ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
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 reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

CRESEMBA 200 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 200 mg isavuconazole (as 372.6 mg isavuconazonium sulfate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion
White to yellow powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CRESEMBA is indicated in adults for the treatment of
• invasive aspergillosis
• mucormycosis in patients for whom amphotericin B is inappropriate (see sections 4.4 and 5.1)

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

4.2 Posology and method of administration

Posology

Loading dose

The recommended loading dose is one vial after reconstitution and dilution (equivalent to 200 mg of isavuconazole) every 8 hours for the first 48 hours (6 administrations in total).

Maintenance dose

The recommended maintenance dose is one vial after reconstitution and dilution (equivalent to 200 mg of isavuconazole) once daily, starting 12 to 24 hours after the last loading dose.

Duration of therapy should be determined by the clinical response (see section 5.1).

For long-term treatment beyond 6 months, the benefit-risk balance should be carefully considered (see sections 5.1 and 5.3).

Switch to oral isavuconazole

CRESEMBA is also available as hard capsules containing 100 mg isavuconazole, equivalent to 186 mg isavuconazonium sulfate.
On the basis of the high oral bioavailability (98%, see section 5.2), switching between intravenous and oral administration is appropriate when clinically indicated.

**Elderly**

No dose adjustment is necessary for elderly patients; however the clinical experience in elderly patients is limited.

**Renal impairment**

No dose adjustment is necessary in patients with renal impairment, including patients with end-stage renal disease (see section 5.2).

**Hepatic impairment**

No dose adjustment is necessary in patients with mild or moderate hepatic impairment (Child-Pugh Classes A and B) (see sections 4.4 and 5.2).

CRESEMBA has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). Use in these patients is not recommended unless the potential benefit is considered to outweigh the risks. See sections 4.4, 4.8 and 5.2.

**Paediatric population**

The safety and efficacy of CRESEMBA in children aged below 18 years has not yet been established. No data are available.

**Method of administration**

Intravenous use.

**Precautions to be taken before handling or administering the medicinal product**

CRESEMBA must be reconstituted and then further diluted to a concentration corresponding to approximately 0.8 mg/mL isavuconazole prior to administration by intravenous infusion over a minimum of 1 hour to reduce the risk of infusion-related reactions. The infusion must be administered via an infusion set with an in-line filter with a microporous membrane made of polyethersulfone (PES) and with a pore size of 0.2 μm to 1.2 μm. CRESEMBA must only be given as an intravenous infusion.

For detailed instructions on the reconstitution and dilution of CRESEMBA before administration, see section 6.6.

**4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Co-administration with ketoconazole (see section 4.5).

Co-administration with high-dose ritonavir (>200 mg every 12 hours) (see section 4.5).

Co-administration with strong CYP3A4/5 inducers such as rifampicin, rifabutin, carbamazepine, long-acting barbiturates (e.g. phenobarbital), phenytoin and St. John’s wort or with moderate CYP3A4/5 inducers such as efavirenz, nafcinilin and etravirine (see section 4.5).

Patients with familial short QT syndrome (see section 4.4).
4.4 Special warnings and precautions for use

**Hypersensitivity**

Caution should be used in prescribing isavuconazole to patients with hypersensitivity to other azole antifungal agents. Hypersensitivity to isavuconazole may result in adverse reactions that include: hypotension, respiratory failure, dyspnoea, drug eruption, pruritus, and rash.

**Infusion-related reactions**

During intravenous administration of isavuconazole, infusion-related reactions including hypotension, dyspnoea, dizziness, paraesthesia, nausea, and headache were reported (see section 4.8). The infusion should be stopped if these reactions occur.

**Severe cutaneous adverse reactions**

Severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, have been reported during treatment with azole antifungal agents. If a patient develops a severe cutaneous adverse reaction, CRESEMBA should be discontinued.

**Cardiovascular**

**QT shortening**

CRESEMBA is contraindicated in patients with familial short QT syndrome (see section 4.3). In a QT study in healthy human subjects, isavuconazole shortened the QTc interval in a concentration-related manner. For the 200 mg dosing regimen, the least squares mean (LSM) difference from placebo was 13.1 ms at 2 hours post dose [90% CI: 17.1, 9.1 ms]. Increasing the dose to 600 mg resulted in an LSM difference from placebo of 24.6 ms at 2 hours post dose [90% CI: 28.7, 20.4 ms].

Caution is warranted when prescribing CRESEMBA to patients taking other medicinal products known to decrease the QT interval, such as rufinamide.

**Elevated liver transaminases**

Elevated liver transaminases have been reported in clinical studies (see section 4.8). The elevations in liver transaminases rarely required discontinuation of CRESEMBA. Monitoring of hepatic enzymes should be considered, as clinically indicated.

**Severe hepatic impairment**

CRESEMBA has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). Use in these patients is not recommended unless the potential benefit is considered to outweigh the risks. These patients should be carefully monitored for potential drug toxicity. See sections 4.2, 4.8 and 5.2.

**Concomitant use with other medicinal products**

**CYP3A4/5 inhibitors**

Ketoconazole is contraindicated (see section 4.3). For the strong CYP3A4 inhibitor lopinavir/ritonavir, a two-fold increase in isavuconazole exposure was observed. For other strong CYP3A4/5 inhibitors, a less pronounced effect can be expected. No dose adjustment of CRESEMBA is necessary when co-
administered with strong CYP3A4/5 inhibitors, however caution is advised as adverse drug reactions may increase (see section 4.5).

**CYP3A4/5 inducers**

Co-administration with mild CYP3A4/5 inducers such as aprepitant, prednisone, and pioglitazone, may result in mild to moderate decreases of isavuconazole plasma levels; co-administration with mild CYP3A4/5 inducers should be avoided unless the potential benefit is considered to outweigh the risk (see section 4.5).

**CYP3A4/5 substrates including immunosuppressants**

Isavuconazole can be considered a moderate inhibitor of CYP3A4/5, and systemic exposure to medicinal products metabolised by CYP3A4 may be increased when co-administered with CRESEMBA. Concomitant use of CRESEMBA with CYP3A4 substrates such as the immunosuppressants tacrolimus, sirolimus or ciclosporin may increase the systemic exposure to these medicinal products. Appropriate therapeutic drug monitoring and dose adjustment may be necessary during co-administration (see section 4.5).

**CYP2B6 substrates**

Isavuconazole is an inducer of CYP2B6. Systemic exposure to medicinal products metabolised by CYP2B6 may be decreased when co-administered with CRESEMBA. Therefore, caution is advised when CYP2B6 substrates, especially medicinal products with a narrow therapeutic index such as cyclophosphamide, are co-administered with CRESEMBA. The use of the CYP2B6 substrate efavirenz with CRESEMBA is contraindicated because efavirenz is a moderate inducer of CYP3A4/5 (see section 4.3).

**P-gp substrates**

Isavuconazole may increase the exposure of medicinal products that are P-gp substrates. Dose adjustment of medicinal products that are P-gp substrates, especially medicinal products with a narrow therapeutic index such as digoxin, colchicine and dabigatran etexilate, may be needed when concomitantly administered with CRESEMBA (see section 4.5).

**Limitations of the clinical data**

The clinical data for isavuconazole in the treatment of mucormycosis are limited to one prospective non-controlled clinical study in 37 patients with proven or probable mucormycosis who received isavuconazole for primary treatment, or because other antifungal treatments (predominantly amphotericin B) were inappropriate. For individual *Mucorales* species, the clinical efficacy data are very limited, often to one or two patients (see section 5.1). Susceptibility data were available in only a small subset of cases. These data indicate that concentrations of isavuconazole required for inhibition *in vitro* are very variable between genera/species within the order of *Mucorales*, and generally higher than concentrations required to inhibit *Aspergillus* species. It should be noted that there was no dose-finding study in mucormycosis, and patients were administered the same dose of isavuconazole as was used for the treatment of invasive aspergillosis.

**4.5 Interaction with other medicinal products and other forms of interaction**

Potential of medicinal products to affect the pharmacokinetics of isavuconazole

Isavuconazole is a substrate of CYP3A4 and CYP3A5 (see section 5.2). Co-administration of medicinal products which are inhibitors of CYP3A4 and/or CYP3A5 may increase the plasma
concentrations of isavuconazole. Co-administration of medicinal products which are inducers of CYP3A4 and/or CYP3A5 may decrease the plasma concentrations of isavuconazole.

**Medicinal products that inhibit CYP3A4/5**

Co-administration of CRESEMBA with the strong CYP3A4/5 inhibitor ketoconazole is contraindicated, since this medicinal product can significantly increase plasma concentrations of isavuconazole (see sections 4.3 and 4.5).

For the strong CYP3A4 inhibitor lopinavir/ritonavir, a two-fold increase in isavuconazole exposure was observed. For other strong CYP3A4 inhibitors, such as clarithromycin, indinavir and saquinavir, a less pronounced effect can be expected, based on their relative potency. No dose adjustment of CRESEMBA is necessary when co-administered with strong CYP3A4/5 inhibitors, however caution is advised as adverse drug reactions may increase (see section 4.4).

No dose adjustment is warranted for moderate to mild CYP3A4/5 inhibitors.

**Medicinal products that induce CYP3A4/5**

Co-administration of CRESEMBA with potent CYP3A4/5 inducers such as rifampicin, rifabutin, carbamazepine, long-acting barbiturates (e.g., phenobarbital), phenytoin and St. John’s wort, or with moderate CYP3A4/5 inducers such as efavirenz, nafcillin and etravirine, is contraindicated, since these medicinal products can significantly decrease plasma concentrations of isavuconazole (see section 4.3).

Co-administration with mild CYP3A4/5 inducers such as aprepitant, prednisone and pioglitazone, may result in mild to moderate decreases of isavuconazole plasma levels; co-administration with mild CYP3A4/5 inducers should be avoided unless the potential benefit is considered to outweigh the risk (see section 4.4).

Co-administration with high-dose ritonavir (>200 mg twice daily) is contraindicated, as at high doses ritonavir may induce CYP3A4/5 and decrease isavuconazole plasma concentrations (see section 4.3).

**Potential for CRESEMBA to affect exposures of other medicines**

**Medicinal products metabolised by CYP3A4/5**

Isavuconazole is a moderate inhibitor of CYP3A4/5; co-administration of CRESEMBA with medicinal products which are substrates of CYP3A4/5 may result in increased plasma concentrations of these medicinal products.

**Medicinal products metabolised by CYP2B6**

Isavuconazole is a mild CYP2B6 inducer; co-administration of CRESEMBA may result in decreased plasma concentrations of CYP2B6 substrates.

**Medicinal products transported by P-gp in the intestine**

Isavuconazole is a mild inhibitor of P-glycoprotein (P-gp); co-administration with CRESEMBA may result in increased plasma concentrations of P-gp substrates.

**Medicinal products transported by BCRP**

Isavuconazole is an inhibitor in vitro of BCRP, and plasma concentrations of substrates of BCRP may therefore be increased. Caution is advised when CRESEMBA is given concomitantly with substrates of BCRP.
Medicinal products renally excreted via transport proteins

Isavuconazole is a mild inhibitor of the organic cation transporter 2 (OCT2). Co-administration of CRESEMB A with medicinal products which are substrates of OCT2 may result in increased plasma concentrations of these medicinal products.

Uridine diphosphate-glucuronosyltransferases (UGT) substrates

Isavuconazole is a mild inhibitor of UGT. Co-administration of CRESEMB A with medicinal products which are substrates of UGT may result in mildly increased plasma concentrations of these medicinal products.

Interaction table

Interactions between isavuconazole and co-administered medicinal products are listed in Table 1 (increase is indicated as “↑”, decrease as “↓”), ordered by therapeutic class. Unless otherwise stated, studies detailed in Table 1 have been performed with the recommended dose of CRESEMB A.

Table 1  Interactions

<table>
<thead>
<tr>
<th>Co-administered medicinal product by therapeutic area</th>
<th>Effects on drug concentrations / Geometric Mean Change (%) in AUC, C\text{\textsubscript{max}} (Mode of action)</th>
<th>Recommendation concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine, phenobarbital and phenytoin</td>
<td>Isavuconazole concentrations may decrease (CYP3A induction by carbamazepine, phenytoin and long-acting barbiturates such as phenobarbital).</td>
<td>The concomitant administration of CRESEMB A and carbamazepine, phenytoin and long-acting barbiturates such as phenobarbital is contraindicated.</td>
</tr>
<tr>
<td>(strong CYP3A4/5 inducers)</td>
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<tr>
<td><strong>Antibacterials</strong></td>
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</tbody>
</table>
| Rifampicin                                           | Isavuconazole: AUC\text{\textsubscript{tau}}: ↓ 90%  
C\text{\textsubscript{max}}: ↓ 75%  
(CYP3A4/5 induction) | The concomitant administration of CRESEMB A and rifampicin is contraindicated. |
| (strong CYP3A4/5 inducer)                            |                                                                                  |                                                 |
| Rifabutin                                            | Not studied. Isavuconazole concentrations may significantly decrease.  
(CYP3A4/5 induction) | The concomitant administration of CRESEMB A and rifabutin is contraindicated. |
| (strong CYP3A4/5 inducer)                            |                                                                                  |                                                 |
| Nafcillin                                            | Not studied. Isavuconazole concentrations may significantly decrease.  
(CYP3A4/5 induction) | The concomitant administration of CRESEMB A and nafcillin is contraindicated. |
| (moderate CY3A4/5 inducer)                           |                                                                                  |                                                 |
| Clarithromycin                                       | Not studied. Isavuconazole concentrations may increase.  
(CYP3A4/5 inhibition) | No CRESEMB A dose adjustment necessary; caution is advised as adverse drug reactions may increase. |
| (strong CYP3A4/5 inhibitor)                          |                                                                                  |                                                 |
| **Antifungals**                                      |                                                                                  |                                                 |
| Ketoconazole                                         | Isavuconazole: AUC\text{\textsubscript{tau}}: ↑ 422%  
C\text{\textsubscript{max}}: ↑ 9%  | The concomitant administration of CRESEMB A and ketoconazole is contraindicated. |
<p>| (strong CYP3A4/5 inhibitor)                          |                                                                                  |                                                 |</p>
<table>
<thead>
<tr>
<th><strong>Herbal medicines</strong></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>St John’s wort (strong CYP3A4/5 inducer)</td>
<td>Not studied. Isavuconazole concentrations may significantly decrease.</td>
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</table>

