Posaconazole for the Treatment and Prophylaxis of Invasive Fungal infections

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Posaconazole: Mechanism of Action

- Primary mode of action: **inhibition** of fungal **ergosterol biosynthesis** (cytochrome P450–dependent enzyme lanosterol 14α-demethylase [CYP51A1])
- Extended side chain likely result in tighter and more stable binding to receptor sites

Overview of Posaconazole (Noxafil®)

- Extended-spectrum triazole
- Bioavailable oral suspension
- In vitro activity against wide range of moulds and yeasts
- In vivo activity against several moulds and yeasts
- Broad activity against several pathogens, including Aspergillus, Fusarium, Coccidioides, agents of chromoblastomycosis and mycetoma, Candida, Cryptococcus, Histoplasma, and Zygomycetes
- Well tolerated in clinical studies

The clinical significance of in vitro studies is not established, and results from these studies do not necessarily predict clinical activity.
Noxafil [summary of product characteristics]. Brussels, Belgium; SP Europe; 2006.
Posaconazole Indications in European Union & Turkey

- **Invasive aspergillosis** in patients with disease that is refractory to amphotericin B or itraconazole or in patients who are intolerant of these medicinal products
- **Fusariosis** in patients with disease that is refractory to amphotericin B or in patients who are intolerant of amphotericin B
- **Chromoblastomycosis and mycetoma** in patients with disease that is refractory to itraconazole or in patients who are intolerant of itraconazole
- **Coccidioidomycosis** in patients with disease that is refractory to amphotericin B, itraconazole, or fluconazole or in patients who are intolerant of these medicinal products
- **Oropharyngeal candidiasis**: as first-line therapy in patients who have severe disease or are immunocompromised, in whom response to topical therapy is expected to be poor

Posaconazole Indications in European Union & Turkey

- Noxafil is also indicated for prophylaxis of invasive fungal infections in the following patients:
  - Patients receiving remission-induction chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS) expected to result in prolonged neutropenia and who are at high risk of developing invasive fungal infections;
  - Hematopoietic stem cell transplant (HSCT) recipients who are undergoing high-dose immunosuppressive therapy for graft versus host disease and who are at high risk of developing invasive fungal infections.

In Vitro Data
for Posaconazole Compared to Other Antifungal Agents
Summary of Posaconazole
In Vitro Activity

• Posaconazole has a broad spectrum of *in vitro* activity against many fungi, including:
  – Moulds: including *Aspergillus*, *Fusarium*, and the Zygomycetes
  – Yeasts: including *C. albicans*, *C. krusei*, and *C. glabrata*
  – Dimorphic fungi, including *Coccidioides*, *Histoplasma*, and *Blastomyces*
  – Rare fungi, such as *Scedosporium* (primarily *S. apiospermum*) and agents of chromoblastomycosis, mycetoma, and phaeohyphomycosis

• Posaconazole exhibited potent antifungal activity against a wide variety of clinically important fungal pathogens and was frequently *more active than other azoles and amphotericin B*

The clinical significance of *in vitro* studies is not established, and results from these studies do not necessarily predict clinical activity.
Posaconazole Treatment of Refractory Invasive Fungal Infections
Aspergillosis
(MITT Population)
## Posaconazole Treatment of Refractory Invasive Fungal Infections

