isavuconazole, 200mg powder for concentrate for solution for infusion and 100mg hard capsules (Cresemba®) SMC No. (1129/16)

Basilea Pharmaceutica International Ltd

04 March 2016

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 Scotland.

The advice is summarised as follows:

**ADVICE**: following a full submission considered under the orphan process

**isavuconazole (Cresemba®)** is accepted for use within NHS Scotland.

**Indication under review**: in adults for the treatment of:
- invasive aspergillosis
- mucormycosis in patients for whom amphotericin B is inappropriate

A phase III, randomised, double-blind, non-inferiority study demonstrated that, in the treatment of invasive aspergillosis, isavuconazole was non-inferior to a triazole antifungal for all-cause mortality through day 42, and had a similar overall response at the end of treatment. A phase III, open-label, single-arm study demonstrated that, in the treatment of mucormycosis, isavuconazole had a treatment effect on all-cause mortality and overall response. The treatment effect was considered to be comparable to that observed in external control studies of a polycene antifungal.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of isavuconazole. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

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

Overleaf is the detailed advice on this product.

**Chairman,**
**Scottish Medicines Consortium**

Published 11 April 2016
**Indication**

In adults for the treatment of:

- invasive aspergillosis
- mucormycosis in patients for whom amphotericin B is inappropriate

**Dosing Information**

Orally (swallowed whole), or by intravenous infusion (over at least one hour), loading dose of 200mg isavuconazole every eight hours for the first 48 hours, then maintenance dose of 200mg once daily, starting 12 to 24 hours after the last loading dose. On the basis of the high oral bioavailability (98%), switching between intravenous and oral administration is appropriate when clinically indicated. The duration of therapy should be determined by the clinical response. For long-term treatment beyond six months, the benefit-risk balance should be carefully considered.

Consideration should be given to official guidance on the appropriate use of antifungal agents.

**Product availability date**

December 2015

Isavuconazole has been designated an orphan medicine by the European Medicines Agency for both indications. Isavuconazole meets SMC orphan criteria.

**Summary of evidence on comparative efficacy**

Invasive aspergillosis and mucormycosis are very rare, life-threatening fungal infections that can attack the vital organs of immunocompromised patients, including the lungs and the brain.\(^{1,2,3}\)

Isavuconazole is a triazole antifungal drug and the active moiety of isavuconazonium sulphate. It exerts a fungicidal effect by blocking the synthesis of ergosterol, a key component of the fungal cell membrane.\(^3\)

Clinical evidence derives from two key studies, SECURE and VITAL. SECURE was a phase III, randomised, multicentre, double-blind, non-inferiority study which evaluated the efficacy and safety of isavuconazole versus voriconazole in the primary treatment of adults with a proven, probable, or possible invasive fungal disease caused by the *Aspergillus* species or other filamentous fungi. Patients were randomised equally to treatment with isavuconazole (n=263) or voriconazole (n=264) until a treatment endpoint, or a maximum of 84 treatment days, was reached. Isavuconazole was administered as a loading dose of 200mg three times a day by intravenous (IV) infusion for two days followed by a maintenance dose of 200mg once daily either by IV infusion or orally. Voriconazole was administered as a loading dose of 6mg/kg every 12 hours by IV infusion on day one, followed by a maintenance dose of 4mg/kg every 12 hours by IV infusion on day two. From day three, patients received 4mg/kg every 12 hours by IV infusion or 200mg every 12 hours orally. Patients were switched from IV to oral treatment as early as possible from day three onwards. Therapeutic drug monitoring was not conducted and this was considered acceptable by the Committee for Medicinal Products for Human Use (CHMP).\(^{3,4}\)
The protocol-defined primary outcome was the crude rate of all-cause mortality (the percentage of patients who died from any cause) up to day 42 in the intention-to-treat (ITT) population (all randomised patients who received at least one dose of study drug). Non-inferiority was demonstrated if the upper bound of the two-sided 95% confidence interval (CI) for the treatment difference was less than 10%. Non-inferiority was demonstrated with an all-cause mortality rate of 19% (48/258) in the isavuconazole group and 20% (52/258) in the voriconazole group; adjusted treatment difference (isavuconazole minus voriconazole) -1.0% (95% CI: -7.8% to 5.7%). All-cause mortality through day 84 in the ITT population was assessed as a secondary outcome, and the result supported that seen in the primary outcome analysis: 29% (75/258) in the isavuconazole group and 31% (80/258) in the voriconazole group; adjusted treatment difference (isavuconazole minus voriconazole) -1.4% (95% CI: -9.2% to 6.3%).