<table>
<thead>
<tr>
<th><strong>Immunosuppressants</strong></th>
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</table>
| Ciclosporin, sirolimus, tacrolimus (CYP3A4/5 substrates) | Ciclosporin: AUC$_{\text{inf}}$: ↑ 29%  
C$\text{max}$: ↑ 6%  
Sirolimus: AUC$_{\text{inf}}$: ↑ 84%  
C$\text{max}$: ↑ 65%  
Tacrolimus: AUC$_{\text{inf}}$: ↑ 125%  
C$\text{max}$: ↑ 42% | No CRESEMBA dose adjustment necessary. Ciclosporin, sirolimus, tacrolimus: monitoring of plasma levels and appropriate dose adjustment if required. |

| Mycophenolate mofetil (MMF) (UGT substrate) | Mycophenolic acid (MPA, active metabolite): AUC$_{\text{inf}}$: ↑ 35%  
C$\text{max}$: ↓ 11% | No CRESEMBA dose adjustment necessary. MMF: monitoring for MPA-related toxicities is advised. |

| Prednisone (CYP3A4 substrate) | Prednisolone (active metabolite): AUC$_{\text{inf}}$: ↑ 8%  
C$\text{max}$: ↓ 4% | Co-administration should be avoided unless the potential benefit is considered to outweigh the risk. |

<table>
<thead>
<tr>
<th><strong>Opioids</strong></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Short-acting opiates (alfentanil, fentanyl) (CYP3A4/5 substrate)</td>
<td>Not studied. Short-acting opiate concentrations may increase.</td>
</tr>
</tbody>
</table>

| Methadone (CYP3A4/5, 2B6 and 2C9 substrate) | S-methadone (inactive opiate isomer)  
AUC$_{\text{inf}}$: ↓ 35%  
C$\text{max}$: ↑ 1%  
40% reduction in terminal half-life  
R-methadone (active opiate isomer):  
AUC$_{\text{inf}}$: ↓ 10%  
C$\text{max}$: ↑ 4% | No CRESEMBA dose adjustment necessary. Methadone: no dose adjustment required. |
<table>
<thead>
<tr>
<th><strong>Anti-cancer</strong></th>
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</thead>
<tbody>
<tr>
<td>Vinca alkaloids (vincristine, vinblastine) (P-gp substrates)</td>
<td>Not studied. Vinca alkaloid concentrations may increase. (P-gp inhibition)</td>
<td>No CRESE MBA dose adjustment necessary. Vinca alkaloids: careful monitoring for any occurrence of drug toxicity, and dose reduction if required.</td>
</tr>
<tr>
<td>Cyclophosphamide (CYP2B6 substrate)</td>
<td>Not studied. Cyclophosphamide concentrations may decrease. (CYP2B6 induction)</td>
<td>No CRESE MBA dose adjustment necessary. Cyclophosphamide: careful monitoring for any occurrence of lack of efficacy, and dose increase if required.</td>
</tr>
<tr>
<td>Methotrexate (BCRP, OAT1, OAT3 substrate)</td>
<td>Methotrexate: AUC&lt;sub&gt;inf&lt;/sub&gt;: ↓ 3% C&lt;sub&gt;max&lt;/sub&gt;: ↓ 11% 7-hydroxymetabolite: AUC&lt;sub&gt;inf&lt;/sub&gt;: ↑ 29% C&lt;sub&gt;max&lt;/sub&gt;: ↑ 15% (Mechanism unknown)</td>
<td>No CRESE MBA dose adjustment necessary. Methotrexate: no dose adjustment required.</td>
</tr>
<tr>
<td>Other anticancer agents (daunorubicin, doxorubicin, imatinib, irinotecan, lapatinib, mitoxantrone, topotecan) (BCRP substrates)</td>
<td>Not studied. Daunorubicin, doxorubicin, imatinib, irinotecan, lapatinib, mitoxantrone, topotecan concentrations may increase. (BCRP inhibition)</td>
<td>No CRESE MBA dose adjustment necessary. Daunorubicin, doxorubicin, imatinib, irinotecan, lapatinib, mitoxantrone or topotecan: careful monitoring for any occurrence of drug toxicity, and dose reduction if required.</td>
</tr>
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<table>
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<tr>
<th><strong>Antiemetics</strong></th>
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<tbody>
<tr>
<td>Aprepitant (mild CYP3A4/5 inducer)</td>
<td>Not studied. Ivsavuconazole concentrations may decrease. (CYP3A4/5 induction)</td>
<td>Co-administration should be avoided unless the potential benefit is considered to outweigh the risk.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Antidiabetics</strong></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin (OCT1, OCT2 and MATE1 substrate)</td>
<td>Metformin: AUC&lt;sub&gt;inf&lt;/sub&gt;: ↑ 52% C&lt;sub&gt;max&lt;/sub&gt;: ↑ 23% (OCT2 inhibition)</td>
<td>No CRESE MBA dose adjustment necessary. Metformin: dose reduction may be required.</td>
</tr>
<tr>
<td>Repaglinide (CYP2C8 and OATP1B1 substrate)</td>
<td>Repaglinide: AUC&lt;sub&gt;inf&lt;/sub&gt;: ↓ 8% C&lt;sub&gt;max&lt;/sub&gt;: ↓ 14%</td>
<td>No CRESE MBA dose adjustment necessary. Repaglinide: no dose adjustment required.</td>
</tr>
</tbody>
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<tr>
<th><strong>Anticoagulants</strong></th>
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</thead>
<tbody>
<tr>
<td>Dabigatran etexilate (P-gp substrate)</td>
<td>Not studied. Dabigatran etexilate concentrations may increase. (P-gp inhibition).</td>
<td>No CRESE MBA dose adjustment necessary. Dabigatran etexilate has a narrow therapeutic index and should be monitored, and dose reduction if required.</td>
</tr>
<tr>
<td>Warfarin (CYP2C9 substrate)</td>
<td>S-warfarin AUC&lt;sub&gt;inf&lt;/sub&gt;: ↑ 11% C&lt;sub&gt;max&lt;/sub&gt;: ↓ 12%</td>
<td>No CRESE MBA dose adjustment necessary. Warfarin: no dose adjustment required.</td>
</tr>
</tbody>
</table>
R-warfarin  
\[ AUC\inf: \uparrow 20\% \]  
\[ C_{\text{max}}: \downarrow 7\% \]  
required.

### Antiretroviral agents

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Drug A</th>
<th>Drug B</th>
<th>Notes</th>
</tr>
</thead>
</table>
| Lopinavir 400 mg / Ritonavir 100 mg (CYP3A4/5 strong inhibitors and substrates) | Lopinavir:  
\[ AUC_{\text{inf}}: \downarrow 27\% \]  
\[ C_{\text{max}}: \downarrow 23\% \]  
\[ C_{\min, \text{ss}}: \downarrow 16\%\text{a) }\]  
Ritonavir:  
\[ AUC_{\text{inf}}: \downarrow 31\% \]  
\[ C_{\text{max}}: \downarrow 33\% \]  
(Mechanism unknown)  
Isavuconazole:  
\[ AUC_{\text{inf}}: \uparrow 96\% \]  
\[ C_{\text{max}}: \uparrow 74\% \]  
(CYP3A4/5 inhibition) | No CRESEMBA dose adjustment necessary; caution is advised as adverse drug reactions may increase.  
Lopinavir/ritonavir: no dose adjustment for lopinavir 400 mg / ritonavir 100 mg every 12 hours required, but careful monitoring for any occurrence of lack of anti-viral efficacy. |
| Ritonavir (at doses >200 mg every 12 hours) (strong CYP3A4/5 inducer) | Not studied. Ritonavir at high doses may significantly decrease isavuconazole concentrations.  
(Isavuconazole drug concentrations may significantly decrease.) | The concomitant administration of CRESEMBA and high doses of ritonavir (>200 mg every 12 hours) is contraindicated. |
| Efavirenz (CYP3A4/5 moderate inducer and CYP2B6 substrate) | Not studied. Efavirenz concentrations may decrease.  
(CYP2B6 induction)  
Isavuconazole drug concentrations may significantly decrease.  
(CYP3A4/5 induction) | The concomitant administration of CRESEMBA and efavirenz is contraindicated. |
| Etravirine (moderate CYP3A4/5 inducer) | Not studied. Isavuconazole concentrations may significantly decrease.  
(CYP3A4/5 induction) | The concomitant administration of CRESEMBA and etravirine is contraindicated. |
| Indinavir (CYP3A4/5 strong inhibitor and substrate) | Indinavir:b)  
\[ AUC_{\text{inf}}: \downarrow 36\% \]  
\[ C_{\text{max}}: \downarrow 52\% \]  
(Mechanism unknown)  
Isavuconazole concentrations may increase.  
(CYP3A4/5 inhibition) | No CRESEMBA dose adjustment necessary; caution is advised as adverse drug reactions may increase.  
Indinavir: careful monitoring for any occurrence of lack of anti-viral efficacy, and dose increase if required. |
| Saquinavir (strong CYP3A4 inhibitor) | Not studied. Saquinavir concentrations may decrease (as observed with lopinavir/ritonavir) or increase (CYP3A4 inhibition).  
Isavuconazole concentrations may increase.  
(CYP3A4 inhibition) | No CRESEMBA dose adjustment necessary; caution is advised as adverse drug reactions may increase.  
Saquinavir: careful monitoring for any occurrence of drug toxicity and/or lack of anti-viral efficacy. |
<table>
<thead>
<tr>
<th>Interaction</th>
<th>Effect</th>
<th>CRESEMBA Dose Adjustment</th>
</tr>
</thead>
</table>
| **Other protease inhibitors** (e.g., amprenavir, nelfinavir) (CYP3A4/5 strong or moderate inhibitors and substrates) | Not studied. 
Protease inhibitor concentrations may decrease (as observed with lopinavir/ritonavir) or increase. 
(CYP3A4 inhibition) 
Isavuconazole concentrations may increase. 
(CYP3A4/5 inhibition). | No CRESEMBA dose adjustment necessary. 
Protease inhibitors: careful monitoring for any occurrence of drug toxicity and/or lack of anti-viral efficacy, and dose adjustment if required. |
| **Other NNRTI (e.g., delavirdine, and nevaripine) (CYP3A4/5 and 2B6 inducers and substrates)** | Not studied. 
NNRTI concentrations may decrease (CYP2B6 induction by isavuconazole) or increase. 
(CYP3A4/5 inhibition) | No CRESEMBA dose adjustment necessary. 
NNRTIs: careful monitoring for any occurrence of drug toxicity and/or lack of anti-viral efficacy, and dose adjustment if required. |
| **Antiacids** | Isavuconazole: 
AUC\text{inf}: ↑ 8% 
C_{\text{max}}: ↑ 5% | No CRESEMBA dose adjustment necessary. 
Isavuconazole: no dose adjustment required. |
| Esomeprazole (CYP2C19 substrate and gastric pH ↑) | 
Omeprazole: 
AUC\text{inf}: ↓ 11% 
C_{\text{max}}: ↓ 23% | No CRESEMBA dose adjustment necessary. 
Omeprazole: no dose adjustment required. |
| Omeprazole (CYP2C19 substrate and gastric pH ↑) | Atorvastatin: 
AUC\text{inf}: ↑ 37% 
C_{\text{max}}: ↑ 3% 
Other statins were not studied. 
Statins concentrations may increase. 
(CYP3A4/5 or BCRP inhibition) | No CRESEMBA dose adjustment necessary. 
Based on results with atorvastatin, no statin dose adjustment required. Monitoring of adverse reactions typical of statins is advised. |
| Pioglitazone (mild CYP3A4/5 inducer) | Not studied. 
Isavuconazole concentrations may decrease. 
(CYP3A4/5 induction) | Co-administration should be avoided unless the potential benefit is considered to outweigh the risk. |
| **Antiarrhythmics** | Digoxin: 
AUC\text{inf}: ↑ 25% 
C_{\text{max}}: ↑ 33% | No CRESEMBA dose adjustment necessary. 
Digoxin: serum digoxin concentrations should be monitored and used for titration of the digoxin dose. |
| Digoxin (P-gp substrate) | Ethinyl oestradiol: 
AUC\text{inf}: ↑ 8% 
C_{\text{max}}: ↑ 14% 
Norethindrone: 
AUC\text{inf}: ↑ 16% | No CRESEMBA dose adjustment necessary. 
Ethinyl oestradiol and norethindone: no dose adjustment required. |
<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug/Agent</th>
<th>Interaction</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| **Antitussives**  | Dextromethorphan (CYP2D6 substrate) | Dextromethorphan:  
AUC\(_{\text{inf}}\): ↑ 18%  
C\(_{\text{max}}\): ↑ 17%  
Dextrorphan (active metabolite):  
AUC\(_{\text{inf}}\): ↑ 4%  
C\(_{\text{max}}\): ↓ 2%  | No CRESEMBA dose adjustment necessary.  
Dextromethorphan: no dose adjustment required. |
| **Benzodiazepines** | Midazolam (CYP3A4/5 substrate)     | Oral midazolam:  
AUC\(_{\text{inf}}\): ↑ 103%  
C\(_{\text{max}}\): ↑ 72%  
(CYP3A4 inhibition)  | No CRESEMBA dose adjustment necessary.  
Midazolam: careful monitoring of clinical signs and symptoms recommended, and dose reduction if required. |
| **Antigout agent** | Colchicine (P-gp substrate)       | Not studied.  
Colchicine concentrations may increase.  
(P-gp inhibition)  | No CRESEMBA dose adjustment necessary.  
Colchicine has a narrow therapeutic index and should be monitored, dose reduction if required. |
| **Natural products** | Caffeine (CYP1A2 substrate)       | Caffeine:  
AUC\(_{\text{inf}}\): ↑ 4%  
C\(_{\text{max}}\): ↓ 1%  | No CRESEMBA dose adjustment necessary.  
Caffeine: no dose adjustment required. |
| **Smoking cessation aids** | Bupropion (CYP2B6 substrate)      | Bupropion:  
AUC\(_{\text{inf}}\): ↓ 42%  
C\(_{\text{max}}\): ↓ 31%  
(CYP2B6 induction)  | No CRESEMBA dose adjustment necessary.  
Bupropion: dose increase if required. |

NNRTI, non-nucleoside reverse-transcriptase inhibitor; P-gp, P-glycoprotein.
a) % decrease of the mean trough level values
b) Indinavir was only studied after a single dose of 400 mg isavuconazole.

AUC\(_{\text{inf}}\) = area under the plasma concentration-time profiles extrapolated to infinity; AUC\(_{\text{tau}}\) = area under the plasma concentration-time profiles during the 24 h interval at steady state; C\(_{\text{max}}\) = peak plasma concentration; C\(_{\text{min,ss}}\) = trough levels at steady state.

### 4.6 Fertility, pregnancy and lactation

#### Pregnancy

There are no data from the use of CRESEMBA in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

CRESEMBA must not be used during pregnancy except in patients with severe or potentially life-threatening fungal infections, in whom isavuconazole may be used if the anticipated benefits outweigh the possible risks to the foetus.

#### Women of child-bearing potential

CRESEMBA is not recommended for women of childbearing potential who are not using contraception.
Breast-feeding

Available pharmacodynamic/toxicological data in animals have shown excretion of isavuconazole/metabolites in milk (see section 5.3).

A risk to newborns and infants cannot be excluded.

Breast-feeding should be discontinued during treatment with CRESEMBA.

