**Supplementary table 1: Type and properties of distributions used in the probabilistic sensitivity analysis**

|  |  |  |
| --- | --- | --- |
| **Parameter** | **Type of distribution** | **Properties of distribution** |
| * Costs (drug, hospitalization, AE, laboratory analysis) * Number of tests, hospital and treatment days | Gamma | Bounded at 0, positively skewed. Derived from mean and its standard error (SE). SE was set at deterministic cost/4. Alpha and Beta values were calculated as follows: Alpha = (mean/SE)2 Beta = SE2/Mean |
| * Percentage requiring second-line treatment * Percentage receiving oral or IV therapy * Percentage with pathogen information * Incidence of AEs * Prevalence of mucormycosis * Mortality * Quality of life | Beta | Bounded between 0 and 1. As the sample size and the number of events were specified alpha and beta values were calculated accordingly |

**Supplementary table 2: Parameters tested in scenario analysis**

|  |  |  |  |
| --- | --- | --- | --- |
| Scenario and Parameter | Tested value | | Source |
| **Isavuconazole** | **Voriconazole** |
| 1. Patients with renal impairment | | | |
| Number of serum creatinine tests per course of treatment | 2 | 3 | Assumption |
| Number of urinalysis tests per course of treatment | 2 | 3 | Assumption |
| Number of hospital days | 9 (IA),  9.7 (mucormycosis) | 19 (IA),  19.7 (mucormycosis) | SECURE trial  Assumption |
| Percentage of patients receiving voriconazole starting on IV therapy | - | 0% | SmPC |
| 1. Patients with hepatic impairment | | | |
| Number of liver function tests per course of treatment | 10% increase in base case value:  4.09 (IA),  15.22 (mucormycosis) | 30% increase in base case value: 9.67 (IA) | Assumption |
| Maintenance dose of voriconazole | - | 50% decrease in doses for day 2 and after:  IV: 2mg/kg  Oral: 100mg | SmPC |
| 1. Immunosuppressed patients\* | | | |
| Number of therapeutic drug monitoring tests of immunosuppressants per course of treatment | 0 | 0 | Information not available |
| 1. Patients with renal and hepatic impairment | | | |
| All parameters and values included in scenarios 1 and 2 | | | |
| 1. Patients with renal impairment who are immunosuppressed\* | | | |
| All parameters and values included in scenarios 1 and 3 | | | |
| 1. Patients with hepatic impairment who are immunosuppressed\* | | | |
| All parameters and values included in scenarios 2 and 3 | | | |
| 1. Patients with renal and hepatic impairment who are immunosuppressed\* | | | |
| All parameters and values included in scenarios 1, 2 and 3 | | | |
| \*At the time of model development no information was available on the data for the number of therapeutic drug monitoring tests of immunosuppressant medication. Therefore, currently these analyses provide identical results to the scenarios excluding patients who are immunosuppressed.  IA: Invasive aspergillosis; IV: Intravenous; SmPC: Summary of product characteristics  Source: adapted from[33,59] | | | |