The key protocol-defined secondary outcome and the CHMP key efficacy outcome was overall response (success) at the end of treatment (EOT; last day of study drug administration) in the modified-ITT (mITT) population, assessed by an independent, blinded, data review committee (DRC). Overall response was based on DRC-assessment of clinical, mycological and radiological response, and success was defined as a complete or partial response. The mITT population included ITT patients who had proven or probable invasive fungal disease as determined by the DRC. The percentage of patients with an overall response at EOT was similar between the treatment groups, 35% (50/143) in the isavuconazole group and 36% (47/129) in the voriconazole group; adjusted treatment difference (voriconazole minus isavuconazole) 1.6% (95% CI: -9.3% to 12.6%).

VITAL was a phase III, open-label, single-arm, multicentre study which evaluated the efficacy and safety of isavuconazole in adults requiring: primary therapy for aspergillosis who had impaired kidney function (creatinine clearance <50mL/minute); or primary therapy or therapy where refractory/intolerant to current treatment for invasive fungal disease caused by rare moulds, yeasts or dimorphic fungi; or therapy for mucormycosis. All patients received treatment with isavuconazole (n=146) administered as a loading dose of 200mg three times a day by IV infusion or orally for two days, followed by a maintenance dose of 200mg once daily by IV infusion or orally until a treatment endpoint or a maximum of 84 or 180 treatment days were reached (duration dependent on country-specific amendments). The study population of most relevance to the mucormycosis indication was the mITT-Mucorales population which included 37 patients with DRC-classified Mucorales only. In this population, isavuconazole was the primary therapy in 57% (21/37) of patients, used in those refractory to previous therapy in 30% (11/37) of patients, and in those intolerant to previous therapy in 14% (5/37) of patients. A total of 13 patients who had received prior amphotericin B were considered relevant to the indication.

The primary outcome was the percentage of patients with DRC-assessed overall response (success) at day 42, day 84 and EOT based on the assessment of clinical, mycological and radiological response. Overall response at EOT was defined as the CHMP key efficacy outcome. No statistical hypothesis was tested. In the mITT Mucorales population at EOT there was an overall response in 31% (11/35) of patients (36% [4/11] in those refractory to prior treatment and 20% [1/5] in those intolerant of prior treatment).

All-cause mortality was assessed as a secondary outcome. In the mITT-Mucorales population, the rate of all-cause mortality at day 42 was 38% (14/37), 46% (5/11) in those refractory to prior treatment and 40% (2/5) in those intolerant of prior treatment. At day 84, the all-cause mortality rate was 43% (16/37); 46% (5/11) in those refractory to prior treatment and 40% (2/5) in those intolerant of prior treatment.
Additional analyses were requested by the CHMP to assess the all-cause mortality and overall response rates in the VITAL study within the context of external control data. The data presented were mainly based on amphotericin B, which the CHMP considered to be acceptable. Three studies provided historical control data for patients treated with liposomal amphotericin B and were used for comparison with the results of the VITAL study. The overall response (success) rates reported in the external studies (range 32% to 42%) were found to be consistent with the DRC-assessed overall response (success) rate at EOT in the mITT-Mucorales population receiving isavuconazole as primary therapy in the VITAL study (32%).

The CHMP was also presented with a literature review of efficacy data for amphotericin B and posaconazole in the treatment of mucormycosis for comparison with the results of the VITAL study. Ten relevant studies (eight for amphotericin B and two for posaconazole) presented all-cause mortality in patients with mixed underlying infections and, despite the limitations of the comparison, most studies reported mortality rates in the range of 35% to 45% which is consistent with the 38% rate at day 42 and 43% rate at day 84 for the VITAL study.³

Patients in the VITAL study who received isavuconazole as a primary therapy for proven/probable mucormycosis were compared in a matched control analysis with patients from the Fungiscope Registry Database who received primary therapy with amphotericin B for the same indication. Twenty-one eligible patients from the VITAL study were matched with 33 Fungiscope controls. Although differences between the cases and controls were apparent, thereby limiting the comparison, the all-cause crude mortality rates through day 42 were similar (33% in VITAL and 39% in the Fungiscope database), as were the survival rates up to day 84 (57% in VITAL and 50% in the Fungiscope database). The CHMP concluded that the analysis demonstrated isavuconazole had comparable survival benefits to amphotericin B.³⁷