### Baseline Characteristics: Aspergillosis

<table>
<thead>
<tr>
<th>Characteristic, n (%)</th>
<th>Posaconazole (n = 107)</th>
<th>External Control (n = 86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic malignancy</td>
<td>79 (74)</td>
<td>70 (81)</td>
</tr>
<tr>
<td>Hematopoietic stem cell transplant</td>
<td>55 (51)</td>
<td>38 (44)</td>
</tr>
<tr>
<td>Allogeneic</td>
<td>48 (45)</td>
<td>34 (40)</td>
</tr>
<tr>
<td>Neutropenia at baseline (ANC &lt;500 cells/mm³)</td>
<td>21 (20)</td>
<td>26 (30)</td>
</tr>
<tr>
<td>Solid organ transplant</td>
<td>12 (11)</td>
<td>7 (8)</td>
</tr>
<tr>
<td>Acquired immunodeficiency</td>
<td>28 (26)</td>
<td>19 (22)</td>
</tr>
<tr>
<td>Congenital immunodeficiency</td>
<td>2 (2)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Nonhematologic malignancy</td>
<td>13 (12)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Mechanical ventilation at baseline</td>
<td>4 (4)</td>
<td>Not allowed per protocol</td>
</tr>
<tr>
<td>Death within 72 hours of baseline</td>
<td>4 (4)</td>
<td>Not allowed per protocol</td>
</tr>
</tbody>
</table>

Study report P02952, pp 60, 61, 80. SPRI, Kenilworth, NJ, USA; March 2004.
**Posaconazole Treatment of Refractory Invasive Fungal Infections**

**Global Response**: Aspergillosis

*Primary efficacy analysis (logistic regression).*

**Responders (%)**

| Treatment vs control: OR, 4.06 (95% CI, 1.5–11.04). |
|-----------------|-----------------|
| Posaconazole (n = 107) | 45/107 |
| External Control (n = 86) | 22/86 |

*P = .006*

Posaconazole Treatment of Refractory Invasive Fungal Infections

Global Response*: Kaplan-Meier Analysis of All-Cause Mortality

*Global response in MITT subset with Aspergillus as primary pathogen.
Study report P02952, pp 76, 300. SPRI, Kenilworth, NJ, USA; March 2004.
Posaconazole Registration Data for Refractory Invasive Fungal Infections
Results for Other Pathogens
**Posaconazole for Zygomycosis**

**Study Design**

- Patients identified through enrollment forms from the Schering-Plough compassionate use protocol
  - Refractory zygomycosis
  - Intolerant of other antifungal therapy
- 91 patients with proven or probable* zygomycosis included in analysis
- Team of experts reviewed each case and determined outcome at $\leq 12$ weeks after initiation of posaconazole
  - Complete response: resolution of infection
  - Partial response: clinically meaningful improvement
  - Stable disease: no improvement, but no deterioration
  - Failure: deterioration


Posaconazole for Zygomycosis
Success Rate by Reason for Enrollment

Posaconazole Activity Against Fusariosis

- Overall success: 46% (11/24)\(^1,2\)
  - 18 refractory/intolerant cases
  - 6 proven infections but not refractory/intolerant (4/6 success)
- Refractory/intolerant infections: 39% (7/18)\(^2-4\)
  - 9 patients had disseminated disease
  - 14 were refractory, 4 were intolerant
  - Prior therapy was amphotericin B
  - 6 patients were neutropenic at baseline, no response in the setting of persistent neutropenia\(^3\)

Posaconazole Registration Data for Prophylaxis in High-Risk Neutropenic Patients
Posaconazole Prophylaxis in Neutropenic Patients

Study Purpose and Primary Objective

- **Purpose**
  - Evaluate the efficacy, safety, and tolerability of posaconazole as prophylaxis for invasive fungal infections in 602 high-risk patients with acute myelogenous leukemia or myelodysplastic syndrome and prolonged neutropenia

- **Primary objective**
  - Determine efficacy of posaconazole versus pooled standard azoles (fluconazole and itraconazole) in preventing proven or probable invasive fungal infections from randomization to 7 days after last dose

Posaconazole Prophylaxis in Neutropenic Patients
Selected Inclusion Criteria

- Patients ≥13 years of age
- Anticipated neutropenia (absolute neutrophil count ≤500 cells/mm³) for ≥7 days
- Treatment with intensive chemotherapy for:
  - Newly diagnosed acute myelogenous leukemia
  - Relapse of acute myelogenous leukemia
  - Myelodysplastic syndrome