**Supplementary table 3: Deterministic sensitivity analysis inputs**

|  |  |  |  |
| --- | --- | --- | --- |
| **Rank** | **Input** | **ICER (£)** | |
| **Lower bound** | **Upper bound** |
| 1 | Mortality - isavuconazole-IA | 3,529.71 | -24,314.31 |
| 2 | Mortality - voriconazole-IA | -24,278.40 | 3,534.90 |
| 3 | Isavuconazole-IA - treatment duration (responders) | -2,117.18 | 18,601.16 |
| 4 | Voriconazole-IA - treatment duration (responders) | 17,636.73 | -1,152.75 |
| 5 | Voriconazole-IA - mean treatment duration | -3,324.60 | 15,181.94 |
| 6 | Isavuconazole-IA - mean treatment duration | 19,738.99 | 1,343.79 |
| 7 | Isavuconazole-IA - hospital days | -361.98 | 16,845.96 |
| 8 | Voriconazole-IA - hospital days | 16,845.96 | -361.98 |
| 9 | Isavuconazole - oral price | 5,416.90 | 11,067.08 |
| 10 | % second line - voriconazole-IA | 10,771.72 | 5,712.26 |
| 11 | % second line - isavuconazole-IA | 5,953.62 | 10,530.36 |
| 12 | Mucormycosis prevalence | 10,856.45 | 6,673.31 |
| 13 | Mortality - isavuconazole-mucormycosis | 6,706.68 | 10,692.27 |
| 14 | Mortality - delayed therapy (L-AMB+posa) | 10,585.95 | 6,966.83 |
| 15 | Isavuconazole - IV price | 6,434.08 | 10,049.90 |
| 16 | Quality of life | 10,302.49 | 6,868.32 |
| 17 | Life expectancy | 10,278.23 | 7,037.43 |
| 18 | Mortality - Untreated | 11,096.30 | 7,920.29 |
| 19 | Isavuconazole-mucormycosis - duration of 1st line treatment response | 6,698.80 | 9,785.18 |
| 20 | Isavuconazole-IA - duration prior to switching | 7,096.23 | 9,387.75 |
| 21 | Voriconazole-IA - duration prior to switching | 9,281.08 | 7,202.90 |
| 22 | Isavuconazole-mucormycosis - mean treatment duration | 9,276.67 | 7,621.18 |
| 23 | Voriconazole - IV price | 9,053.51 | 7,430.47 |
| 24 | Isavuconazole-mucormycosis - hospital days | 7,467.61 | 9,016.37 |
| 25 | Voriconazole-IA - IV days before switching to oral | 7,483.27 | 9,000.71 |
| 26 | % with pathogen information | 8,966.04 | 7,464.28 |
| 27 | % starting on IV therapy - IA | 7,513.86 | 8,970.12 |
| 28 | Voriconazole-IA - IV days before switching to oral | 8,770.15 | 7,713.83 |
| 29 | Voriconazole - oral price | 8,707.25 | 7,776.73 |
| 30 | L-AMB+posa/voriconazole-mucormycosis - hospital days | 8,554.92 | 7,929.06 |
| 31 | Voriconazole-mucormycosis - hospital days (full course) | 8,552.89 | 7,931.09 |
| 32 | L-AMB - IV price | 8,547.65 | 7,936.33 |
| 33 | L-AMB+posa/voriconazole-mucormycosis - mean treatment duration | 8,525.15 | 7,958.83 |
| 34 | Voriconazole-mucormycosis - hospital days | 8,419.19 | 8,064.79 |
| 35 | Isavuconazole-mucormycosis - IV days before switching to oral | 8,118.91 | 8,365.07 |
| 36 | % second line - Isavuconazole-mucormycosis | 8,124.74 | 8,359.24 |
| 37 | Voriconazole-mucormycosis - treatment duration | 8,304.97 | 8,178.71 |
| 38 | Voriconazole-IA - therapeutic drug monitoring of antifungal agents | 8,279.81 | 8,204.17 |