In pooled data from the SECURE and VITAL studies in patients with Aspergillus infection presented in the European Public Assessment Report (EPAR), the DRC-assessed overall response (success) rates and clinical response rates were reported to be similar for patients with and without renal impairment at EOT.³

Other data were also assessed but remain commercially confidential.*

### Summary of evidence on comparative safety

The EPAR considered the safety profile of isavuconazole to be in accordance with that expected of a triazole antifungal and to compare favorably with that of voriconazole. In the combined safety population of patients receiving isavuconazole in the SECURE (n=257) and VITAL (n=146) studies, drug related adverse events were reported in 42% (169/403) of patients. Serious drug-related adverse events were reported in 10% (41/403) of patients and treatment discontinuation as a result of drug-related adverse events occurred in 6.9% (28/403) of patients.³

In the isavuconazole and voriconazole groups of the SECURE study, drug-related adverse events were reported in 42% (109/257) and 60% (155/259) of patients, respectively. Severe treatment-related adverse events were reported in 53% (137/257) and 58% (149/259) respectively. Serious drug-related adverse events were reported in 11% of patients in both groups (28/257 in the isavuconazole group and 29/259 in the voriconazole group). Treatment discontinuation as a result of drug-related adverse events occurred less frequently in the
isavuconazole group (8.2% [21/257]) than in the voriconazole group (14% [35/259]). The EPAR noted that in most system organ classes, isavuconazole had numerically lower rates of treatment-emergent adverse events.³

In the SECURE study, the most commonly reported adverse events in the isavuconazole group were nausea (28% [71/257], versus 30% [78/259] in the voriconazole group), vomiting (25% [64/257] versus 28% [73/259]), diarrhoea (24% [61/257] versus 23% [60/259]), and pyrexia (22% [57/257] versus 30% [78/259]).³

In the VITAL study, isavuconazole was found to be well-tolerated and suitable for the long-term treatment of patients with renal impairment.³

### Summary of clinical effectiveness issues

Invasive aspergillosis and mucormycosis are very rare, life-threatening fungal infections. The *Aspergillus* fungus is the causative pathogen of invasive aspergillosis, which can infect the lungs of immunocompromised patients and spread via the bloodstream to other vital organs, such as the heart, kidney, liver and brain.²,³ Voriconazole is currently recommended as the first-line treatment for invasive aspergillosis,³ with liposomal amphotericin B as an alternative.⁸-¹⁰,¹²-¹⁴ Other treatment options include caspofungin,⁸-¹⁰,¹⁴ triaconazole,⁸,⁹ and posaconazole.⁸,¹⁰ The submitting company has indicated that, based on advice from an advisory board of Scottish healthcare professionals, oral posaconazole is used as step-down therapy after IV liposomal amphotericin B. Mucormycosis is caused by the Mucorales fungi, and immunocompromised patients are at risk of serious infection of the sinuses, brain, lungs and skin. Depending on the organ involved, symptoms may include facial pain, chest pain, fever and ulcerations.⁷ Liposomal amphotericin B is currently recommended as the first-line treatment for mucormycosis;⁹,¹¹,¹⁵,¹⁶ posaconazole is an alternative (‘off-label’ use).⁹,¹⁰,¹⁵

Orphan designation was granted for isavuconazole by the European Medicines Agency in 2014 for the treatment of invasive aspergillosis and mucormycosis.¹,² The EPAR notes that both conditions continue to be associated with high mortality rates and there is an urgent unmet medical need for new effective antifungal drugs to treat invasive fungal disease.³

The SECURE study demonstrated that, for the treatment of invasive aspergillosis, isavuconazole was non-inferior to voriconazole for all-cause mortality through day 42, and had an overall response at the end of treatment that was similar to voriconazole. Treatment discontinuation as a result of treatment-related adverse events occurred less frequently in the isavuconazole group than in the voriconazole group, and the EPAR considered that this apparent safety advantage may constitute a benefit for isavuconazole in the treatment of aspergillosis.³

There are no direct comparative data for isavuconazole versus liposomal amphotericin B or posaconazole in the treatment of invasive aspergillosis. The company presented a Bayesian network meta-analysis (NMA) comprising three studies which compared isavuconazole, voriconazole, amphotericin B deoxycholate and liposomal amphotericin B (AmBisome®) for this indication. All-cause mortality and overall response were reported as efficacy outcomes; safety outcomes were not reported due to insufficient data. Three separate analyses (a primary scenario and two sensitivity analyses) were run for each outcome using fixed and random effects models. For both outcomes, regardless of the model or scenario used, the 95% credible
intervals overlapped for isavuconazole and the comparators suggesting no important differences. When the treatments were ranked on the probability of being best, isavuconazole was rated as first or second (depending on the scenario) for all-cause mortality, and as second or third (depending on the scenario) for overall response. The results of the NMA were limited by heterogeneity in study population; time points for measuring response; and the definition of overall response.

