin group) with a weighted treatment difference of -1.5% and 95% confidence interval (CI): -11% to 7.7%, which met the prespecified non-inferiority margin of 20%. In the rezafungin and caspofungin groups, respectively, mycological eradication occurred in 73% and 65% of patients at day 5 (weighted treatment difference: 10% [95% CI: -0.3% to 20%]), and in 72% and 68% of patients at day 14 (weighted treatment difference: 4.3% [95% CI: -6.2% to 15%]). Pooled analysis of global response at day 14 was also conducted as a post hoc exploratory outcome, however this was limited by significant differences between studies in terms of outcome definition (radiological response was only included in ReSTORE) and assessment (by independent DRC in ReSTORE versus by investigator in STRIVE). Global response rates in the rezafungin and caspofungin groups respectively were 65% and 63% (weighted treatment difference: 2.3% [95% CI -8.2 to 13.9]). [2, 15]

2.4. Indirect evidence to support clinical and cost-effectiveness comparisons

There is direct evidence comparing rezafungin with caspofungin, however there were no direct data for the other comparators. Therefore, an indirect treatment comparison was performed as summarised in Table 2.3. This was used to support the assumption of clinical equivalence in the economic base case and as a source of efficacy data in an economic scenario analysis.

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Bayesian NMA.
Population	Adults (≥18 years) with (confirmed) candidaemia and invasive candidiasis.
Comparators	Caspofungin, micafungin, fluconazole, anidulafungin, isavuconazole, amphotericin B.
Studies included	Eight studies.
Outcomes	All-cause mortality, global response, mycological response, clinical response.
Results	The submitting company presented results using caspofungin (rather than rezafungin) as the reference treatment, however results with rezafungin as the reference treatment were provided on request. There was no evidence of a difference in efficacy between rezafungin and the comparators, except isavuconazole, compared with which rezafungin appeared to perform better in terms of mycological response. NMA results were considered confidential by the company.
Abbreviations: CrI: credible interval; NMA: network meta-analysis; OR: odds ratio.	

*Other data were also assessed but remain confidential.**

3. Summary of Safety Evidence

The safety profile of rezafungin appeared consistent with what is known from other medicines in the therapeutic class of echinocandins. However, in clinical studies, rezafungin showed more liver-related adverse effects compared with caspofungin, with seven patients meeting Hy's criteria and two cases of drug-induced liver injury reported only with rezafungin, which was of concern for regulators. The potential for serious hepatotoxicity could not be ruled out. A warning about liver

effects is included in the Summary of Product Characteristics (SPC), similar to warnings found in SPCs for other echinocandins. [1, 2]

In the ReSTORE study, any treatment-emergent adverse event (AE) was reported by 91% of patients in the rezafungin group and 85% in the caspofungin group and these were considered treatment-related in 16% and 9.2% respectively. In the rezafungin and caspofungin groups respectively, patients with a reported serious AE were 56% versus 53% and the proportion of AEs that led to study treatment discontinuation prior to day 14 were 8.2% versus 7.1%.[11]

The most frequently reported treatment-emergent AEs of any grade with an incidence >10% in the rezafungin group versus the caspofungin group were pyrexia (14% versus 5.1%), hypokalaemia (13% versus 9.2%), pneumonia (10% versus 3.1%) and septic shock (10% versus 9.2%). [11]

The proportion of patients with at least one serious AE resulting in death was 29% and 26% respectively. However, none of these events were considered related to study treatment.[2, 11, 15]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In a randomised, double-blind, phase III study, rezafungin was non-inferior to caspofungin for global cure at day 14 in patients with candidaemia and/or invasive candidiasis and one or more systemic signs attributable to these conditions. [1, 2, 11]
- Other outcomes were supportive of the primary outcome. [1, 2, 11]