**Posaconazole Prophylaxis in Neutropenic Patients**

**Study Design**

- Open-label, evaluator-blinded, randomized (1:1 ratio) trial
- Posaconazole 200 mg oral suspension 3x daily
- Standardazole*
  - Fluconazole 400 mg oral suspension 1x daily or
  - Itraconazole 200 mg oral solution 2x daily
- Patients unable to tolerate oral drug could receive intravenous prophylaxis at the same dose for ≤3 days per chemotherapy cycle
  - Intravenous alternative for posaconazole: amphotericin B deoxycholate 0.3 to 0.5 mg/kg daily

*Comparator to be used throughout study determined by each center prior to study commencement. Cornely OA et al. *N Engl J Med.* 2007;356:348-359.
**Posaconazole Prophylaxis in Neutropenic Patients**

*Primary End Point*

- Incidence of proven or probable **invasive fungal infection** during treatment phase* for the intent-to-treat population (N = 602) versus pooled standard azoles (fluconazole or itraconazole) as evaluated in two stages
  - Noninferiority of posaconazole versus pooled standard azoles and, if demonstrated,
  - Superiority of posaconazole versus pooled standard azoles

- Invasive fungal infections were adjudicated by an independent data review committee

*On-treatment period.
Posaconazole Prophylaxis in Neutropenic Patients
Enrollment Summary

602 patients enrolled from 89 centers worldwide

- Posaconazole: n = 304
- Standard azoles:
  - Fluconazole (n = 240)
  - Itraconazole (n = 58)

# Posaconazole Prophylaxis in Neutropenic Patients

## Summary of Cumulative Prophylaxis and Study Duration

<table>
<thead>
<tr>
<th></th>
<th>Posaconazole (n = 304)</th>
<th>Standard Azoles (n = 298)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration of prophylaxis, days</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD(^1,2)</td>
<td>29 ± 21</td>
<td>25 ± 17</td>
</tr>
<tr>
<td>Median (range)(^2)</td>
<td>23 (1–110)</td>
<td>20 (1–80)</td>
</tr>
<tr>
<td><em><em>Study duration</em>, days</em>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD(^1,2)</td>
<td>93 ± 33</td>
<td>90 ± 33</td>
</tr>
</tbody>
</table>

*From randomization to last contact.
**Posaconazole Prophylaxis in Neutropenic Patients**

Results – Proven/Probable Invasive Fungal Infections

- **Posaconazole (n = 304)**
- **Standard azoles (n = 298)**

Number of IFIs

- **All IFIs**
  - Posaconazole: 25 (8%) vs. Standard azoles: 20 (7%)
  - P < .001

- **Aspergillosis**
  - Posaconazole: 11% vs. Standard azoles: 5%
  - P = .003

- **100-day Period After Randomization**
  - **All IFIs**
    - Posaconazole: 33 (P < .001) vs. Standard azoles: 14%
  - Fixed-time period.

- **Aspergillosis**
  - Posaconazole: 9% vs. Standard azoles: 4%
  - P < .001

IFI indicates invasive fungal infection.


*On-treatment period.
†Fixed-time period.
Posaconazole Prophylaxis in Neutropenic Patients

Results – Time to Invasive Fungal Infection

*Estimated using log-rank statistics.
Censoring time is the minimum of the last contact date and day 100.
Posaconazole Prophylaxis in Neutropenic Patients
Results – Death From Any Cause

*Estimated using log-rank statistics.
Censoring time is the minimum of the last contact date and day 100.
Posaconazole Prophylaxis in Neutropenic Patients
Results – Time to Invasive Fungal Infection or Death