| 39 | Hospitalization cost per day (hema) | 8,268.64 | 8,215.34 |
| 40 | Isavuconazole-mucormycosis - duration prior to switching | 8,217.87 | 8,266.11 |
| 41 | Voriconazole-mucormycosis - IV days before switching to oral | 8,264.38 | 8,219.60 |
| 42 | Voriconazole-IA - liver function tests | 8,263.66 | 8,220.32 |
| 43 | % starting on IV therapy – mucormycosis | 8,261.02 | 8,222.96 |
| 44 | Isavuconazole-IA - therapeutic drug monitoring of antifungal agents | 8,223.14 | 8,260.84 |
| 45 | Test costs - therapeutic drug monitoring | 8,259.44 | 8,224.54 |
| 46 | Voriconazole-mucormycosis - duration prior to switching | 8,256.90 | 8,227.08 |
| 47 | Isavuconazole-IA - liver function tests | 8,231.19 | 8,252.79 |
| 48 | Hospital stay with nephrotoxicity | 8,250.73 | 8,233.25 |
| 49 | Hospitalization cost per day (nephro) | 8,250.73 | 8,233.25 |
| 50 | Hallucination - cost per event | 8,249.84 | 8,234.14 |
| 51 | Test costs - liver function tests | 8,249.68 | 8,234.30 |
| 52 | Visual hallucination - cost per event | 8,249.25 | 8,234.73 |
| 53 | Abnormal hepatic function - cost per event | 8,247.28 | 8,236.70 |
| 54 | Increased GGT - cost per event | 8,246.47 | 8,237.50 |
| 55 | L-AMB+posa-IA - liver function tests | 8,246.01 | 8,237.97 |
| 56 | L-AMB+voriconazole-IA - liver function tests | 8,237.97 | 8,246.01 |
| 57 | QT prolonged - cost per event | 8,246.00 | 8,237.98 |
| 58 | Visual impairment - cost per event | 8,245.80 | 8,238.18 |
| 59 | Increased ALT - cost per event | 8,245.77 | 8,238.21 |
| 60 | Hyperbilirubinemia - cost per event | 8,245.72 | 8,238.26 |
| 60 | Increased ALP - cost per event | 8,245.31 | 8,238.67 |
| 62 | Increased AST - cost per event | 8,245.31 | 8,238.67 |
| 63 | Isavuconazole-mucormycosis - liver function tests | 8,238.76 | 8,245.22 |
| 64 | Dyspnoea - cost per event | 8,238.85 | 8,245.13 |
| 65 | Posaconazole - oral price | 8,244.65 | 8,239.33 |
| 66 | Hepatic failure - cost per event | 8,244.37 | 8,239.61 |
| 67 | Cholestasis - cost per event | 8,244.37 | 8,239.61 |
| 68 | Jaundice - cost per event | 8,243.58 | 8,240.40 |
| 69 | Isavuconazole-mucormycosis - therapeutic drug monitoring of antifungal agents | 8,240.48 | 8,243.50 |
| 70 | Reduced visual acuity - cost per event | 8,243.05 | 8,240.93 |
| 71 | L-AMB+posa-mucormycosis - liver function tests | 8,242.04 | 8,241.94 |
| 72 | Mortality – L-AMB+posa/voriconazole-IA | 8,241.99 | 8,241.99 |
| 73 | L-AMB+posa/voriconazole-IA - mean treatment duration | 8,241.99 | 8,241.99 |
| 74 | L-AMB+posa/voriconazole-IA - mean treatment duration (response) | 8,241.99 | 8,241.99 |
| 75 | Test costs - serum creatinine | 8,241.99 | 8,241.99 |
| 76 | Test costs - urinalysis | 8,241.99 | 8,241.99 |
| 77 | Test costs - Test1 | 8,241.99 | 8,241.99 |
| 78 | Test costs - Test2 | 8,241.99 | 8,241.99 |
| 79 | Isavuconazole-IA - laboratory analysis days | 8,241.99 | 8,241.99 |
| 80 | Isavuconazole-IA - serum creatinine tests | 8,241.99 | 8,241.99 |