4.2. Key uncertainties

- There remains some uncertainty regarding the comparative efficacy of rezafungin against caspofungin, primarily due to the use of a wide 20% non-inferiority margin in ReSTORE, which was intended to allow for a reasonable number of patients to be included within a shorter time. Additionally, the lower bound of the 95% confidence interval observed for the primary outcome was approximately -15%. Regulators acknowledged this uncertainty, which they noted was likely due to the relatively small size of the key study. They considered data were still limited to support that rezafungin should be considered as effective as other echinocandins; but they acknowledged there are relatively few antifungal agents available and the overall assessment of efficacy results, including the FDA primary outcome of all-cause mortality at day 30, supports the conclusion that rezafungin has efficacy in the studied population. [2]
- The submitting company claims potential advantages with rezafungin over caspofungin in terms of early mycological eradication, time to negative blood culture, hospital stay and earlier hospital discharge. However, the clinical data presented do not provide sufficient evidence to conclude significant advantages with rezafungin over caspofungin.
- The submitting company considered that the relevant comparators are caspofungin, anidulafungin, micafungin and fluconazole. Clinical experts consulted by SMC confirmed either echinocandins (such as caspofungin, anidulafungin and micafungin) or azoles (such as fluconazole) may be used. Some experts also mentioned voriconazole, posaconazole and isavuconazole. Experts generally considered that the options most likely to be displaced by

rezafungin are the other echinocandins, primarily anidulafungin or caspofungin. Direct data are available only against caspofungin. Therefore, an indirect treatment comparison was performed, which had several limitations. Sparse data were included for some comparators and outcomes. There was considerable heterogeneity across studies in terms of baseline characteristics, as well as methodological differences in terms of outcome definitions, timepoints and assessment. Generalisability of results to patients with fluconazole resistance or an intolerance or inadequate response to fluconazole is uncertain, as this was rarely reported in the included studies. Also, limited number of patients had neutropenia or severe disease. Most studies were published several years ago and therefore may not reflect current clinical practice. Wide credible intervals, especially in the random effects model, suggest uncertainty. Safety was also not assessed. Due to these limitations, the company's conclusion that rezafungin has equivalent efficacy to the comparators is uncertain. Clinical experts consulted by SMC generally considered the assumption of clinical equivalence versus comparators reasonable, but they highlighted the lack of direct comparisons versus anidulafungin or fluconazole and questioned the equivalence in patients with neutropenia and in terms of safety.

- Some factors affect the generalisability of ReSTORE results to the Scottish population. Only approximately 17% of patients had Acute Physiology and Chronic Health Evaluation II (APACHE II) scores ≥20, complicating the assessment of rezafungin efficacy in critically ill patients. Certain types of invasive candidiasis, such as osteomyelitis, endocarditis or myocarditis, were excluded. In addition, only eleven isolates were resistant to fluconazole at baseline (with four receiving rezafungin). Regulators noted given the small number of patients with fluconazole-resistant isolates, it is challenging to make any conclusions regarding the potential influence of fluconazole resistance on the outcomes of patients treated with either rezafungin or caspofungin; however, fluconazole resistance did not seem to affect the minimum inhibitory concentration (MIC) of echinocandins. [2]

4.3. Clinical expert input

Clinical experts consulted by SMC noted that there are options currently available including in the same therapeutic class as rezafungin; however, these require daily administration. They considered that this new echinocandin may offer advantages in terms of treatment administration due to its once-weekly dosing, unlike other antifungals used in this indication that require daily administration.

4.4. Service implications

Clinical experts consulted by SMC considered the once-weekly dosing could potentially facilitate earlier discharge or management through outpatient parenteral antimicrobial therapy (OPAT) or Hospital at Home services, where applicable. Some clinical experts highlighted potential implications for laboratory services regarding tests associated with the introduction of rezafungin.