Fertility

There are no data on the effect of isavuconazole on human fertility. Studies in animals did not show impairment of fertility in male or female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Isavuconazole has a moderate potential to influence the ability to drive and use machines. Patients should avoid driving or operating machinery if symptoms of confusional state, somnolence, syncope, and/or dizziness are experienced.

4.8 Undesirable effects

Summary of the safety profile

The frequency of adverse reactions shown in Table 2 is based on data from 403 patients with invasive fungal infections treated with CRESEMBA in phase 3 studies.

The most common treatment-related adverse reactions were elevated liver chemistry tests (7.9%), nausea (7.4%), vomiting (5.5%), dyspnoea (3.2%), abdominal pain (2.7%), diarrhoea (2.7%), injection site reaction (2.2%), headache (2.0%), hypokalaemia (1.7%) and rash (1.7%).

The adverse reactions which most often led to permanent discontinuation of CRESEMBA treatment were confusional state (0.7%), acute renal failure (0.7%), increased blood bilirubin (0.5%), convulsion (0.5%), dyspnoea (0.5%), epilepsy (0.5%), respiratory failure (0.5%) and vomiting (0.5%).

Tabulated list of adverse reactions

Table 2 presents adverse reactions with isavuconazole in the treatment of invasive fungal infections, by System Organ Class and frequency.

The frequency of adverse reactions is defined as follows: very common (≥1/10); common (≥1/100 to <1/10); and uncommon (≥1/1,000 to <1/100).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.
Table 2 Summary of adverse reactions by MedDRA System Organ Class and frequency

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse Drug Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Neutropenia; Thrombocytopenia^; Pancytopenia; Leukopenia^; Anaemia^</td>
</tr>
<tr>
<td><strong>Immune system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Hypersensitivity^</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Hypokalaemia; Decreased appetite</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Hypomagnesaemia; Hypoglycaemia; Hypoalbuminaemia; Malnutrition^;</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Delirium^;</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Depression; Insomnia^</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Headache; Somnolence</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Convulsion^; Syncope; Dizziness ; Paraesthesia^; Encephalopathy; Presyncope; Neuropathy peripheral; Dysgeusia;</td>
</tr>
<tr>
<td><strong>Ear and labyrinth disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Vertigo</td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Atrial fibrillation; Tachycardia; Bradycardia^; Palpitations Atrial flutter; Electrocardiogram QT shortened; Supraventricular tachycardia; Ventricular extrasystoles ; Supraventricular extrasystoles</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Thrombophlebitis^</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Circulatory collapse; Hypotension</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Dyspnoea;^ Acute respiratory failure^</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Bronchospasm; Tachypnoea; Haemoptysis; Epistaxis</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Vomiting; Diarrhoea; Nausea; Abdominal pain^;</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Dyspepsia; Constipation; Abdominal distension</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Elevated liver chemistry tests^#</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Hepatomegaly</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Rash^; Pruritus</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Petechiae; Alopecia; Drug eruption; Dermatitis^</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Back pain</td>
</tr>
<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Renal failure</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Chest pain^; Fatigue; Injection site reaction^</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Oedema peripheral;^ Malaise; Asthenia</td>
</tr>
</tbody>
</table>

^ Indicates that grouping of appropriate preferred terms into a single medical concept occurred. 
# See section Description of selected adverse reactions below

**Description of selected adverse reactions**

Delirium includes reactions of confusional state.
Elevated liver chemistry tests includes events of alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased, blood lactate dehydrogenase increased, gamma-glutamyltransferase increased, hepatic enzyme increased,
hepatic function abnormal, hyperbilirubinemia, liver function test abnormal, and transaminases increased.

Laboratory effects

In a double-blind, randomized, active-controlled clinical study of 516 patients with invasive fungal disease caused by *Aspergillus* species or other filamentous fungi, elevated liver transaminases (alanine aminotransferase or aspartate aminotransferase) > 3 × Upper Limit of Normal (ULN) were reported at the end of study treatment in 4.4% of patients who received CRESEMBA. Marked elevations of liver transaminases > 10 × ULN developed in 1.2% of patients on isavuconazole.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms

Symptoms reported more frequently at supratherapeutic doses of CRESEMBA (equivalent to isavuconazole 600 mg/day) evaluated in a QT study than in the therapeutic dose group (equivalent to isavuconazole 200 mg/day dose) included: headache, dizziness, paraesthesia, somnolence, disturbance in attention, dysgeusia, dry mouth, diarrhoea, oral hypoesthesia, vomiting, hot flush, anxiety, restlessness, palpitations, tachycardia, photophobia and arthralgia

Management of overdose

Isavuconazole is not removed by haemodialysis. There is no specific antidote for isavuconazole. In the event of an overdose, supportive treatment should be instituted.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives, ATC code: J02AC05

Mechanism of action

Isavuconazole is the active moiety formed after oral or intravenous administration of isavuconazonium sulfate (see section 5.2).

Isavuconazole demonstrates a fungicidal effect by blocking the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450-dependent enzyme lanosterol 14-alpha-demethylase, responsible for the conversion of lanosterol to ergosterol. This results in an accumulation of methylated sterol precursors and a depletion of ergosterol within the cell membrane, thus weakening the structure and function of the fungal cell membrane.

Microbiology

In animal models of disseminated and pulmonary aspergillosis, the pharmacodynamic (PD) index important in efficacy is exposure divided by minimum inhibitory concentration (MIC) (AUC/MIC).
No clear correlation between in vitro MIC and clinical response for the different species (Aspergillus and Mucorales) could be established.

Concentrations of isavuconazole required to inhibit Aspergillus species and genera/species of the order Mucorales in vitro have been very variable. Generally, concentrations of isavuconazole required to inhibit Mucorales are higher than those required to inhibit the majority of Aspergillus species.

Clinical efficacy has been demonstrated for the following Aspergillus species: *Aspergillus fumigatus*, *A. flavus*, *A. niger*, and *A. terreus* (see further below).

**Mechanism(s) of resistance**

Reduced susceptibility to triazole antifungal agents has been associated with mutations in the fungal cyp51A and cyp51B genes coding for the target protein lanosterol 14-alpha-demethylase involved in ergosterol biosynthesis. Fungal strains with reduced in vitro susceptibility to isavuconazole have been reported, and cross-resistance with voriconazole and other triazole antifungal agents cannot be excluded.

**Breakpoints**

EUCAST MIC breakpoints are defined for the following species (susceptible S; resistant R):

- *Aspergillus fumigatus*: S ≤ 1 mg/L, R > 1 mg/L
- *Aspergillus nidulans*: S ≤ 0.25 mg/L, R > 0.25 mg/L
- *Aspergillus terreus*: S ≤ 1 mg/L, R > 1 mg/L

There are currently insufficient data to set clinical breakpoints for other Aspergillus species.

**Clinical efficacy and safety**

*Treatment of invasive aspergillosis*

The safety and efficacy of isavuconazole for the treatment of patients with invasive aspergillosis was evaluated in a double-blind, active-controlled clinical study in 516 patients with invasive fungal disease caused by *Aspergillus* species or other filamentous fungi. In the intent-to-treat (ITT) population, 258 patients received isavuconazole and 258 patients received voriconazole. CRESEMBA was administered intravenously (equivalent to 200 mg isavuconazole) every 8 hours for the first 48 hours, followed by once-daily intravenous or oral treatment (equivalent to 200 mg isavuconazole). The protocol-defined maximum treatment duration was 84 days. Median treatment duration was 45 days.

The overall response at end-of-treatment (EOT) in the ITT population (patients with proven and probable invasive aspergillosis based on cytology, histology, culture or galactomannan testing) was assessed by an independent blinded Data Review Committee. The ITT population comprised 123 patients receiving isavuconazole and 108 patients receiving voriconazole. The overall response in this population was n = 43 (35%) for isavuconazole and n = 42 (38.9%) for voriconazole. The adjusted treatment difference (voriconazole–isavuconazole) was 4.0 (95% confidence interval: −7.9; 15.9).

The all-cause mortality at Day 42 in this population was 18.7% for isavuconazole and 22.2% for voriconazole. The adjusted treatment difference (isavuconazole–voriconazole) was −2.7% (95% confidence interval: −12.9; 7.5).

*Treatment of mucormycosis*

In an open-label non-controlled study, 37 patients with proven or probable mucormycosis received isavuconazole at the same dose regimen as that used to treat invasive aspergillosis. Median treatment duration was 84 days for the overall mucormycosis patient population, and 102 days for the 21
patients not previously treated for mucormycosis. For patients with probable or proven mucormycosis as defined by the independent Data Review Committee (DRC), all-cause mortality at Day 84 was 43.2% (16/37) for the overall patient population, 42.9% (9/21) for mucormycosis patients receiving isavuconazole as primary treatment, and 43.8% (7/16) for mucormycosis patients receiving isavuconazole who were refractory to, or intolerant of, prior antifungal therapy (mainly amphotericin B-based treatments). The DRC-assessed overall success rate at EOT was 11/35 (31.4%), with 5 patients considered completely cured and 6 patients partially cured. A stable response was observed in an additional 10/35 patients (28.6%). In 9 patients with mucormycosis due to *Rhizopus* spp., 4 patients showed a favourable response to isavuconazole. In 5 patients with mucormycosis due to *Rhizomucor* spp., no favourable responses were observed. The clinical experience in other species is very limited (*Lichtheimia* spp. n=2, *Cunninghamella* spp. n=1, *Actinomucor elegans* n=1).

**Paediatric population**

The European Medicines Agency has deferred the obligation to submit the results of studies with CRESEMBA in one or more subsets of the paediatric population in the treatment of invasive aspergillosis and the treatment of mucormycosis (see section 4.2 for information on paediatric use).

### 5.2 Pharmacokinetic properties

Isavuconazonium sulfate is a water-soluble prodrug that can be administered as an intravenous infusion or orally as hard capsules. Following administration, isavuconazonium sulfate is rapidly hydrolysed by plasma esterases to the active moiety isavuconazole; plasma concentrations of the prodrug are very low, and detectable only for a short time after intravenous dosing.

**Absorption**

Following oral administration of CRESEMBA in healthy subjects, the active moiety isavuconazole is absorbed and reaches maximum plasma concentrations (C\text{max}) approximately 2–3 hours after single and multiple dosing (see Table 3).

#### Table 3 Steady state pharmacokinetic parameters of isavuconazole following oral administration of CRESEMBA

<table>
<thead>
<tr>
<th>Parameter Statistic</th>
<th>Isavuconazole 200 mg (n = 37)</th>
<th>Isavuconazole 600 mg (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C\text{max} (ng/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>7499</td>
<td>20028</td>
</tr>
<tr>
<td>SD</td>
<td>1893.3</td>
<td>3584.3</td>
</tr>
<tr>
<td>CV %</td>
<td>25.2</td>
<td>17.9</td>
</tr>
<tr>
<td>t\text{max} (h)</td>
<td>3.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Range</td>
<td>2.0 – 4.0</td>
<td>2.0 – 4.0</td>
</tr>
<tr>
<td>AUC (h*ng/mL)</td>
<td>121402</td>
<td>352805</td>
</tr>
<tr>
<td>Mean</td>
<td>35768.8</td>
<td>72018.5</td>
</tr>
<tr>
<td>SD</td>
<td>29.5</td>
<td>20.4</td>
</tr>
<tr>
<td>CV %</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

As shown in table 4 below, the absolute bioavailability of isavuconazole following oral administration of a single dose of CRESEMBA is 98%. Based on these findings, intravenous and oral dosing can be used interchangeably.

#### Table 4 Pharmacokinetic comparison for oral and intravenous dose (Mean)

<table>
<thead>
<tr>
<th>Parameter Statistic</th>
<th>ISA 400 mg oral</th>
<th>ISA 400 mg i.v.</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (h*ng/mL)</td>
<td>189462.8</td>
<td>193906.8</td>
</tr>
<tr>
<td>CV %</td>
<td>36.5</td>
<td>37.2</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>110</td>
<td>115</td>
</tr>
</tbody>
</table>
Effect of food on absorption

Oral administration of CRESEMBA equivalent to 400 mg isavuconazole with a high-fat meal reduced isavuconazole $C_{\text{max}}$ by 9% and increased AUC by 9%. CRESEMBA can be taken with or without food.

Distribution

Isavuconazole is extensively distributed, with a mean steady state volume of distribution ($V_{ss}$) of approximately 450 L. Isavuconazole is highly bound (> 99%) to human plasma proteins, predominantly to albumin.

Biotransformation

*In vitro / in vivo* studies indicate that CYP3A4, CYP3A5, and subsequently uridine diphosphate-glucuronosyltransferases (UGT), are involved in the metabolism of isavuconazole.

Following single doses of [cyano-$^{14}$C] isavuconazonium and [pyridinylmethyl-$^{14}$C] isavuconazonium sulfate in humans, in addition to the active moiety (isavuconazole) and the inactive cleavage product, a number of minor metabolites were identified. Except for the active moiety isavuconazole, no individual metabolite was observed with an AUC > 10% of total radio-labelled material.

Elimination

Following oral administration of radio-labelled isavuconazonium sulfate to healthy subjects, a mean of 46.1% of the radioactive dose was recovered in faeces, and 45.5% was recovered in urine.

Renal excretion of intact isavuconazole was less than 1% of the dose administered.

The inactive cleavage product is primarily eliminated by metabolism and subsequent renal excretion of the metabolites.

Linearity/non-linearity

Studies in healthy subjects have demonstrated that the pharmacokinetics of isavuconazole are proportional up to 600 mg per day.

Pharmacokinetics in special populations

*Paediatric patients*

The pharmacokinetics in paediatric patients (< 18 years) have not yet been evaluated. No data are available.

*Renal impairment*

No clinically relevant changes were observed in the total $C_{\text{max}}$ and AUC of isavuconazole in subjects with mild, moderate or severe renal impairment compared to subjects with normal renal function. Of the 403 patients who received CRESEMB in the Phase 3 studies, 79 (20%) of patients had an estimated glomerular filtration rate (GFR) less than 60 mL/min/1.73 m$^2$. No dose adjustment is required in patients with renal impairment, including those patients with end-stage renal disease. Isavuconazole is not readily dialysable (see section 4.2).

*Hepatic impairment*

After a single 100 mg dose of isavuconazole was administered to 32 patients with mild (Child-Pugh Class A) hepatic insufficiency and 32 patients with moderate (Child-Pugh Class B) hepatic insufficiency (16 intravenous and 16 oral patients per Child-Pugh class), the least square mean systemic exposure (AUC) increased 64% in the Child-Pugh Class A group, and 84% in the Child-Pugh Class B group, relative to 32 age- and weight-matched healthy subjects with normal hepatic function. Mean plasma concentrations ($C_{\text{max}}$) were 2% lower in the Child-Pugh Class A group and 30% lower in the Child-Pugh Class B group. The population pharmacokinetic evaluation of isavuconazole in healthy subjects and patients with mild or moderate hepatic dysfunction demonstrated that the mild and
moderate hepatic impairment populations had 40% and 48% lower isavuconazole clearance (CL) values, respectively, than the healthy population.