| 81 | Isavuconazole-IA - urinalysis tests | 8,241.99 | 8,241.99 |
| 82 | Isavuconazole-IA - Test1 | 8,241.99 | 8,241.99 |
| 83 | Isavuconazole-IA - Test2 | 8,241.99 | 8,241.99 |
| 84 | Voriconazole-IA - laboratory analysis days | 8,241.99 | 8,241.99 |
| 85 | Voriconazole-IA - serum creatinine tests | 8,241.99 | 8,241.99 |
| 86 | Voriconazole-IA - urinalysis tests | 8,241.99 | 8,241.99 |
| 87 | Voriconazole-IA - Test1 | 8,241.99 | 8,241.99 |
| 88 | Voriconazole-IA - Test2 | 8,241.99 | 8,241.99 |
| 89 | L-AMB+posa-IA - laboratory analysis days | 8,241.99 | 8,241.99 |
| 90 | L-AMB+posa-IA - serum creatinine tests | 8,241.99 | 8,241.99 |
| 91 | L-AMB+posa-IA - urinalysis tests | 8,241.99 | 8,241.99 |
| 92 | L-AMB+posa-IA - therapeutic drug monitoring of antifungal agents | 8,241.99 | 8,241.99 |
| 93 | L-AMB+posa-IA - Test1 | 8,241.99 | 8,241.99 |
| 94 | L-AMB+posa-IA - Test1 | 8,241.99 | 8,241.99 |
| 95 | L-AMB+vori-IA - laboratory analysis days | 8,241.99 | 8,241.99 |
| 96 | L-AMB+vori-IA - serum creatinine tests | 8,241.99 | 8,241.99 |
| 97 | L-AMB+vori-IA - urinalysis tests | 8,241.99 | 8,241.99 |
| 98 | L-AMB+vori-IA - therapeutic drug monitoring of antifungal agents | 8,241.99 | 8,241.99 |
| 99 | L-AMB+vori-IA - Test1 | 8,241.99 | 8,241.99 |
| 100 | L-AMB+vori-IA - Test1 | 8,241.99 | 8,241.99 |
| 101 | Isavuconazole-mucormycosis - laboratory analysis days | 8,241.99 | 8,241.99 |
| 102 | Isavuconazole-mucormycosis - serum creatinine tests | 8,241.99 | 8,241.99 |
| 103 | Isavuconazole-mucormycosis - urinalysis tests | 8,241.99 | 8,241.99 |
| 104 | Isavuconazole-mucormycosis - Test1 | 8,241.99 | 8,241.99 |
| 105 | Isavuconazole-mucormycosis - Test2 | 8,241.99 | 8,241.99 |
| 106 | L-AMB+posa-mucormycosis - laboratory analysis days | 8,241.99 | 8,241.99 |
| 107 | L-AMB+posa-mucormycosis - serum creatinine tests | 8,241.99 | 8,241.99 |
| 108 | L-AMB+posa-mucormycosis - urinalysis tests | 8,241.99 | 8,241.99 |
| 109 | L-AMB+posa-mucormycosis - therapeutic drug monitoring of antifungal agents | 8,241.99 | 8,241.99 |
| 110 | L-AMB+posa-mucormycosis - Test1 | 8,241.99 | 8,241.99 |
| 111 | L-AMB+posa-mucormycosis - Test1 | 8,241.99 | 8,241.99 |
| 112 | L-AMB+posa/voriconazole-IA - hospital days | 8,241.99 | 8,241.99 |
| 113 | AE1 - cost | 8,241.99 | 8,241.99 |
| 114 | AE2 - cost | 8,241.99 | 8,241.99 |
| 115 | Isavuconazole- AE1 - incidence | 8,241.99 | 8,241.99 |
| 116 | Isavuconazole - AE2 - incidence | 8,241.99 | 8,241.99 |
| 117 | Voriconazole - AE1 - incidence | 8,241.99 | 8,241.99 |
| 118 | Voriconazole - AE2 - incidence | 8,241.99 | 8,241.99 |
| 119 | L-AMB - Adverse event 1 (incidence) - cost | 8,241.99 | 8,241.99 |
| 120 | L-AMB - Adverse event 2 (incidence) - cost | 8,241.99 | 8,241.99 |
| 121 | % second line - Voriconazole-mucormycosis | 8,241.99 | 8,241.99 |
| 122 | % L-AMB patients receiving oral posa (vs voriconazole) | 8,241.99 | 8,241.99 |