5. Summary of Patient and Carer Involvement

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of rezafungin, as an orphan medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Invasive candidiasis is a complication usually of high intensity hospital care including invasive surgery, critical care, broad spectrum antibiotic use, immunosuppression and cancer therapy. It is a serious and potentially fatal infection that has a negative impact on patients, carers and families. Candidaemia has high mortality of approximately 40%. Invasive candidiasis can cause patients significant discomfort with the most common symptoms being fever or chills, abdominal pain, muscle aches, skin rashes and fatigue. Additional symptoms can develop if an infection spreads to other parts of the body where it can cause long-term damage. Patients who develop invasive candidiasis are usually hospitalised if they are not already in hospital which can have a devastating effect on patients and their families. Returning to or extending a patient's stay in hospital can particularly affect their mental health and wellbeing, often feeling like a considerable set back in their recovery process.

- Approximately 10-20% of patients with invasive candidiasis require echinocandin therapy due to treatment failure, resistance, toxicity or interactions with azole antifungals. Currently available echinocandins are administered daily as an intravenous infusion. There is unmet need for a small proportion of these patients who become fit for discharge and the only reason they are in hospital is to receive echinocandin treatment. These patients may be treated at an OPAT or equivalent service that they would be required to visit daily for administration via an ongoing indwelling vascular device. Some patients are unable to attend an OPAT service daily so would remain as a hospital inpatient to complete their treatment.

- Rezafungin is administered once weekly by intravenous infusion and may be at least as effective as once daily echinocandins. This would mean that the patient would only need to attend as an outpatient once a week rather than daily. This would have benefits for the patient including reducing their hospital stay and associated risks (such as healthcare-related infections) and reducing the time and costs associated with travelling to daily outpatient appointments, which may be far from home. This is expected to have psychological benefits by reducing isolation and allowing patients to return to normal life, work and family activities sooner which would overall improve their quality of life and reduce the financial impact. Patients would not require an indwelling vascular device and therefore avoid the associated risk of complications including infections while also providing a more comfortable treatment experience.

- A very small number of patients would be expected to receive rezafungin. Specifically, those who are fit for discharge but require continued echinocandin treatment. It would not be used for inpatients apart from in exceptional circumstances (for example restricted

intravenous access). Rezafungin would therefore be used within the licensed indication for patients who would benefit from the reduced administration schedule. PACE clinicians highlighted that patients can be started on another echinocandin and switched to rezafungin on discharge.

- Rezafungin should be a protected antifungal agent authorised by an infection specialist and only used within OPAT or equivalent services. Use should be carefully monitored via antimicrobial management teams and local antimicrobial stewardship programmes. PACE clinicians noted that other echinocandins are also protected antifungal medicines and must be approved by a microbiologist or infectious diseases clinician.

Additional Patient and Carer Involvement

We received a patient group submission from Anthony Nolan which is a registered charity. Anthony Nolan has received 0.01% pharmaceutical company funding in the past two years, with none from the submitting company. A representative from Anthony Nolan participated in the PACE meeting. The key points of their submission from have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case, as described in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-minimisation analysis (CMA)
Time horizon	The time horizon in the CMA was the duration of the acute infection (up to 30 days).
Population	Rezafungin is indicated for the treatment of invasive candidiasis in adults (>18 years old).
Comparators	Rezafungin was compared to the once daily treatments of caspofungin, fluconazole IV and anidulafungin.
Model description	For the CMA, a short-term decision tree was developed to capture invasive candidiasis treatment up to 30 days. Each pathway in the decision tree was defined by the probabilities of events occurring and the associated costs. Patients with invasive candidiasis started on either once weekly rezafungin, or one of the once daily comparator treatments. Treatment effectiveness was assessed on day 5 or 14. Treatment success at day 5 or day 14 meant patients could stay on the same treatment or step down to oral fluconazole. Treatment switching to a second line treatment could occur at day 14, and it was assumed that patients can only experience one treatment failure.
Clinical data	Direct evidence for once weekly rezafungin and once daily caspofungin was sourced from the phase III, randomised double-blind ReSTORE study and the phase II randomised double-blind STRIVE study.[1, 2, 11, 13, 14] A pooled analysis of the two studies was used in the base case for parameters such as patient characteristics, length of stay in hospital, step-down to oral treatment and safety. The ReSTORE study was used to inform treatment duration and early discharge variables. Early discharge was defined as the duration between the observed point of discharge in the study and the point of discharge the company believed may be achieved in