No dose adjustment is required in patients with mild to moderate hepatic impairment.

Cresemba has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). Use in these patients is not recommended unless the potential benefit is considered to outweigh the risks. See sections 4.2 and 4.4.

5.3 Preclinical safety data

In rats and rabbits, isavuconazole at systemic exposures below the therapeutic level were associated with dose-related increases in the incidence of skeletal anomalies (rudimentary supernumerary ribs) in offspring. In rats, a dose-related increase in the incidence of zygomatic arch fusion was also noted in offspring (see section 4.6).

Administration of isavuconazonium sulfate to rats at a dose of 90 mg/kg/day (2.3-fold the human maintenance dose [200 mg] based on mg/m²/day) during pregnancy through the weaning period showed an increased perinatal mortality of the pups. In utero exposure to the active moiety isavuconazole had no effect on the fertility of the surviving pups.

Intravenous administration of ¹⁴C-labelled isavuconazonium sulfate to lactating rats resulted in the recovery of radiolabel in the milk.

Isavuconazole did not affect the fertility of male or female rats treated with oral doses up to 90 mg/kg/day (2.3-fold the clinical maintenance dose based on mg/m²/day comparisons).

Isavuconazole has no discernible mutagenic or genotoxic potential. Isavuconazole was negative in a bacterial reverse mutation assay, was weakly clastogenic at cytotoxic concentrations in the L5178Y tk+/- mouse lymphoma chromosome aberration assay, and showed no biologically relevant or statistically significant increase in the frequency of micronuclei in an in vivo rat micronucleus test.

No carcinogenicity studies have been performed.

Isavuconazole inhibited the hERG potassium channel and the L-type calcium channel with an IC₅₀ of 5.82 µM and 6.57 µM respectively (34- and 38-fold the human non-protein bound Cₘₐₓ at maximum recommended human dose [MRHD], respectively). The in vivo 39-week repeated-dose toxicology studies in monkeys did not show QTcF prolongation at doses up to 40 mg/kg/day (2.1-fold the recommended clinical maintenance dose, based on mg/m²/day comparisons).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Sulfuric acid (for pH-adjustment)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

24 months
Chemical and physical in-use stability after reconstitution and dilution has been demonstrated for 24 hours at 2 °C to 8 °C, or 6 hours at room temperature.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C, unless reconstitution and dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2 °C to 8 °C).

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

One 10 mL Type I glass vial with rubber stopper and an aluminum cap with plastic seal.

6.6 Special precautions for disposal and other handling

Reconstitution

One vial of the powder for concentrate for solution for infusion should be reconstituted by addition of 5 mL water for injections to the vial. The vial should be shaken to dissolve the powder completely. The reconstituted solution should be inspected visually for particulate matter and discoloration. Reconstituted concentrate should be clear and free of visible particulate. It must be further diluted prior to administration.

Dilution and administration

After reconstitution, the entire content of the reconstituted concentrate should be removed from the vial and added to an infusion bag containing at least 250 mL of either sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) dextrose solution. The infusion solution contains approximately 1.5 mg/mL isavuconazonium sulfate (corresponding to approximately 0.8 mg isavuconazole per mL). After the reconstituted concentrate is further diluted, the diluted solution may show fine white-to-translucent particulates of isavuconazole, that do not sediment (but will be removed by in-line filtration). The diluted solution should be mixed gently, or the bag should be rolled to minimise the formation of particulates. Unnecessary vibration or vigorous shaking of the solution should be avoided. The solution for infusion must be administered via an infusion set with an in-line filter (pore size 0.2 μm to 1.2 μm) made of polyether sulfone (PES).

Isavuconazole should not be infused into the same line or cannula concomitantly with other intravenous products.

Storage conditions after reconstitution and dilution are provided in section 6.3.

If possible, the intravenous administration of isavuconazole should be completed within 6 hours after reconstitution and dilution at room temperature. If this is not possible, the infusion solution should be immediately refrigerated after dilution, and infusion should be completed within 24 hours. Further information regarding the storage conditions after reconstitution and dilution of the medicinal product is provided in section 6.3.

An existing intravenous line should be flushed with sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) dextrose solution.

This medicinal product is for single use only. Discard partially-used vials.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Basilea Medical Ltd (c/o Cox Costello & Horne Limited)
Langwood House
63–81 High Street
Rickmansworth
Hertfordshire WD3 1EQ
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1036/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.
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 reactions. See section 4.8 for how to report adverse reactions.

1. **NAME OF THE MEDICINAL PRODUCT**

CRESEMBA 100 mg hard capsules

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

For the full list of excipients, see section 6.1.

Each capsule contains 100 mg isavuconazole (as 186.3 mg isavuconazonium sulfate).

3. **PHARMACEUTICAL FORM**

Hard capsule

Swedish Orange (reddish-brown) capsule body marked with ”100” in black ink and a white cap marked with ”C” in black ink. Capsules length: 24.2 mm.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

CRESEMBA is indicated in adults for the treatment of

- invasive aspergillosis
- mucormycosis in patients for whom amphotericin B is inappropriate (see sections 4.4 and 5.1)

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

4.2 **Posology and method of administration**

**Posology**

*Loading dose*

The recommended loading dose is two capsules (equivalent to 200 mg of isavuconazole) every 8 hours for the first 48 hours (6 administrations in total).

*Maintenance dose*

The recommended maintenance dose is two capsules (equivalent to 200 mg of isavuconazole) once daily, starting 12 to 24 hours after the last loading dose.

Duration of therapy should be determined by the clinical response (see section 5.1).

For long-term treatment beyond 6 months, the benefit-risk balance should be carefully considered (see sections 5.1 and 5.3).
Switch to intravenous infusion

CRESEMBA is also available as powder for concentrate for solution for infusion containing 200 mg isavuconazole, equivalent to 372 mg isavuconazonium sulfate.

On the basis of the high oral bioavailability (98%, see section 5.2), switching between intravenous and oral administration is appropriate when clinically indicated.

Elderly

No dose adjustment is necessary for elderly patients; however the clinical experience in elderly patients is limited.

Renal impairment

No dose adjustment is necessary in patients with renal impairment, including patients with end-stage renal disease (see section 5.2).

Hepatic impairment

No dose adjustment is necessary in patients with mild or moderate hepatic impairment (Child-Pugh Classes A and B) (see sections 4.4 and 5.2).

CRESEMBA has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). Use in these patients is not recommended unless the potential benefit is considered to outweigh the risks. See sections 4.4, 4.8 and 5.2.

Paediatric population

The safety and efficacy of CRESEMBA in children aged below 18 years has not yet been established. No data are available.

Method of administration

CRESEMBA capsules can be taken with or without food. CRESEMBA capsules should be swallowed whole. Do not chew, crush, dissolve or open the capsules.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Co-administration with ketoconazole (see section 4.5).

Co-administration with high-dose ritonavir (>200 mg every 12 hours) (see section 4.5).

Co-administration with strong CYP3A4/5 inducers such as rifampicin, rifabutin, carbamazepine, long-acting barbiturates (e.g. phenobarbital), phenytoin and St. John’s wort or with moderate CYP3A4/5 inducers such as efavirenz, nafcillin and etravirine (see section 4.5).

Patients with familial short QT syndrome (see section 4.4).
4.4 Special warnings and precautions for use

Hypersensitivity

Caution should be used in prescribing isavuconazole to patients with hypersensitivity to other azole antifungal agents. Hypersensitivity to isavuconazole may result in adverse reactions that include: hypotension, respiratory failure, dyspnoea, drug eruption, pruritus, and rash.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, have been reported during treatment with azole antifungal agents. If a patient develops a severe cutaneous adverse reaction, CRESEMBA should be discontinued.

Cardiovascular

QT shortening

CRESEMBA is contraindicated in patients with familial short QT syndrome (see section 4.3). In a QT study in healthy human subjects, isavuconazole shortened the QTc interval in a concentration-related manner. For the 200 mg dosing regimen, the least squares mean (LSM) difference from placebo was 13.1 ms at 2 hours post dose [90% CI: 17.1, 9.1 ms]. Increasing the dose to 600 mg resulted in an LSM difference from placebo of 24.6 ms at 2 hours post dose [90% CI: 28.7, 20.4 ms].

Caution is warranted when prescribing CRESEMBA to patients taking other medicinal products known to decrease the QT interval, such as rufinamide.

Elevated liver transaminases

Elevated liver transaminases have been reported in clinical studies (see section 4.8). The elevations in liver transaminases rarely required discontinuation of CRESEMBA. Monitoring of hepatic enzymes should be considered, as clinically indicated.

Severe hepatic impairment

CRESEMBA has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). Use in these patients is not recommended unless the potential benefit is considered to outweigh the risks. These patients should be carefully monitored for potential drug toxicity. See sections 4.2, 4.8 and 5.2.

Concomitant use with other medicinal products

CYP3A4/5 inhibitors

Ketoconazole is contraindicated (see section 4.3). For the strong CYP3A4 inhibitor lopinavir/ritonavir, a two-fold increase in isavuconazole exposure was observed. For other strong CYP3A4/5 inhibitors, a less pronounced effect can be expected. No dose adjustment of CRESEMBA is necessary when co-administered with strong CYP3A4/5 inhibitors, however caution is advised as adverse drug reactions may increase (see section 4.5).

CYP3A4/5 inducers

Co-administration with mild CYP3A4/5 inducers such as aprepitant, prednisone, and pioglitazone, may result in mild to moderate decreases of isavuconazole plasma levels; co-administration with mild
CYP3A4/5 inducers should be avoided unless the potential benefit is considered to outweigh the risk (see section 4.5).

**CYP3A4/5 substrates including immunosuppressants**

Isavuconazole can be considered a moderate inhibitor of CYP3A4/5, and systemic exposure to medicinal products metabolised by CYP3A4 may be increased when co-administered with CRESEMBA. Concomitant use of CRESEMBA with CYP3A4 substrates such as the immunosuppressants tacrolimus, sirolimus or ciclosporin may increase the systemic exposure to these medicinal products. Appropriate therapeutic drug monitoring and dose adjustment may be necessary during co-administration (see section 4.5).

**CYP2B6 substrates**

Isavuconazole is an inducer of CYP2B6. Systemic exposure to medicinal products metabolised by CYP2B6 may be decreased when co-administered with CRESEMBA. Therefore, caution is advised when CYP2B6 substrates, especially medicinal products with a narrow therapeutic index such as cyclophosphamide, are co-administered with CRESEMBA. The use of the CYP2B6 substrate efavirenz with CRESEMBA is contraindicated because efavirenz is a moderate inducer of CYP3A4/5 (see section 4.3).

**P-gp substrates**

Isavuconazole may increase the exposure of medicinal products that are P-gp substrates. Dose adjustment of medicinal products that are P-gp substrates, especially medicinal products with a narrow therapeutic index such as digoxin, colchicine and dabigatran etexilate, may be needed when concomitantly administered with CRESEMBA (see section 4.5).

**Limitations of the clinical data**

The clinical data for isavuconazole in the treatment of mucormycosis are limited to one prospective non-controlled clinical study in 37 patients with proven or probable mucormycosis who received isavuconazole for primary treatment, or because other antifungal treatments (predominantly amphotericin B) were inappropriate. For individual *Mucorales* species, the clinical efficacy data are very limited, often to one or two patients (see section 5.1). Susceptibility data were available in only a small subset of cases. These data indicate that concentrations of isavuconazole required for inhibition *in vitro* are very variable between genera/species within the order of *Mucorales*, and generally higher than concentrations required to inhibit *Aspergillus* species. It should be noted that there was no dose-finding study in mucormycosis, and patients were administered the same dose of isavuconazole as was used for the treatment of invasive aspergillosis.

**4.5 Interaction with other medicinal products and other forms of interaction**

**Potential of medicinal products to affect the pharmacokinetics of isavuconazole**

Isavuconazole is a substrate of CYP3A4 and CYP3A5 (see section 5.2). Co-administration of medicinal products which are inhibitors of CYP3A4 and/or CYP3A5 may increase the plasma concentrations of isavuconazole. Co-administration of medicinal products which are inducers of CYP3A4 and/or CYP3A5 may decrease the plasma concentrations of isavuconazole.

**Medicinal products that inhibit CYP3A4/5**

Co-administration of CRESEMBA with the strong CYP3A4/5 inhibitor ketoconazole is contraindicated, since this medicinal product can significantly increase plasma concentrations of isavuconazole (see sections 4.3 and 4.5).
For the strong CYP3A4 inhibitor lopinavir/ritonavir, a two-fold increase in isavuconazole exposure was observed. For other strong CYP3A4 inhibitors, such as clarithromycin, indinavir and saquinavir, a less pronounced effect can be expected, based on their relative potency. No dose adjustment of CRESEMBA is necessary when co-administered with strong CYP3A4/5 inhibitors, however caution is advised as adverse drug reactions may increase (see section 4.4).

No dose adjustment is warranted for moderate to mild CYP3A4/5 inhibitors.

**Medicinal products that induce CYP3A4/5**

Co-administration of CRESEMBA with potent CYP3A4/5 inducers such as rifampicin, rifabutin, carbamazepine, long-acting barbiturates (e.g., phenobarbital), phenytoin and St. John’s wort, or with moderate CYP3A4/5 inducers such as efavirenz, nafcillin and etravirine, is contraindicated, since these medicinal products can significantly decrease plasma concentrations of isavuconazole (see section 4.3).

Co-administration with mild CYP3A4/5 inducers such as aprepitant, prednisone and pioglitazone, may result in mild to moderate decreases of isavuconazole plasma levels; co-administration with mild CYP3A4/5 inducers should be avoided unless the potential benefit is considered to outweigh the risk (see section 4.4).

Co-administration with high-dose ritonavir (>200 mg twice daily) is contraindicated, as at high doses ritonavir may induce CYP3A4/5 and decrease isavuconazole plasma concentrations (see section 4.3).

**Potential for CRESEMBA to affect exposures of other medicines**

**Medicinal products metabolised by CYP3A4/5**

Isavuconazole is a moderate inhibitor of CYP3A4/5; co-administration of CRESEMBA with medicinal products which are substrates of CYP3A4/5 may result in increased plasma concentrations of these medicinal products.

**Medicinal products metabolised by CYP2B6**

Isavuconazole is a mild CYP2B6 inducer; co-administration of CRESEMBA may result in decreased plasma concentrations of CYP2B6 substrates.

**Medicinal products transported by P-gp in the intestine**

Isavuconazole is a mild inhibitor of P-glycoprotein (P-gp); co-administration with CRESEMBA may result in increased plasma concentrations of P-gp substrates.

**Medicinal products transported by BCRP**

Isavuconazole is an inhibitor *in vitro* of BCRP, and plasma concentrations of substrates of BCRP may therefore be increased. Caution is advised when CRESEMBA is given concomitantly with substrates of BCRP.