The VITAL study demonstrated that, in patients with mucormycosis, isavuconazole had a treatment effect on overall response and all-cause mortality and, in patients with Aspergillus infection, response was similar in patients with and without renal impairment. For individual Mucorales species, the clinical efficacy data are very limited. VITAL was of uncontrolled, open-label, single-arm design, though this was considered to be acceptable by the CHMP in light of the lack of published head-to-head randomised controlled studies comparing antifungals for the treatment of mucormycosis, and the expectation of enrolment of low patient numbers in a study of a rare disease. The treatment effect was considered by the CHMP to be comparable to that observed in external control studies of amphotericin B.

Isavuconazole is available in IV and oral formulations (which have high oral bioavailability). It is administered as a once-daily (maintenance) fixed-dose regimen without the need for therapeutic drug monitoring. No dose adjustments are required for the IV or oral formulation in the elderly, in those with renal impairment or in those with mild to moderate hepatic impairment.

## Summary of patient and clinician engagement (PACE)

A Patient and Clinician Engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of isavuconazole, as an orphan medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- Invasive aspergillosis (IA) and mucormycosis are severe fungal infections which affect immunocompromised patients and have significant mortality rates.

- Isavuconazole provides an alternative licensed treatment option for IA and mucormycosis.

- There is an unmet need where current treatment options are inappropriate e.g. for patients with potential drug-drug interactions or previous tolerability issues.

- It offers the potential for fewer side effects and less drug-drug interactions than other treatment options.

- It may provide added convenience as it is a once daily, oral treatment that does not need to be taken with food/drink.
Summary of comparative health economic evidence

The submitting company presented a cost-minimisation analysis for both the invasive aspergillosis and mucormycosis indications comparing isavuconazole to voriconazole and to liposomal amphotericin B (AmBisome®) followed by oral posaconazole, and liposomal amphotericin B (AmBisome®) followed by oral posaconazole for the respective indications. For the invasive aspergillosis indication, the company used a weighted average of both comparators of 75% and 25% for voriconazole and liposomal amphotericin B (AmBisome®) respectively. SMC clinical experts have highlighted that these comparators are appropriate. The time horizon of the analysis is until the fungal infection is cleared, which was assumed to be 46.7 days based on the mean time on treatment in the SECURE study.

Evidence used to support the cost minimisation analysis for the invasive aspergillosis indication was taken from the SECURE study and the NMA described above. The SECURE study was a non-inferiority study comparing isavuconazole and voriconazole. In the intention-to-treat population at 42 days, the all-cause mortality rate was 19% in the isavuconazole arm and 20% in the voriconazole group. Therefore, the study met the primary objective of demonstrating non-inferiority of isavuconazole to voriconazole. For the mucormycosis indication, the results of the VITAL study for the sub-group of patients with mucormycosis compared with data from a matched control population (the Fungiscope registry) demonstrated that isavuconazole provided similar survival benefits to liposomal amphotericin B (AmBisome®) at day 42.

Costs included in the model were drug acquisition, hospitalisations, monitoring, IV preparation and administration and also the treatment of adverse events.

For the invasive aspergillosis indication, the results indicated that isavuconazole costs £15,917 per patient compared to £16,019 for the weighted average of the comparators. Thus isavuconazole costs £102 less per patient than the weighted average of the comparators. On this basis, isavuconazole is the preferred treatment option. These savings are driven by £75 of adverse event cost savings.

For the mucormycosis indication, the results indicated that isavuconazole costs £25,982 per patient compared to £37,254 for liposomal amphotericin B (AmBisome®) followed by posaconazole. Thus isavuconazole costs £11,272 less per patient than liposomal amphotericin B (AmBisome®) followed by posaconazole. On this basis, isavuconazole is the preferred treatment option. The main driver of these costs saving is nearly £8k of drug costs and £3k of reduced hospitalisation costs.

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 NHS Scotland. Under the PAS, a simple discount was offered on the list price. SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the without-PAS figures can be presented.