	Scottish clinical practice. The pooled analysis primary endpoint was all-cause mortality at day 30 and a secondary endpoint is proportion of patients with mycological eradication at day 5 and day 14. Each study and the pooled analysis showed that rezafungin was non-inferior to caspofungin. A Network meta-analysis (NMA) was conducted to establish clinical equivalence between rezafungin, caspofungin, fluconazole and anidulafungin.
Extrapolation	No extrapolation of clinical data was necessary in the CMA.
Quality of life	The analysis assumed clinical equivalence between rezafungin and comparators, meaning health benefits were not included.
Costs and resource use	Costs included medicine acquisition costs for rezafungin and the comparators, disease management costs and adverse events costs. The medicine acquisition costs included the cost of the step-down oral treatment and second line treatment costs. Disease management costs included hospitalisation costs (ICU and general ward), laboratory testing costs, medicine administration costs, aseptic reconstitution costs and outpatient parenteral antibiotic therapy (OPAT) costs.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price of rezafungin.

6.2. Results

The cost minimisation analysis is based on the assumptions that once weekly rezafungin and the once daily comparators are equally effective in terms of 5-day, 14-day and the 30-day outcomes. The results of that analysis, utilising list prices for rezafungin are shown in Table 6.2. The results suggested that while rezafungin was associated with a higher acquisition cost, it resulted in lower disease management costs, particularly from shorter ICU hospital stay, than the comparators.

Table 6.2: Cost results for cost minimisation analysis (list price for rezafungin)

Cost description	Rezafungin	Caspofungin	Fluconazole	Anidulafungin
Acquisition	£6,976	£1,548	£1,321	£1,777
Disease management	£39,870	£50,223	£50,038	£50,692
TEAE costs	£524	£558	£558	£558
Total costs	£47,370	£52,328	£51,917	£53,027
Incremental costs	-	-£4,958	-£4,547	-£5,657

Abbreviations: TEAE: treatment emergent adverse events

*Other data were also assessed but remain confidential.**

6.3. Sensitivity analyses

The company explored uncertainty within the modelling through probabilistic sensitivity analysis, deterministic sensitivity analysis and scenario analysis. A select range of the conducted scenario analyses are presented in tables 6.3a and 6.3b. These results exclude the PAS discount on rezafungin.

Table 6.3a: Scenario analysis for cost minimisation analysis (list price for rezafungin)

#	Parameter	Base case	Scenario	Incremental costs vs		
				caspo.	flucon.	anidula.
0	Base case			-£4,958	-£4,547	-£5,657
1	Source of treatment efficacy and length of stay estimates	Pooled analysis	ReSTORE study	£1,286	£1,697	£587
2			STRIVE study	-£9,093	-£8,681	-£9,792
3	Earlier discharge from general ward	Included	Removed	-£4,387	-£3,975	-£5,086
4	% of patients stepping down to oral treatment	ReSTORE study: 28% for rezafungin and 36% for caspofungin, fluconazole and anidulafungin	Scottish clinical expert: 95% for fluconazole IV and 10% for rezafungin, caspofungin and anidulafungin	-£4,952	-£4,549	-£5,648
5	Length of ICU stay	Pooled analysis: 6.8 days for rezafungin, 9.8 days for comparators	Uniform ICU length of stay (9.8 days) across the intervention and comparator arms	£3,458	£3,870	£2,759
6	length of general ward and ICU stay	Pooled analysis: 6.8 ICU days and 20.8 general ward days for rezafungin, 9.8 ICU days and 21.0 general ward days for comparators	Uniform ICU (9.8 days) and general ward length of stay (21.0 days) across treatment arms	£3,201	£3,613	£2,502