**Medicinal products renally excreted via transport proteins**

Isavuconazole is a mild inhibitor of the organic cation transporter 2 (OCT2). Co-administration of CRESEMBA with medicinal products which are substrates of OCT2 may result in increased plasma concentrations of these medicinal products.
Uridine diphosphate-glucuronosyltransferases (UGT) substrates

Isavuconazole is a mild inhibitor of UGT. Co-administration of CRESEMBA with medicinal products which are substrates of UGT may result in mildly increased plasma concentrations of these medicinal products.

Interaction table
Interactions between isavuconazole and co-administered medicinal products are listed in Table 1 (increase is indicated as “↑”, decrease as “↓”), ordered by therapeutic class. Unless otherwise stated, studies detailed in Table 1 have been performed with the recommended dose of CRESEMBA.

Table 1 Interactions

<table>
<thead>
<tr>
<th>Co-administered medicinal product by therapeutic area</th>
<th>Effects on drug concentrations / Geometric Mean Change (%) in AUC, C\text{max} (Mode of action)</th>
<th>Recommendation concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine, phenobarbital and phenytoin</td>
<td>Isavuconazole concentrations may decrease (CYP3A induction by carbamazepine, phenytoin and long-acting barbiturates such as phenobarbital).</td>
<td>The concomitant administration of CRESEMBA and carbamazepine, phenytoin and long-acting barbiturates such as phenobarbital is contraindicated.</td>
</tr>
<tr>
<td>(strong CYP3A4/5 inducers)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antibacterials</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Isavuconazole: AUC\text{tau}: ↓ 90% AUC\text{max}: ↓ 75% (CYP3A4/5 induction)</td>
<td>The concomitant administration of CRESEMBA and rifampicin is contraindicated.</td>
</tr>
<tr>
<td>(strong CYP3A4/5 inducer)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Not studied. Isavuconazole concentrations may significantly decrease. (CYP3A4/5 induction)</td>
<td>The concomitant administration of CRESEMBA and rifabutin is contraindicated.</td>
</tr>
<tr>
<td>(strong CYP3A4/5 inducer)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nafcillin</td>
<td>Not studied. Isavuconazole concentrations may significantly decrease. (CYP3A4/5 induction)</td>
<td>The concomitant administration of CRESEMBA and nafcillin is contraindicated.</td>
</tr>
<tr>
<td>(moderate CYP3A4/5 inducer)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Not studied. Isavuconazole concentrations may increase. (CYP3A4/5 inhibition)</td>
<td>No CRESEMBA dose adjustment necessary; caution is advised as adverse drug reactions may increase.</td>
</tr>
<tr>
<td>(strong CYP3A4/5 inhibitor)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antifungals</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Isavuconazole: AUC\text{tau}: ↑ 422% AUC\text{max}: ↑ 9% (CYP3A4/5 inhibition)</td>
<td>The concomitant administration of CRESEMBA and ketoconazole is contraindicated.</td>
</tr>
<tr>
<td>(strong CYP3A4/5 inhibitor)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Herbal medicines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>St John’s wort</td>
<td>Not studied. Isavuconazole concentrations may significantly decrease. (CYP3A4 induction).</td>
<td>The concomitant administration of CRESEMBA and St John’s wort is contraindicated.</td>
</tr>
</tbody>
</table>
| **Immunosuppressants** | Ciclosporin, sirolimus, tacrolimus (CYP3A4/5 substrates) | Ciclosporin:  
AUC<sub>inf</sub>: ↑ 29%  
C<sub>max</sub>: ↑ 6%  
Sirolimus:  
AUC<sub>inf</sub>: ↑ 84%  
C<sub>max</sub>: ↑ 65%  
Tacrolimus:  
AUC<sub>inf</sub>: ↑ 125%  
C<sub>max</sub>: ↑ 42%  
(CYP3A4 inhibition) | No CRESEMBA dose adjustment necessary. Ciclosporin, sirolimus, tacrolimus: monitoring of plasma levels and appropriate dose adjustment if required. |
| | Mycophenolate mofetil (MMF) (UGT substrate) | Mycophenolic acid (MPA, active metabolite):  
AUC<sub>inf</sub>: ↑ 35%  
C<sub>max</sub>: ↓ 11%  
(UGT inhibition) | No CRESEMBA dose adjustment necessary. MMF: monitoring for MPA-related toxicities is advised. |
| | Prednisone (CYP3A4 substrate) | Prednisolone (active metabolite):  
AUC<sub>inf</sub>: ↑ 8%  
C<sub>max</sub>: ↓ 4%  
(CYP3A4 inhibition)  
Isavuconazole concentrations may decrease.  
(CYP3A4/5 induction) | Co-administration should be avoided unless the potential benefit is considered to outweigh the risk. |
| **Opioids** | Short-acting opiates (alfentanil, fentanyl) (CYP3A4/5 substrate) | Not studied. Short-acting opiate concentrations may increase.  
| | Methadone (CYP3A4/5, 2B6 and 2C9 substrate) | S-methadone (inactive opiate isomer)  
AUC<sub>inf</sub>: ↓ 35%  
C<sub>max</sub>: ↑ 1%  
40% reduction in terminal half-life  
R-methadone (active opiate isomer).  
AUC<sub>inf</sub>: ↓ 10%  
C<sub>max</sub>: ↑ 4%  
(CYP2B6 induction) | No CRESEMBA dose adjustment necessary. Methadone: no dose adjustment required. |
| **Anti-cancer** | Vinca alkaloids (vincristine, vinblastine) (P-gp substrates) | Not studied. Vinca alkaloid concentrations may increase.  
(P-gp inhibition) | No CRESEMBA dose adjustment necessary. Vinca alkaloids: careful monitoring for any occurrence of drug toxicity, and dose reduction if required. |
| | Cyclophosphamide (CYP2B6 substrate) | Not studied. Cyclophosphamide concentrations | No CRESEMBA dose adjustment necessary. |
May decrease.
(CYP2B6 induction)

**Cyclophosphamide**: careful monitoring for any occurrence of lack of efficacy, and dose increase if required.

<table>
<thead>
<tr>
<th>Methotrexate (BCRP, OAT1, OAT3 substrate)</th>
<th>Methotrexate:</th>
<th>No CRESEMBA dose adjustment necessary. Methotrexate: no dose adjustment required.</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;inf&lt;/sub&gt;: ↓3%</td>
<td>C&lt;sub&gt;max&lt;/sub&gt;: ↓11%</td>
<td></td>
</tr>
<tr>
<td>7-hydroxymetabolite:</td>
<td>AUC&lt;sub&gt;inf&lt;/sub&gt;: ↑29%</td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;: ↑15%</td>
<td>(Mechanism unknown)</td>
<td></td>
</tr>
</tbody>
</table>

**Other anticancer agents (daunorubicin, doxorubicin, imatinib, irinotecan, lapatinib, mitoxanthrone, topotecan) (BCRP substrates)**

Not studied.
Daunorubicin, doxorubicin, imatinib, irinotecan, lapatinib, mitoxanthrone, topotecan concentrations may increase.
(BCRP inhibition)

<table>
<thead>
<tr>
<th>Metformin (OCT1, OCT2 and MATE1 substrate)</th>
<th>Metformin:</th>
<th>No CRESEMBA dose adjustment necessary. Metformin: dose reduction may be required.</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;inf&lt;/sub&gt;: ↑52%</td>
<td>C&lt;sub&gt;max&lt;/sub&gt;: ↑23%</td>
<td></td>
</tr>
<tr>
<td>(OCT2 inhibition)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Repaglinide (CYP2C8 and OATP1B1 substrate)**

Repaglinide:
AUC<sub>inf</sub>: ↓8%
C<sub>max</sub>: ↓14%

No CRESEMBA dose adjustment necessary. Repaglinide: no dose adjustment required.

**Dabigatran etexilate (P-gp substrate)**

Not studied.
Dabigatran etexilate concentrations may increase.
(P-gp inhibition).

**Warfarin (CYP2C9 substrate)**

S-warfarin
AUC<sub>inf</sub>: ↑11%
C<sub>max</sub>: ↓12%
R-warfarin
AUC<sub>inf</sub>: ↑20%
C<sub>max</sub>: ↓7%

No CRESEMBA dose adjustment necessary. Warfarin: no dose adjustment required.

**Lopinavir 400 mg / Ritonavir 100 mg (CYP3A4/5 strong inhibitors and substrates)**

Lopinavir:
AUC<sub>inf</sub>: ↓27%
C<sub>max</sub>: ↓23%
C<sub>min</sub> ss: ↓16%
Ritonavir:

No CRESEMBA dose adjustment necessary; caution is advised as adverse drug reactions may increase.
<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Isavuconazole Concentrations</th>
<th>Ritonavir (at doses &gt;200 mg every 12 hours) (strong CYP3A4/5 inducer)</th>
<th>Efavirenz (CYP3A4/5 moderate inducer and CYP2B6 substrate)</th>
<th>Etravirine (moderate CYP3A4/5 inducer)</th>
<th>Indinavir (CYP3A4/5 strong inhibitor and substrate)</th>
<th>Saquinavir (strong CYP3A4 inhibitor)</th>
<th>Other protease inhibitors (e.g., amprenavir, nelfinavir) (CYP3A4/5 strong or moderate inhibitors and substrates)</th>
</tr>
</thead>
</table>
|                  | AUC<sub>τ</sub>: ↓ 31%  
|                  | C<sub>max</sub>: ↓ 33%  
| (Mechanism unknown) |                            | Not studied.  
|                  | Isavuconazole:  
|                  | AUC<sub>τ</sub>: ↑ 96%  
|                  | C<sub>max</sub>: ↑ 74%  
| (CYP3A4/5 inhibition) | Not studied.  
|                  | Ritonavir at high doses may significantly decrease isavuconazole concentrations.  
|                  | (CYP3A4/5 induction) | Not studied.  
|                  | Efavirenz concentrations may decrease.  
| (CYP2B6 induction) | Isavuconazole drug concentrations may significantly decrease.  
| (CYP3A4/5 induction) | Not studied.  
|                  | Isavuconazole concentrations may significantly decrease.  
| (CYP3A4/5 induction) | Indinavir:b)  
|                  | AUC<sub>inf</sub>: ↓ 36%  
|                  | C<sub>max</sub>: ↓ 52%  
| (Mechanism unknown) | No CRESEMBA dose adjustment necessary; caution is advised as adverse drug reactions may increase.  
|                  | Indinavir: careful monitoring for any occurrence of lack of anti-viral efficacy, and dose increase if required.  
| (CYP3A4/5 inhibition) | No CRESEMBA dose adjustment necessary; caution is advised as adverse drug reactions may increase.  
|                  | Saquinavir: careful monitoring for any occurrence of drug toxicity and /or lack of anti-viral efficacy, and dose adjustment if required  
| (CYP3A4/5 inhibition) | No CRESEMBA dose adjustment necessary.  
|                  | Protease inhibitor concentrations may decrease (as observed with lopinavir/ritonavir) or increase.  
| (CYP3A4 inhibition) | No CRESEMBA dose adjustment necessary.  
|                  | Protease inhibitors: careful monitoring for any occurrence of drug toxicity and /or lack of anti-viral efficacy, and dose increase if required.  
| (CYP3A4 inhibition) |  

Lopinavir/ritonavir: no dose adjustment for lopinavir 400 mg / ritonavir 100 mg every 12 hours required, but careful monitoring for any occurrence of lack of anti-viral efficacy.
<table>
<thead>
<tr>
<th>Drug Interaction</th>
<th>Effect</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isavuconazole concentrations may increase. (CYP3A4/5 inhibition).</td>
<td>adjustment if required.</td>
<td>Other NNRTI (e.g., delavirdine, and nevaripine) (CYP3A4/5 and 2B6 inducers and substrates) Not studied. NNRTI concentrations may decrease (CYP2B6 induction by isavuconazole) or increase. (CYP3A4/5 inhibition)</td>
</tr>
<tr>
<td>Antiacids</td>
<td>Isavuconazole: AUC&lt;sub&gt;tau&lt;/sub&gt;: ↑ 8% C&lt;sub&gt;max&lt;/sub&gt;: ↑ 5%</td>
<td>No CRESEMB dose adjustment necessary. Esomeprazole: no dose adjustment required.</td>
</tr>
<tr>
<td>Esomeprazole (CYP2C19 substrate and gastric pH ↑)</td>
<td>Esomeprazole: AUC&lt;sub&gt;inf&lt;/sub&gt;: ↓ 11% C&lt;sub&gt;max&lt;/sub&gt;: ↓ 23%</td>
<td>No CRESEMB dose adjustment necessary. Omeprazole: no dose adjustment required.</td>
</tr>
<tr>
<td>Omeprazole (CYP2C19 substrate and gastric pH ↑)</td>
<td>Atorvastatin: AUC&lt;sub&gt;inf&lt;/sub&gt;: ↑ 37% C&lt;sub&gt;max&lt;/sub&gt;: ↑ 3% Other statins were not studied. Statins concentrations may increase. (CYP3A4/5 or BCRP inhibition)</td>
<td>No CRESEMB dose adjustment necessary. Based on results with atorvastatin, no statin dose adjustment required. Monitoring of adverse reactions typical of statins is advised.</td>
</tr>
<tr>
<td>Lipid-lowering agents</td>
<td>Pioglitazone (mild CYP3A4/5 inducer) Not studied. Isavuconazole concentrations may decrease. (CYP3A4/5 induction)</td>
<td>Co-administration should be avoided unless the potential benefit is considered to outweigh the risk.</td>
</tr>
<tr>
<td>Antiarhythmics</td>
<td>Digoxin (P-gp substrate) Digoxin: AUC&lt;sub&gt;inf&lt;/sub&gt;: ↑ 25% C&lt;sub&gt;max&lt;/sub&gt;: ↑ 33% (P-gp inhibition)</td>
<td>No CRESEMB dose adjustment necessary. Digoxin: serum digoxin concentrations should be monitored and used for titration of the digoxin dose.</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Ethinyl oestradiol and norethindrone (CYP3A4/5 substrates) Ethinyl oestradiol AUC&lt;sub&gt;inf&lt;/sub&gt;: ↑ 8% C&lt;sub&gt;max&lt;/sub&gt;: ↑ 14% Norethindrone AUC&lt;sub&gt;inf&lt;/sub&gt;: ↑ 16% C&lt;sub&gt;max&lt;/sub&gt;: ↑ 6%</td>
<td>No CRESEMB dose adjustment necessary. Ethinyl oestradiol and norethindrone: no dose adjustment required.</td>
</tr>
<tr>
<td>Antitussives</td>
<td>Dextromethorphan (CYP2D6 substrate) Dextromethorphan: AUC&lt;sub&gt;inf&lt;/sub&gt;: ↑ 18% C&lt;sub&gt;max&lt;/sub&gt;: ↑ 17% Dextrorphan (active metabolite): AUC&lt;sub&gt;inf&lt;/sub&gt;: ↑ 4% C&lt;sub&gt;max&lt;/sub&gt;: ↓ 2%</td>
<td>No CRESEMB dose adjustment necessary. Dextromethorphan: no dose adjustment required.</td>
</tr>
</tbody>
</table>
**Benzodiazepines**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on Midazolam</th>
<th>CRESEMBA Dose Adjustment</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam (CYP3A4/5 substrate)</td>
<td>Oral midazolam: AUC(<em>{\text{inf}}): ↑103% C(</em>{\text{max}}): ↑72% (CYP3A4 inhibition)</td>
<td>No CRESEMBA dose adjustment necessary. Midazolam: careful monitoring of clinical signs and symptoms recommended, and dose reduction if required.</td>
<td></td>
</tr>
</tbody>
</table>

**Antigout agent**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on Colchicine</th>
<th>CRESEMBA Dose Adjustment</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colchicine (P-gp substrate)</td>
<td>Not studied. Colchicine concentrations may increase. (P-gp inhibition)</td>
<td>No CRESEMBA dose adjustment necessary. Colchicine has a narrow therapeutic index and should be monitored, dose reduction if required.</td>
<td></td>
</tr>
</tbody>
</table>

**Natural products**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on Caffeine</th>
<th>CRESEMBA Dose Adjustment</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine (CYP1A2 substrate)</td>
<td>Caffeine: AUC(<em>{\text{inf}}): ↑4% C(</em>{\text{max}}): ↓1%</td>
<td>No CRESEMBA dose adjustment necessary. Caffeine: no dose adjustment required.</td>
<td></td>
</tr>
</tbody>
</table>

**Smoking cessation aids**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on Bupropion</th>
<th>CRESEMBA Dose Adjustment</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion (CYP2B6 substrate)</td>
<td>Bupropion: AUC(<em>{\text{inf}}): ↓42% C(</em>{\text{max}}): ↓31% (CYP2B6 induction)</td>
<td>No CRESEMBA dose adjustment necessary. Bupropion: dose increase if required.</td>
<td></td>
</tr>
</tbody>
</table>

a) % decrease of the mean trough level values  
b) Indinavir was only studied after a single dose of 400 mg isavuconazole.  