The company provided a number of sensitivity analyses for both indications. For the invasive aspergillosis indication, the results were most sensitive to altering the comparator proportion mix to 80% voriconazole and 20% liposomal Amphotericin B as this resulted in an incremental cost with isavuconazole of £182 (without PAS). For the mucormycosis indication, the company has
provided two sensitivity analyses, of which the results are sensitive to both. Posaconazole is not licensed for this indication. However, the company provided sensitivity analysis assuming posaconazole is the only comparator with one as an oral tablet and another as oral suspension. The analysis based on the oral tablet results in incremental costs associated with isavuconazole of £3,772 (without PAS). The analysis based on the oral suspension results in incremental costs associated with isavuconazole of £1,601 (without PAS). Although posaconazole is not licensed for this indication, SMC clinical experts have highlighted that posaconazole is used off-label to treat mucormycosis. Therefore, it may be the case that this is a realistic comparison in current clinical practice for some centres.

The following weaknesses were noted:

For the invasive aspergillosis indication:
- The results were presented in terms of a weighted average approach. While SMC clinical experts have suggested that there is variability in terms of the medicine used as current therapy and thus the weighted average approach is reasonable, it is noted that assuming voriconazole is the only comparator results in incremental costs of £1,322 associated with isavuconazole without the PAS. In addition, as noted above, the results showed some variability in terms of isavuconazole being the cost-minimising treatment when different assumptions were made about the proportions used in the weighted average comparator.
- The economic analysis is based on a liposomal amphotericin B (AmBisome®) dose of 5mg/kg, and this dose is unlicensed. When the licensed dose of 3mg/kg is applied in the analysis, the results are no longer cost-saving and are associated with an incremental cost of £700 (without PAS). In addition, in an analysis varying the dose so that 50% received 3mg/kg and 50% receive 5mg/kg, there was an incremental cost associated with isavuconazole of £302 (without PAS). SMC clinical experts have suggested that there is some variation in the dose used in clinical practice.

For the mucormycosis analysis, as noted above, the results were not cost-minimising when posaconazole was used as the comparator treatment, and this may be a relevant comparator in some areas.

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

After considering all the available evidence, the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted isavuconazole for use in NHS Scotland.

*Other data were also assessed but remain commercially confidential.*
Summary of patient and public involvement

The following information reflects the views of the specified Patient Group.

- A submission was received from the National Aspergillosis Centre (NAC) and the Fungal Infection Trust. The NAC is an NHS Specialist Centre and the Fungal Infection Trust is a registered charity.

- The NAC has not received any pharmaceutical company funding in the past two years. The Fungal Infection Trust has received pharmaceutical company funding in the past two years, but not from the submitting company.

- Patients may have to switch antifungal drugs as their infection has become resistant to an antifungal drug they had been taking. Isavuconazole would provide another treatment option.

- There are often improvements in breathlessness and other respiratory symptoms and a less well defined sense of ‘feeling better’ when taking antifungal medication but side effects are the biggest problem. Patients agreed that if isavuconazole provides an opportunity for reduced side effects or a different side effect profile compared to other treatment options, this could lead to an improved quality of life.

- Isavuconazole can be taken orally once daily without food. Patients and carers would welcome the freedom of not having to plan their day around taking their medication.

Additional information: guidelines and protocols

International expert opinion on the management of infection caused by azole-resistant *Aspergillus fumigates* was published in 2015. It was recommended that in patients at risk of invasive aspergillosis in regions with no/minimal azole resistance in the environment, initial treatment should be with voriconazole. Following culture for *Aspergillus fumigates*, those with wild type susceptibility should continue treatment with voriconazole. Those with azole resistance should avoid azole monotherapy and switch to liposomal amphotericin B, or voriconazole and an echinocandin, or another non-azole based regimen. In regions with environmental resistance of ≥10%, voriconazole and an echinocandin, or liposomal amphotericin B should be used first-line. Where there is evidence of azole resistance, treatment should be adjusted according to phenotype/genotype. Patients should convert to voriconazole if wild type is identified, unless there is reason not to. In patients whose culture is negative, the susceptibility unknown, and in whom after two weeks there is clinical improvement, trial de-escalation can be considered with conversion to voriconazole or posaconazole; careful monitoring should be continued.¹⁸

The Infectious Disease Society of America published clinical practice guidelines for the treatment of aspergillosis in 2008. These guidelines generally recommend that the primary treatment of aspergillosis is with voriconazole. For patients refractory to, or intolerant of, primary antifungal therapy, alternative treatment strategies include liposomal amphotericin B, amphotericin B lipid complex, caspofungin, micafungin, posaconazole (approved for the salvage
treatment of invasive aspergillosis in the European Union but has not been evaluated as primary therapy for invasive aspergillosis), and itraconazole.\textsuperscript{19}