Abbreviations: Caspo: caspofungin, Flucon: fluconazole, Anidula: anidulafungin, ICU: intensive care unit

6.4. Key strengths

- The presence of direct comparative evidence and the non-inferiority result demonstrated in the ReSTORE study supports the premise of clinical equivalence between rezafungin and caspofungin.
- All cost data utilised in the model were sourced from reliable databases and publications. The model also included the potential for step-down treatment to oral fluconazole and second line treatment costs, which were tested for in the scenario analysis.

6.5. Key uncertainties

- The results of the clinical studies and NMA conducted by the company suggested that there was no statistical difference in the efficacy of rezafungin and the other comparators included in the economics. The company used these results to justify the use of a cost-minimisation analysis. Those findings were subject to uncertainty due to wide confidence intervals, which in

turn introduced uncertainty into economics. However, expert advice received by the SMC supported the idea of clinical equivalence between the included treatments.

- As length of stay, particularly in ICU settings, was a critical parameter of the economic model, various scenarios were explored. Variability in the ICU length of stay estimates impacted the economic outcomes, as evidenced by Scenarios 5 and 6. These scenarios demonstrated that small changes in length of stay can lead to large fluctuations in cost savings, highlighting the sensitivity of the economic model. Clinical feedback received by the SMC determined that the length of stay in ICU was unlikely to be shorter for rezafungin patients in Scottish practice. Consequently, the magnitude of the cost savings, through reduced ICU days for once-weekly rezafungin, are unlikely to be realised.
- The assumption of an earlier discharge, applied to general ward length of stay parameter, introduced uncertainty. The ReSTORE study was blinded meaning that patients receiving rezafungin were required to remain in hospital to receive a placebo treatment. Therefore, the study did not provide direct evidence of earlier discharge. Rather the model relied on investigators opinion that in normal practice there was potential to discharge rezafungin patients earlier to either home or OPAT settings (with the speculated length of stay reduction considered as academic in confidence by the company). SMC experts suggested that rezafungin may be used as a treatment option at the point of discharge, switching from the once daily treatment used while the patient is in hospital. This would facilitate earlier discharge. While this was not formally modelled, it would reduce the acquisition costs associated with rezafungin, which may improve the economic case relative to the scenario where rezafungin is used across the full treatment duration.

7. Conclusion

The Committee considered the benefits of rezafungin in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as rezafungin is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted rezafungin for restricted use in NHSScotland.

8. Guidelines and Protocols

The Scottish Antimicrobial Prescribing Group (SAPG) published guidance on the treatment of candidaemia and the use of antifungal agents in March 2019; this guidance is currently under review. [10]

The European Society of Intensive Care Medicine (ESICM) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) published guidance on the management of invasive candidiasis in critically ill patients in March 2019. [5]

ESCMID also published separate guidelines on the diagnosis and management of *Candida* diseases in non-neutropenic adult patients, and in adults with haematological malignancies after haematopoietic stem cell transplantation respectively, in December 2012. [7, 8]

The European Conference on Infections in Leukaemia (ECIL) published guidelines on the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukaemia and haematopoietic stem cell transplant patients in July 2007, which were last updated in March 2017. [9, 16]

The Infectious Diseases Society of America (IDSA) published guidelines on the management of candidiasis in January 2004, which were last updated in February 2016. [4, 17]

9. Additional Information

9.1. Product availability date

20 March 2024

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per administration (£)
rezafungin acetate	**single 400 mg loading dose by IV infusion on day 1, followed by 200 mg on day 8 and once weekly thereafter for a duration based on the patient's clinical and microbiological response**	**First administration: £4,000** **Subsequent administration: £2,000**

Costs from eMC Dictionary of Medicines and Devices Browser on 08/04/2024. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 17 May 2024.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.