\(AUC_{\text{inf}}\) = area under the plasma concentration-time profiles extrapolated to infinity; \(AUC_{\text{tau}}\) = area under the plasma concentration-time profiles during the 24 h interval at steady state; \(C_{\text{max}}\) = peak plasma concentration; \(C_{\text{min,ss}}\) = trough levels at steady state.

4.6 **Fertility, pregnancy and lactation**

**Pregnancy**

There are no data from the use of CRESEMBA in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

CRESEMBA must not be used during pregnancy except in patients with severe or potentially life-threatening fungal infections, in whom isavuconazole may be used if the anticipated benefits outweigh the possible risks to the foetus.

**Women of child-bearing potential**

CRESEMBA is not recommended for women of childbearing potential who are not using contraception.

**Breast-feeding**

Available pharmacodynamic/toxicological data in animals have shown excretion of isavuconazole/metabolites in milk (see section 5.3).

A risk to newborns and infants cannot be excluded.
Breast-feeding should be discontinued during treatment with CRESEMBA.

Fertility

There are no data on the effect of isavuconazole on human fertility. Studies in animals did not show impairment of fertility in male or female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Isavuconazole has a moderate potential to influence the ability to drive and use machines. Patients should avoid driving or operating machinery if symptoms of confusional state, somnolence, syncope, and/or dizziness are experienced.

4.8 Undesirable effects

Summary of the safety profile

The frequency of adverse reactions shown in Table 2 is based on data from 403 patients with invasive fungal infections treated with CRESEMBA in phase 3 studies.

The most common treatment-related adverse reactions were elevated liver chemistry tests (7.9%), nausea (7.4%), vomiting (5.5%), dyspnoea (3.2%), abdominal pain (2.7%), diarrhoea (2.7%), injection site reaction (2.2%), headache (2.0%), hypokalaemia (1.7%) and rash (1.7%).

The adverse reactions which most often led to permanent discontinuation of CRESEMBA treatment were confusional state (0.7%), acute renal failure (0.7%), increased blood bilirubin (0.5%), convulsion (0.5%), dyspnoea (0.5%), epilepsy (0.5%), respiratory failure (0.5%) and vomiting (0.5%).

Tabulated list of adverse reactions

Table 2 presents adverse reactions with isavuconazole in the treatment of invasive fungal infections, by System Organ Class and frequency.

The frequency of adverse reactions is defined as follows: very common (≥1/10); common (≥1/100 to <1/10); and uncommon (≥1/1,000 to <1/100).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.
<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse Drug Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Neutropenia; Thrombocytopenia; Pancytopenia; Leukopenia; Anaemia</td>
</tr>
<tr>
<td><strong>Immune system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Hypokalaemia; Decreased appetite</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Hypomagnesaemia; Hypoglycaemia; Hypoalbuminaemia; Malnutrition</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Delirium</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Depression; Insomnia</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Headache; Somnolence</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Convulsion; Syncope; Dizziness; Paraesthesia; Encephalopathy; Presyncope; Neuropathy peripheral; Dysgeusia</td>
</tr>
<tr>
<td><strong>Ear and labyrinth disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Vertigo</td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Atrial fibrillation; Tachycardia; Bradycardia; Palpitations</td>
</tr>
<tr>
<td></td>
<td>Atrial flutter; Electrocardiogram QT shortened; Supraventricular tachycardia; Ventricular extrasystoles; Supraventricular extrasystoles</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Thrombophlebitis</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Circulatory collapse; Hypotension</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Dyspnoea; Acute respiratory failure</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Bronchospasm; Tachypnoea; Haemoptysis; Epistaxis</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Vomiting; Diarrhoea; Nausea; Abdominal pain</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Dyspepsia; Constipation; Abdominal distension</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Elevated liver chemistry tests</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Hepatomegaly</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Rash; Pruritus</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Petechiae; Alopecia; Drug eruption; Dermatitis</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Back pain</td>
</tr>
<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Renal failure</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Chest pain; Fatigue</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Malaise; Asthenia</td>
</tr>
</tbody>
</table>

^ Indicates that grouping of appropriate preferred terms into a single medical concept occurred.

# See section Description of selected adverse reactions below

**Description of selected adverse reactions**

Delirium includes reactions of confusional state.
Elevated liver chemistry tests includes events of alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased, blood lactate dehydrogenase increased, gamma-glutamyltransferase increased, hepatic enzyme increased,
hepatic function abnormal, hyperbilirubinemia, liver function test abnormal, and transaminases increased.

Laboratory effects

In a double-blind, randomized, active-controlled clinical study of 516 patients with invasive fungal disease caused by Aspergillus species or other filamentous fungi, elevated liver transaminases (alanine aminotransferase or aspartate aminotransferase) > 3 × Upper Limit of Normal (ULN) were reported at the end of study treatment in 4.4% of patients who received CRESEMBA. Marked elevations of liver transaminases > 10 × ULN developed in 1.2% of patients on isavuconazole.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms

Symptoms reported more frequently at supratherapeutic doses of CRESEMBA (equivalent to isavuconazole 600 mg/day) evaluated in a QT study than in the therapeutic dose group (equivalent to isavuconazole 200 mg/day dose) included: headache, dizziness, paraesthesia, somnolence, disturbance in attention, dysgeusia, dry mouth, diarrhoea, oral hypoaesthesia, vomiting, hot flush, anxiety, restlessness, palpitations, tachycardia, photophobia and arthralgia

Management of overdose

Isavuconazole is not removed by haemodialysis. There is no specific antidote for isavuconazole. In the event of an overdose, supportive treatment should be instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives, ATC code: J02AC05

Mechanism of action

Isavuconazole is the active moiety formed after oral or intravenous administration of isavuconazonium sulfate (see section 5.2).

Isavuconazole demonstrates a fungicidal effect by blocking the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450-dependent enzyme lanosterol 14-alpha-demethylase, responsible for the conversion of lanosterol to ergosterol. This results in an accumulation of methylated sterol precursors and a depletion of ergosterol within the cell membrane, thus weakening the structure and function of the fungal cell membrane.

Microbiology

In animal models of disseminated and pulmonary aspergillosis, the pharmacodynamic (PD) index important in efficacy is exposure divided by minimum inhibitory concentration (MIC) (AUC/MIC).
No clear correlation between in vitro MIC and clinical response for the different species (Aspergillus and Mucorales) could be established.

Concentrations of isavuconazole required to inhibit Aspergillus species and genera/species of the order Mucorales in vitro have been very variable. Generally, concentrations of isavuconazole required to inhibit Mucorales are higher than those required to inhibit the majority of Aspergillus species.

Clinical efficacy has been demonstrated for the following Aspergillus species: Aspergillus fumigatus, A. flavus, A. niger, and A. terreus (see further below).

Mechanism(s) of resistance

Reduced susceptibility to triazole antifungal agents has been associated with mutations in the fungal cyp51A and cyp51B genes coding for the target protein lanosterol 14-alpha-demethylase involved in ergosterol biosynthesis. Fungal strains with reduced in vitro susceptibility to isavuconazole have been reported, and cross-resistance with voriconazole and other triazole antifungal agents cannot be excluded.

Breakpoints

EUCAST MIC breakpoints are defined for the following species (susceptible S; resistant R):

- Aspergillus fumigatus: S ≤ 1 mg/L, R > 1 mg/L
- Aspergillus nidulans: S ≤ 0.25 mg/L, R > 0.25 mg/L
- Aspergillus terreus: S ≤ 1 mg/L, R > 1 mg/L

There are currently insufficient data to set clinical breakpoints for other Aspergillus species.

Clinical efficacy and safety

Treatment of invasive aspergillosis

The safety and efficacy of isavuconazole for the treatment of patients with invasive aspergillosis was evaluated in a double-blind, active-controlled clinical study in 516 patients with invasive fungal disease caused by Aspergillus species or other filamentous fungi. In the intent-to-treat (ITT) population, 258 patients received isavuconazole and 258 patients received voriconazole. CRESEMBA was administered intravenously (equivalent to 200 mg isavuconazole) every 8 hours for the first 48 hours, followed by once-daily intravenous or oral treatment (equivalent to 200 mg isavuconazole). The protocol-defined maximum treatment duration was 84 days. Median treatment duration was 45 days.

The overall response at end-of-treatment (EOT) in the myITT population (patients with proven and probable invasive aspergillosis based on cytology, histology, culture or galactomannan testing) was assessed by an independent blinded Data Review Committee. The myITT population comprised 123 patients receiving isavuconazole and 108 patients receiving voriconazole. The overall response in this population was n = 43 (35%) for isavuconazole and n = 42 (38.9%) for voriconazole. The adjusted treatment difference (voriconazole–isavuconazole) was 4.0 (95% confidence interval: −7.9; 15.9).

The all-cause mortality at Day 42 in this population was 18.7% for isavuconazole and 22.2% for voriconazole. The adjusted treatment difference (isavuconazole–voriconazole) was −2.7% (95% confidence interval: −12.9; 7.5).

Treatment of mucormycosis

In an open-label non-controlled study, 37 patients with proven or probable mucormycosis received isavuconazole at the same dose regimen as that used to treat invasive aspergillosis. Median treatment duration was 84 days for the overall mucormycosis patient population, and 102 days for the 21 patients not previously treated for mucormycosis. For patients with probable or proven mucormycosis
as defined by the independent Data Review Committee (DRC), all-cause mortality at Day 84 was 43.2% (16/37) for the overall patient population, 42.9% (9/21) for mucormycosis patients receiving isavuconazole as primary treatment, and 43.8% (7/16) for mucormycosis patients receiving isavuconazole who were refractory to, or intolerant of, prior antifungal therapy (mainly amphotericin B-based treatments). The DRC-assessed overall success rate at EOT was 11/35 (31.4%), with 5 patients considered completely cured and 6 patients partially cured. A stable response was observed in an additional 10/35 patients (28.6%). In 9 patients with mucormycosis due to *Rhizopus* spp., 4 patients showed a favourable response to isavuconazole. In 5 patients with mucormycosis due to *Rhizomucor* spp., no favourable responses were observed. The clinical experience in other species is very limited (*Lichtheimia* spp. n=2, *Cunninghamella* spp. n=1, *Actinomucor* elegans n=1).

**Paediatric population**

The European Medicines Agency has deferred the obligation to submit the results of studies with CRESEMBA in one or more subsets of the paediatric population in the treatment of invasive aspergillosis and the treatment of mucormycosis (see section 4.2 for information on paediatric use).

**5.2 Pharmacokinetic properties**

Isavuconazonium sulfate is a water-soluble prodrug that can be administered as an intravenous infusion or orally as hard capsules. Following administration, isavuconazonium sulfate is rapidly hydrolysed by plasma esterases to the active moiety isavuconazole; plasma concentrations of the prodrug are very low, and detectable only for a short time after intravenous dosing.

**Absorption**

Following oral administration of CRESEMBA in healthy subjects, the active moiety isavuconazole is absorbed and reaches maximum plasma concentrations (**C**<sub>max</sub>) approximately 2–3 hours after single and multiple dosing (see Table 3).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Isavuconazole 200 mg (n = 37)</th>
<th>Isavuconazole 600 mg (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C</strong>&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>7499</td>
<td>20028</td>
</tr>
<tr>
<td>SD</td>
<td>1893.3</td>
<td>3584.3</td>
</tr>
<tr>
<td>CV %</td>
<td>25.2</td>
<td>17.9</td>
</tr>
<tr>
<td><strong>t</strong>&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>3.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Range</td>
<td>2.0 – 4.0</td>
<td>2.0 – 4.0</td>
</tr>
<tr>
<td><strong>AUC</strong> (h•ng/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>121402</td>
<td>352805</td>
</tr>
<tr>
<td>SD</td>
<td>35768.8</td>
<td>72018.5</td>
</tr>
<tr>
<td>CV %</td>
<td>29.5</td>
<td>20.4</td>
</tr>
</tbody>
</table>

As shown in table 4 below, the absolute bioavailability of isavuconazole following oral administration of a single dose of CRESEMBA is 98%. Based on these findings, intravenous and oral dosing can be used interchangeably.

<table>
<thead>
<tr>
<th>Statistic</th>
<th>ISA 400 mg oral</th>
<th>ISA 400 mg i.v.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUC</strong> (h•ng/mL)</td>
<td>189462.8</td>
<td>193906.8</td>
</tr>
<tr>
<td>CV %</td>
<td>36.5</td>
<td>37.2</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>110</td>
<td>115</td>
</tr>
</tbody>
</table>
Effect of food on absorption
Oral administration of CRESEMBA equivalent to 400 mg isavuconazole with a high-fat meal reduced isavuconazole C\text{max} by 9% and increased AUC by 9%. CRESEMBA can be taken with or without food.