In 2014, the European Society for Clinical Microbiology and Infectious Diseases and the European Confederation of Medical Mycology published joint clinical guidelines for the diagnosis and management of mucormycosis. These guidelines recommend that for adults and children, surgical debridement is used in addition to immediate first-line antifungal treatment with liposomal or lipid-complex amphotericin B with a minimum dose of 5mg/kg/day. Due to severe adverse side effects, the guidelines recommend that amphotericin B deoxycholate is better avoided. For salvage treatment, posaconazole 200mg four times daily is strongly recommended, while lipid-based formulations of amphotericin B and a combination of these two compounds are supported with moderate strength.\textsuperscript{16}

### Additional information: comparators

- Invasive aspergillosis: voriconazole, liposomal amphotericin B (AmBisome\textsuperscript{®}), posaconazole.
- Mucormycosis in patients for whom amphotericin B is inappropriate: posaconazole (‘off-label’ use).

### Cost of relevant comparators

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Regimen</th>
<th>Cost per 28 days (£)</th>
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</thead>
<tbody>
<tr>
<td>Isavuconazole</td>
<td>By intravenous infusion, 200mg every eight hours for the first 48 hours, then 200mg once daily</td>
<td>8,340 to 9,531</td>
</tr>
<tr>
<td></td>
<td>Orally, 200mg every eight hours for the first 48 hours, then 200mg once daily</td>
<td>2,397 to 2,740</td>
</tr>
<tr>
<td>Liposomal amphotericin B (AmBisome\textsuperscript{®})</td>
<td>By intravenous infusion, 3mg/kg to 5mg/kg once daily\textsuperscript{†}</td>
<td>11,506 to 16,109</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>By intravenous infusion, 6mg/kg every 12 hours for two doses, then 4mg/kg every 12 hours</td>
<td>8,640 to 8,794</td>
</tr>
<tr>
<td></td>
<td>Orally, bodyweight &gt;40kg, 400mg every 12 hours for two doses then 200mg every 12 hours</td>
<td>2,205 to 2,284</td>
</tr>
<tr>
<td>Posaconazole*</td>
<td>By intravenous infusion, 300mg twice daily on first day, then 300mg once daily</td>
<td>5,908 to 6,119</td>
</tr>
<tr>
<td></td>
<td>Orally, 300mg twice daily on first day, then 300mg once daily\textsuperscript{*}</td>
<td>2,089 to 2,164</td>
</tr>
</tbody>
</table>

The duration of treatment for invasive aspergillosis and mucormycosis should be based on the nature and severity of the underlying disease, recovery from immunosuppression, and the clinical and mycological response;\textsuperscript{3} costs per 28-days treatment are provided. Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 19/11/15, except cost for isavuconazole which is from the company’s submission, and cost for intravenous posaconazole which is from MIMS Online 19/11/15. Costs for intravenous voriconazole and AmBisome\textsuperscript{®} assume a bodyweight of 70kg. *Off-label use for the treatment of mucormycosis; dose stated is the licensed dose for the treatment of refractory invasive fungal infections (IFI)/patients with IFI intolerant to 1\textsuperscript{st}-line therapy.\textsuperscript{7} The British National Formulary notes
that the 5mg/kg dose is unlicensed for indications other than visceral leishmaniasis. The costs do not take any patient access schemes into consideration

Additional information: budget impact

Invasive aspergillosis;
The submitting company estimated the population eligible for treatment to be 93 patients in year 1, increasing to 111 by year 5. The estimated uptake rate is 10% in year 1 and 50% by year 5. Based on the SMC clinical expert responses, this seems to be a reasonable estimate of the number of eligible patients in Scotland.

Mucormycosis;
The submitting company estimated the population eligible for treatment to be 3 patients in year 1, increasing to 4 by year 5. The estimated uptake rate is 50% in year 1 and 85% by year 5. Based on the SMC clinical expert responses, this seems to be a reasonable estimate of the number of eligible patients in Scotland.

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.

Other data were also assessed but remain commercially confidential.*
References
The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.


6. Commercial in Confidence*.

7. Commercial in Confidence*.


This assessment is based on data submitted by the applicant company up to and including 08 January 2016.

*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:*
http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements

Drug 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 drug 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 NHS Scotland 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 NHS Scotland 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.