Distribution
Isavuconazole is extensively distributed, with a mean steady state volume of distribution (V\text{ss}) of approximately 450 L. Isavuconazole is highly bound (> 99%) to human plasma proteins, predominantly to albumin.

Biotransformation
\textit{In vitro} / \textit{in vivo} studies indicate that CYP3A4, CYP3A5, and subsequently uridine diphosphate-glucuronosyltransferases (UGT), are involved in the metabolism of isavuconazole.

Following single doses of [cyano-\textsuperscript{14}C] isavuconazonium and [pyridinylmethyl-\textsuperscript{14}C] isavuconazonium sulfate in humans, in addition to the active moiety (isavuconazole) and the inactive cleavage product, a number of minor metabolites were identified. Except for the active moiety isavuconazole, no individual metabolite was observed with an AUC > 10% of total radio-labelled material.

Elimination
Following oral administration of radio-labelled isavuconazonium sulfate to healthy subjects, a mean of 46.1% of the radioactive dose was recovered in faeces, and 45.5% was recovered in urine.

Renal excretion of intact isavuconazole was less than 1% of the dose administered.

The inactive cleavage product is primarily eliminated by metabolism and subsequent renal excretion of the metabolites.

Linearity/non-linearity
Studies in healthy subjects have demonstrated that the pharmacokinetics of isavuconazole are proportional up to 600 mg per day.

Pharmacokinetics in special populations
\textbf{Paediatric patients}
The pharmacokinetics in paediatric patients (< 18 years) have not yet been evaluated. No data are available.

\textbf{Renal impairment}
No clinically relevant changes were observed in the total C\text{max} and AUC of isavuconazole in subjects with mild, moderate or severe renal impairment compared to subjects with normal renal function. Of the 403 patients who received CRESE MBA in the Phase 3 studies, 79 (20%) of patients had an estimated glomerular filtration rate (GFR) less than 60 mL/min/1.73 m\textsuperscript{2}. No dose adjustment is required in patients with renal impairment, including those patients with end-stage renal disease. Isavuconazole is not readily dialysable (see section 4.2).

\textbf{Hepatic impairment}
After a single 100 mg dose of isavuconazole was administered to 32 patients with mild (Child-Pugh Class A) hepatic insufficiency and 32 patients with moderate (Child-Pugh Class B) hepatic insufficiency (16 intravenous and 16 oral patients per Child-Pugh class), the least square mean systemic exposure (AUC) increased 64% in the Child-Pugh Class A group, and 84% in the Child-Pugh Class B group, relative to 32 age- and weight-matched healthy subjects with normal hepatic function. Mean plasma concentrations (C\text{max}) were 2% lower in the Child-Pugh Class A group and 30% lower in the Child-Pugh Class B group. The population pharmacokinetic evaluation of isavuconazole in healthy subjects and patients with mild or moderate hepatic dysfunction demonstrated that the mild and
moderate hepatic impairment populations had 40% and 48% lower isavuconazole clearance (CL) values, respectively, than the healthy population.

No dose adjustment is required in patients with mild to moderate hepatic impairment.

Cresemba has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). Use in these patients is not recommended unless the potential benefit is considered to outweigh the risks. See sections 4.2 and 4.4.

5.3 Preclinical safety data

In rats and rabbits, isavuconazole at systemic exposures below the therapeutic level were associated with dose-related increases in the incidence of skeletal anomalies (rudimentary supernumerary ribs) in offspring. In rats, a dose-related increase in the incidence of zygomatic arch fusion was also noted in offspring (see section 4.6).

Administration of isavuconazonium sulfate to rats at a dose of 90 mg/kg/day (2.3-fold the human maintenance dose [200 mg] based on mg/m²/day) during pregnancy through the weaning period showed an increased perinatal mortality of the pups. In utero exposure to the active moiety isavuconazole had no effect on the fertility of the surviving pups.

Intravenous administration of 14C-labelled isavuconazonium sulfate to lactating rats resulted in the recovery of radiolabel in the milk.

Isavuconazole did not affect the fertility of male or female rats treated with oral doses up to 90 mg/kg/day (2.3-fold the clinical maintenance dose based on mg/m²/day comparisons).

Isavuconazole has no discernible mutagenic or genotoxic potential. Isavuconazole was negative in a bacterial reverse mutation assay, was weakly clastogenic at cytotoxic concentrations in the L5178Y tk+/- mouse lymphoma chromosome aberration assay, and showed no biologically relevant or statistically significant increase in the frequency of micronuclei in an in vivo rat micronucleus test.

No carcinogenicity studies have been performed.

Isavuconazole inhibited the hERG potassium channel and the L-type calcium channel with an IC₅₀ of 5.82 µM and 6.57 µM respectively (34- and 38-fold the human non-protein bound Cₘₐₓ at maximum recommended human dose [MRHD], respectively). The in vivo 39-week repeated-dose toxicology studies in monkeys did not show QTcF prolongation at doses up to 40 mg/kg/day (2.1-fold the recommended clinical maintenance dose, based on mg/m²/day comparisons).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents
magnesium citrate (anhydrous)
microcrystalline cellulose
talc
silica, colloidal anhydrous
stearic acid

Capsule shell
hypromellose
water
red iron oxide (E172) (capsule body only)
titanium dioxide (E171)
gellan gum
potassium acetate
disodium edetate
sodium laurilsulfate

Printing ink
shellac
propylene glycol
potassium hydroxide
black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

6.4 Special precautions for storage

Store in the original packaging in order to protect from moisture.

6.5 Nature and contents of container

14 hard capsules (in two aluminum blisters), with each capsule pocket connected to a pocket with desiccant.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Basilea Medical Ltd (c/o Cox Costello & Horne Limited)
Langwood House
63–81 High Street
Rickmansworth
Hertfordshire WD3 1EQ
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1036/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT
Detailed information on this medicinal product is available on the website of the European Medicines Agency [http://www.ema.europa.eu].
ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT
A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Almac Pharma Services Limited
Seagoe Industrial Estate
Craigavon
Co Armagh
BT63 5UA
United Kingdom

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- Periodic safety update reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal. The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carton for vial for 200 mg powder for concentrate for solution for infusion</td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

CRESEMBA 200 mg powder for concentrate for solution for infusion
Isavuconazole

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each vial contains 200 mg isavuconazole (as 372.6 mg isavuconazonium sulfate)

3. **LIST OF EXCIPIENTS**

Excipients: mannitol (E421) and sulfuric acid

4. **PHARMACEUTICAL FORM AND CONTENTS**

Powder for concentrate for solution for infusion
1 vial

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.
For intravenous use after reconstitution and dilution
Use an in-line filter for infusion.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

EXP

9. **SPECIAL STORAGE CONDITIONS**

Store in a refrigerator
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Basilea Medical Ltd.
(c/o Cox Costello & Horne Limited)
Langwood House
63-81 High Street
Rickmansworth
Hertfordshire WD3 1EQ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1036/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.
### Minimum Particulars to Appear on Small Immediate Packaging Units

Label on vial for 200 mg powder for concentrate for solution for infusion

<table>
<thead>
<tr>
<th>1. Name of the Medicinal Product and Route(s) of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRESEMBA 200 mg powder for concentrate for solution for infusion</td>
</tr>
<tr>
<td>Isavuconazole</td>
</tr>
<tr>
<td>IV use after reconstitution and dilution</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Method of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>See leaflet</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Expiry Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. Batch Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lot</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. Contents by Weight, by Volume or by Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. Other</th>
</tr>
</thead>
</table>
## PARTICULARS TO APPEAR ON THE OUTER PACKAGING

**Carton for 100 mg hard capsules**

### 1. NAME OF THE MEDICINAL PRODUCT

CRESEMBA 100 mg hard capsules
Isavuconazole

### 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 100 mg isavuconazole (as 186.3 mg isavuconazonium sulfate)

### 3. LIST OF EXCIPIENTS

### 4. PHARMACEUTICAL FORM AND CONTENTS

14 hard capsules

### 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.
The blister card also contains desiccant. Do not swallow the desiccant.

### 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

### 7. OTHER SPECIAL WARNING(S), IF NECESSARY

### 8. EXPIRY DATE

EXP

### 9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

### 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Basilea Medical Ltd.
(c/o Cox Costello & Horne Limited)
Langwood House
63-81 High Street
Rickmansworth
Hertfordshire WD3 1EQ
United Kingdom

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/15/1036/002

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

CRESEMBA 100 mg hard capsules
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blister for 100 mg hard capsules</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRESEMBA 100 mg hard capsules</td>
</tr>
<tr>
<td>Isavuconazole</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. NAME OF THE MARKETING AUTHORISATION HOLDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basilea Medical Ltd.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
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</table>

<table>
<thead>
<tr>
<th>4. BATCH NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lot</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not swallow the desiccant</td>
</tr>
</tbody>
</table>
B. PACKAGE LEAFLET
This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet
1. What Cresemba is and what it is used for
2. What you need to know before you use Cresemba
3. How to use Cresemba
4. Possible side effects
5. How to store Cresemba
6. Contents of the pack and other information

1. What Cresemba is and what it is used for

What Cresemba is
Cresemba is an anti-fungal medicine that contains the active substance isavuconazole.

How Cresemba works
Isavuconazole works by killing or stopping the growth of the fungus, which causes the infection.

What Cresemba is used for
Cresemba is used in adults to treat the following fungal infections:
- invasive aspergillosis, caused by a fungus in the ‘Aspergillus’ group;
- mucormycosis, caused by a fungus belonging to the ‘Mucorales’ group in patients for whom a treatment with amphotericin B is not appropriate.

2. What you need to know before you use Cresemba

Do not use Cresemba:
- if you are allergic to isavuconazole or any of the other ingredients of this medicine (listed in section 6),
- if you have a heart beat problem called ‘familial short QT syndrome’,
- if you are using any of the following medicines:
  - ketoconazole, used for fungal infections,
  - high doses of ritonavir (400 mg every 12 hours), used for HIV,
  - rifampicin, rifabutin, used for tuberculosis,
  - carbamazepine, used for epilepsy,
  - barbiturate medicines like phenobarbital, used for epilepsy and sleep disorders,
  - phenytoin, used for epilepsy,
  - St John’s wort, a herbal medicine used for depression,
  - efavirenz, etravirine, used for HIV,
- nafcillin, used for bacterial infections.

**Warnings and precautions**

Talk to your doctor, pharmacist or nurse before using Cresemba:

- if you have had an allergic reaction to other “azole” anti-fungal treatments in the past, such as ketoconazole, fluconazole, itraconazole, voriconazole or posaconazole,
- if you are suffering from severe liver disease. Your doctor should monitor you for possible side effects,

**Look out for side effects**

Stop using Cresemba and tell your doctor straight away if you notice any of the following side effects:

- rash, swelling of your lips, mouth, tongue or throat with difficulty breathing - these may be signs of an allergic reaction (hypersensitivity).

**Problems while having Cresemba as drip into a vein**

Tell your doctor straight away if you notice any of the following side effects:

- low blood pressure, feel short of breath, nausea, dizziness, headache, tingling, – your doctor may decide to stop the infusion.

**Changes in your liver function**

Cresemba can sometimes affect your liver function. Your doctor may carry out blood tests while you are taking this medicine.

**Skin problems**

Tell your doctor straight away if you get severe blistering of the skin, mouth, eyes or genitals.

**Children and adolescents**

Cresemba should not be used in children or adolescents younger than 18 years because there is no information on use in this age group.

**Other medicines and Cresemba**

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines. Some medicines may affect the way Cresemba works or Cresemba may affect the way they work, if they are taken at the same time.

In particular, do not take this medicine and tell your doctor or pharmacist if you are taking any of the following medicines:

- ketoconazole, used for fungal infections,
- high doses of ritonavir (400 mg every 12 hours), used for HIV,
- rifampicin, rifabutin, used for tuberculosis,
- carbamazepine, used for epilepsy,
- barbiturate medicines like phenobarbital, used for epilepsy and sleep disorders,
- phenytoin, used for epilepsy,
- St John’s wort, a herbal medicine used for depression.
- efavirenz, etravirine, used for HIV,
- nafcillin, used for bacterial infections.

Unless your doctor tells you otherwise, do not take this medicine and tell your doctor or pharmacist if you are taking any of the following medicines:

- rufinamide or other medicines which decrease the QT interval on the heart tracing (ECG),
- aprepitant, used to prevent nausea and vomiting by cancer treatment,
- prednisone, used for rheumatoid arthritis,
- pioglitazone, used for diabetes.

Tell your doctor or pharmacist if you are taking any of the following medicines, as a dose adjustment or monitoring may be required to check that the medicines are still having the desired effect:
- ciclosporin, tacrolimus and sirolimus, used for after having a transplant, called ‘immuno-suppressants’,
- cyclophosphamide, used for cancer,
- digoxin, used to treat heart failure or an uneven heart beat,
- colchicine, used for gout attack,
- dabigatran etexilate, used to stop blood clots after hip or knee replacement surgery,
- clarithromycin, used for bacterial infections,
- saquinavir, amprenavir, nelfinavir, indinavir, delavirdine, nevirapine, lopinavir/ritonavir combination, used for HIV,
- alfentanil, fentanyl, used against strong pain,
- vincristine, vinblastine, used for cancer,
- mycophenolate mofetil (MMF), used in transplant patients,
- midazolam, used for severe insomnia and stress,
- bupropion, used for depression.
- metformin, used for diabetes,
- daunorubicin, doxorubicin, imatinib, irinotecan, lapatinib, mitoxantrone, topotecan, used for different sorts of cancer.

**Pregnancy and breast-feeding**
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

Do not take Cresemba if you are pregnant, unless your doctor tells you otherwise. This is because it is not known if it may affect or harm your unborn baby.

Do not breast-feed if you are taking Cresemba.

**Driving and using machines**
Cresemba may make you feel confused, tired or sleepy. It can also make you pass out. If this happens, do not drive or use machines.

3. **How to use Cresemba**
Cresemba will be given to you by a doctor or nurse.

**Starting dose for the first two days (48 hours)**
The recommended dose is one vial three times a day (every 8 hours).

**Usual dose after the first two days**
This is started 12 to 24 hours after your last starting dose. The recommended dose is one vial once a day.

You will be given this dose until your doctor tells you otherwise. The duration of treatment with Cresemba may be longer than 6 months if your doctor considers this necessary.

The vial will be given as a drip into a vein by your doctor or nurse.

**If you use more Cresemba than you should**
If you think you have been given too much Cresemba, talk to your doctor or nurse straight away. You may have more side effects such as:
- headache, feeling dizzy, restless or sleepy,
- tingling, reduced sense of touch or sensation in the mouth,
- problems being aware of things, hot flushes, anxiety, joint pain,
- changes in the way things taste, dry mouth, diarrhoea, vomiting,
- feeling your heart beat, faster heart rate, being more sensitive to light.
If you forget to use Cresemba
As you will be given this medicine under close medical supervision, it is unlikely that a dose would be missed. However, tell your doctor or nurse if you think that a dose has been forgotten.

If you stop using Cresemba
Cresemba treatment will continue for as long as your doctor tells you. This is to make sure that the fungal infection has gone.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects
Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop using Cresemba and tell your doctor straight away if you notice any of the following side effects:
- rash, swelling of your lips, mouth, tongue or throat with difficulty breathing - these may be signs of an allergic reaction (hypersensitivity).

Tell your doctor straight away if you notice any of the following side effects:
- severe blistering of the skin, mouth, eyes or genitals.

Other side effects
Tell your doctor, pharmacist or nurse if you notice any of the following side effects:

Common: may affect up to 1 in 10 people
- low potassium in your blood,
- decreased appetite,
- hallucinations (delirium),
- headache,
- sleepiness,
- inflamed veins that could lead to blood clots,
- shortness of breath or sudden and severe difficulty breathing,
- feeling sick (nausea), being sick (vomiting), diarrhoea, stomach pain,
- changes in blood tests of liver function,
- rash, itching,
- kidney failure,
- chest pain, feeling tired or sleepy,
- problems where the injection was given.

Uncommon: may affect up to 1 in 100 people
- reduced white blood cells - can increase your risk of infection and fever,
- reduced blood cells called ‘platelets’ - can increase your risk for bleeding or bruising,
- reduced red blood cells - can make you feel weak or short of breath or make your skin pale,
- severe reduction in blood cells - can make you feel weak, cause bruising or make infections more likely,
- rash, swelling of your lips, mouth, tongue or throat with difficulty breathing (hypersensitivity),
- low blood sugar levels,
- low blood levels of magnesium,
- low levels in the blood of a protein called ‘albumin’,
- not getting the right goodness from your diet (malnutrition),
- depression, difficulty sleeping,
- seizure, fainting or feeling faint, dizziness,
- sensation of tingling, tickling, or pricking of the skin (paraesthesia),
- altered mental state (encephalopathy),
- changes in taste (dysgeusia),
- feeling of ‘spinning’ or being dizzy (vertigo),
- heart beat problems - may be too fast or uneven, or extra heart beats – this may show in your heart tracing (electrocardiogram or ECG),
- problems with the blood circulation,
- low blood pressure,
- wheezing, very fast breathing, coughing up blood or blood-stained sputum, nose bleeding,
- indigestion,
- constipation,
- feeling bloated (abdominal distension),
- enlarged liver,
- problems with the skin, red or purple spots on the skin (petechiae), inflamed skin (dermatitis), hair loss,
- back pain,
- swelling of the extremities,
- feeling weak, very tired, or sleepy or generally out of sorts (malaise).

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Cresemba
Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.

Store in in a refrigerator (2°C to 8°C).

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Cresemba contains
- The active substance is isavuconazole. Each vial contains 372.6 mg isavuconazonium sulfate, corresponding to 200 mg isavuconazole.
- The other ingredients (excipients) are mannitol (E421) and sulfuric acid.

What Cresemba looks like and contents of the pack
Cresemba 200 mg is presented in a single use glass vial as a powder for concentrate for solution for infusion.

Marketing Authorisation Holder:
Basilea Medical Ltd
(c/o Cox Costello & Horne Limited)
Langwood House
63–81 High Street
Rickmansworth
Cresemba 200 mg powder for concentrate for solution for infusion must be reconstituted and diluted prior to infusion.

**Reconstitution**

One vial of the powder for concentrate for solution for infusion should be reconstituted by addition of 5 mL water for injection to the vial. The vial should be shaken to dissolve the powder completely. The reconstituted solution should be inspected visually for particulate matter and discoloration. Reconstituted concentrate should be clear and free of visible particulate. It must be further diluted prior to administration.

**Dilution and administration**

After reconstitution, the entire content of the reconstituted concentrate should be removed from the vial and added to an infusion bag containing at least 250 mL of either sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) dextrose solution. The infusion solution contains approximately 1.5 mg/mL isavuconazonium sulfate (corresponding to approximately 0.8 mg isavuconazole per mL). After the reconstituted concentrate is further diluted, the diluted solution may show fine white-to-translucent particulates of isavuconazole that do not sediment (but will be removed by in-line filtration). The diluted solution should be mixed gently, or the bag should be rolled to minimise the formation of particulates. Unnecessary vibration or vigorous shaking of the solution should be avoided. The solution for infusion must be administered via an infusion set with an in-line filter (pore size 0.2 μm to 1.2 μm) made of polyether sulfone (PES).

Isavuconazole should not be infused into the same line or cannula concomitantly with other intravenous products.

Chemical and physical in-use stability after reconstitution and dilution has been demonstrated for 24 hours at 2 °C to 8 °C, or 6 hours at room temperature.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C, unless reconstitution and dilution has taken place in controlled and validated aseptic conditions.
If possible, the intravenous administration of isavuconazole should be completed within 6 hours after reconstitution and dilution at room temperature. If this is not possible, the infusion solution should be immediately refrigerated after dilution, and infusion should be completed within 24 hours.

An existing intravenous line should be flushed with sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) dextrose solution.

This medicinal product is for single use only. Discard partially-used vials.
Package leaflet: Information for the patient

Cresemba 100 mg hard capsules
Isavuconazole

This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet
1. What Cresemba is and what it is used for
2. What you need to know before you take Cresemba
3. How to take Cresemba
4. Possible side effects
5. How to store Cresemba
6. Contents of the pack and other information

1. What Cresemba is and what it is used for

What Cresemba is
Cresemba is an anti-fungal medicine that contains the active substance isavuconazole.

How Cresemba works
Isavuconazole works by killing or stopping the growth of the fungus, which causes the infection.

What Cresemba is used for
Cresemba is used in adults to treat the following fungal infections:
- invasive aspergillosis, caused by a fungus in the ‘Aspergillus’ group;
- mucormycosis, caused by a fungus belonging to the ‘Mucorales’ group in patients for whom a treatment with amphotericin B is not appropriate.

2. What you need to know before you take Cresemba

Do not take Cresemba:
- if you are allergic to isavuconazole or any of the other ingredients of this medicine (listed in section 6),
- if you have a heart beat problem called ‘familial short QT syndrome’,
- if you are using any of the following medicines:
  - ketoconazole, used for fungal infections,
  - high doses of ritonavir (400 mg every 12 hours), used for HIV,
  - rifampicin, rifabutin, used for tuberculosis,
  - carbamazepine, used for epilepsy,
  - barbiturate medicines like phenobarbital, used for epilepsy and sleep disorders,
- phenytoin, used for epilepsy,  
- St John’s wort, a herbal medicine used for depression,  
- efavirenz, etravirine, used for HIV,  
- nafcillin, used for bacterial infections.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Cresemba:  
- if you have had an allergic reaction to other ‘azole’ anti-fungal treatments in the past, such as ketoconazole, fluconazole, itraconazole, voriconazole or posaconazole,  
- if you are suffering from severe liver disease. Your doctor should monitor you for possible side effects

Look out for side effects
Stop taking Cresemba and tell your doctor straight away if you notice any of the following side effects:  
- rash, swelling of your lips, mouth, tongue or throat with difficulty breathing - these may be signs of an allergic reaction (hypersensitivity).

Changes in your liver function
Cresemba can sometimes affect your liver function. Your doctor may carry out blood tests while you are taking this medicine.

Skin problems
Tell your doctor straight away if you get severe blistering of the skin, mouth, eyes or genitals.

Children and adolescents
Cresemba should not be used in children or adolescents younger than 18 years because there is no information on use in this age group.

Other medicines and Cresemba
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines. Some medicines may affect the way Cresemba works or Cresemba may affect the way they work, if they are taken at the same time.

In particular, do not take this medicine and tell your doctor or pharmacist if you are taking any of the following medicines:  
- ketoconazole, used for fungal infections,  
- high doses of ritonavir (400 mg every 12 hours), used for HIV,  
- rifampicin, rifabutin, used for tuberculosis,  
- carbamazepine, used for epilepsy,  
- barbiturate medicines like phenobarbital, used for epilepsy and sleep disorders,  
- phenytoin, used for epilepsy,  
- St John’s wort, a herbal medicine used for depression,  
- efavirenz, etravirine, used for HIV,  
- nafcillin, used for bacterial infections.

Unless your doctor tells you otherwise, do not take this medicine and tell your doctor or pharmacist if you are taking any of the following medicines:  
- rufinamide or other medicines which decrease the QT interval on the heart tracing (ECG),  
- aprepitant, used to prevent nausea and vomiting by cancer treatment,  
- prednisone, used for rheumatoid arthritis,  
- pioglitazone, used for diabetes.

Tell your doctor or pharmacist if you are taking any of the following medicines, as a dose adjustment or monitoring may be required to check that the medicines are still having the desired effect:  
- ciclosporin, tacrolimus and sirolimus, used for after having a transplant, called ‘immuno-suppressants’,
- cyclophosphamide, used for cancer,
- digoxin, used to treat heart failure or an uneven heart beat,
- colchicine, used for gout attack,
- dabigatran etexilate, used to stop blood clots after hip or knee replacement surgery,
- clarithromycin, used for bacterial infections,
- saquinavir, amprenavir, nelfinavir, indinavir, delavirdine, nevirapine, lopinavir/ritonavir combination, used for HIV,
- alfentanil, fentanyl, used against strong pain,
- vincristine, vinblastine, used for cancer,
- mycophenolate mofetil (MMF), used in transplant patients,
- midazolam, used for severe insomnia and stress,
- metformin, used for diabetes,
- daunorubicin, doxorubicin, imatinib, irinotecan, lapatinib, mitoxantrone, topotecan, used for different sorts of cancer.

**Pregnancy and breast-feeding**
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

Do not take Cresemba if you are pregnant, unless your doctor tells you otherwise. This is because it is not known if it may affect or harm your unborn baby.

Do not breast-feed if you are taking Cresemba.

**Driving and using machines**
Cresemba may make you feel confused, tired or sleepy. It can also make you pass out. If this happens, do not drive or use machines.

3. **How to take Cresemba**
Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

**Starting dose for the first two days (48 hours)**
The recommended dose is two capsules three times a day (every 8 hours).

**Usual dose after the first two days**
This is started 12 to 24 hours after your last starting dose. The recommended dose is two capsules once a day.

You will take this dose until your doctor tells you otherwise. The duration of treatment with Cresemba may be longer than 6 months if your doctor considers this necessary.

Capsules can be taken with or without food. Swallow the capsules whole. Do not chew, crush, dissolve or open the capsules.

**If you take more Cresemba than you should**
If you take more Cresemba than you should, talk to a doctor or go to a hospital straight away. Take the medicine pack with you so the doctor knows what you have taken.
You may have more side effects such as:
- headache, feeling dizzy, restless or sleepy,
- tingling, reduced sense of touch or sensation in the mouth,
- problems being aware of things, hot flushes, anxiety, joint pain,
- changes in the way things taste, dry mouth, diarrhoea, vomiting,
- feeling your heart beat, faster heart rate, being more sensitive to light.
If you forget to take Cresemba
Take the capsules as soon as you remember. However, if it is nearly time for the next dose, skip the missed dose.

Do not take a double dose to make up for a forgotten dose.

If you stop taking Cresemba
Do not stop taking Cresemba unless you doctor has told you to do so. It is important to keep taking this medicine as long as your doctor tells you. This is to make sure that the fungal infection has gone.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop taking Cresemba and tell your doctor straight away if you notice any of the following side effects:
- rash, swelling of your lips, mouth, tongue or throat with difficulty breathing - these may be signs of an allergic reaction (hypersensitivity).

Tell your doctor straight away if you notice any of the following side effects:
- severe blistering of the skin, mouth, eyes or genitals.

Other side effects
Tell your doctor, pharmacist or nurse if you notice any of the following side effects:

Common: may affect up to 1 in 10 people
- low potassium in your blood,
- decreased appetite,
- hallucinations (delirium),
- headache,
- sleepiness,
- inflamed veins that could lead to blood clots,
- shortness of breath or sudden and severe difficulty breathing,
- feeling sick (nausea), being sick (vomiting), diarrhoea, stomach pain,
- changes in blood tests of liver function,
- rash, itching,
- kidney failure,
- chest pain, feeling tired or sleepy.

Uncommon: may affect up to 1 in 100 people
- reduced white blood cells - can increase your risk of infection and fever,
- reduced blood cells called ‘platelets’ - can increase your risk for bleeding or bruising,
- reduced red blood cells - can make you feel weak or short of breath or make your skin pale,
- severe reduction in blood cells - can make you feel weak, cause bruising or make infections more likely,
- rash, swelling of your lips, mouth, tongue or throat with difficulty breathing (hypersensitivity),
- low blood sugar levels,
- low blood levels of magnesium,
- low levels in the blood of a protein called ‘albumin’,
- not getting the right goodness from your diet (malnutrition),
- depression, difficulty sleeping,
- seizure, fainting or feeling faint, dizziness,
- sensation of tingling, tickling, or pricking of the skin (paraesthesia),
- altered mental state (encephalopathy),
- changes in taste (dysgeusia),
- feeling of ‘spinning’ or being dizzy (vertigo),
- heart beat problems - may be too fast or uneven, or extra heart beats – this may show in your heart tracing (electrocardiogram or ECG),
- problems with the blood circulation,
- low blood pressure,
- wheezing, very fast breathing, coughing up blood or blood-stained sputum, nose bleeding,
- indigestion,
- constipation,
- feeling bloated (abdominal distension),
- enlarged liver,
- problems with the skin, red or purple spots on the skin (petechiae), inflamed skin (dermatitis), hair loss,
- back pain,
- feeling weak, very tired, or sleepy or generally out of sorts (malaise).

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Cresemba

Keep this medicine out of the sight and reach of children.

Do not take this medicine after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.

Store in the original packaging in order to protect from moisture.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Cresemba contains
- The active substance is isavuconazole. Each capsule contains 186.3 mg isavuconazonium sulfate, corresponding to 100 mg isavuconazole.
- The other ingredients ingredients are:
  - Capsule content: magnesium citrate (anhydrous), microcrystalline cellulose, talc, anhydrous colloidal silica, stearic acid.
  - Capsule shell: hypromellose, water, red iron oxide (E172) (capsule body only), titanium dioxide (E171), gelatin gum, potassium acetate, disodium edetate, sodium laurilsulfate.
  - Printing ink: shellac, propylene glycol, potassium hydroxide, black iron oxide (E172).

What Cresemba looks like and contents of the pack
Cresemba 100 mg hard capsules are capsules with a reddish-brown body marked with “100” in black ink and a white cap marked with “C” in black ink.

Cresemba is available in cartons that contain 14 capsules. Each carton contains 2 aluminium blisters pack, with 7 capsules each.
Each capsule pocket is connected to a pocket that contains ‘desiccant’ to protect the capsule from moisture.

Do not puncture the blister containing the desiccant.

Do not swallow or use the desiccant.

**Marketing Authorisation Holder:**

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**Manufacturer:**

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**This leaflet was last revised in**

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site:  
http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.