*Estimated using log-rank statistics.
# Prophylaxis in Neutropenic Patients

**Serious (≥2%) AEs**

<table>
<thead>
<tr>
<th>Event</th>
<th>Patients, n (%)</th>
<th>POS (n = 304)</th>
<th>FLU/ITZ (n = 298)</th>
<th>FLU (n = 240)</th>
<th>ITZ (n = 58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>159 (52)</td>
<td>175 (59)</td>
<td>143 (60)</td>
<td>32 (55)</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>22 (7)</td>
<td>23 (8)</td>
<td>18 (8)</td>
<td>5 (9)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
<td>8 (3)</td>
<td>3 (1)</td>
<td>2 (1)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Bilirubinemia</td>
<td>7 (2)</td>
<td>5 (2)</td>
<td>4 (2)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>10 (3)</td>
<td>21 (7)</td>
<td>17 (7)</td>
<td>4 (7)</td>
<td></td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>6 (2)</td>
<td>3 (1)</td>
<td>3 (1)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>4 (1)</td>
<td>6 (2)</td>
<td>5 (2)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Cardiorespiratory arrest</td>
<td>4 (1)</td>
<td>5 (2)</td>
<td>4 (2)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2 (1)</td>
<td>6 (2)</td>
<td>5 (2)</td>
<td>1 (2)</td>
<td></td>
</tr>
</tbody>
</table>

*Events are listed for the period from randomization until 30 days after the last dose of the study drug had been administered.

Numbers for subentries may not sum to the total numbers because patients could have more than 1 event.

†Full list of serious adverse events are available with the publication.

Posaconazole Prophylaxis in Neutropenic Patients

Conclusions

- Posaconazole was
  - Superior to standard azoles for prevention of invasive fungal infection
  - Superior to standard azoles for prevention of invasive aspergillosis
  - Associated with a significant survival benefit
- Safety profile of posaconazole was comparable to that of pooled standard azoles
**Posaconazole Prophylaxis in Allogeneic Hematopoietic Stem Cell Transplant Recipients With Graft-Versus-Host Disease**

**Study Purpose and Primary Objective**

- **Purpose**
  - Evaluate the efficacy, safety, and tolerability of posaconazole as prophylaxis for invasive fungal infection in allogeneic hematopoietic stem cell transplant recipients with acute or chronic graft-versus-host disease

- **Primary objective**
  - Determine efficacy of posaconazole versus fluconazole in preventing proven or probable invasive fungal infection from randomization to 112 days after first dose (fixed treatment period)*

*Fixed-time period.
Posaconazole Prophylaxis in Allogeneic Hematopoietic Stem Cell Transplant Recipients With Graft-Versus-Host Disease
Selected Inclusion Criteria

- Allogeneic hematopoietic stem cell transplant recipients $\geq 13$ years of age
- Acute or chronic extensive graft-versus-host disease
- Treatment with intensive immunosuppressive therapy
  - High-dose corticosteroids
  - Antithymocyte globulin
  - Steroid-sparing regimen comprising a combination of $\geq 2$ immunosuppressive agents or modalities

Posaconazole Prophylaxis in Allogeneic Hematopoietic Stem Cell Transplant Recipients With Graft-Versus-Host Disease
Study Design

- **Double-blind, double-dummy, randomized trial**
- Posaconazole 200 mg 3x daily *or*
- Fluconazole 400 mg oral capsule 1x daily
- Patients unable to tolerate oral study drug:
  - Suspension of study drug until oral medication could be tolerated
  - Non-azole intravenous prophylaxis could be substituted for no more than 4 days

Posaconazole Prophylaxis in Allogeneic Hematopoietic Stem Cell Transplant Recipients With Graft-Versus-Host Disease
Primary End Point

- **Incidence** of proven or probable **invasive fungal infection** during the fixed treatment period* for the intent-to-treat population versus fluconazole as evaluated in 2 stages:
  - Noninferiority of posaconazole versus fluconazole and if demonstrated,
  - Superiority of posaconazole versus fluconazole

*Fixed-time period.
### Posaconazole Prophylaxis in Allogeneic Hematopoietic Stem Cell Transplant Recipients With Graft-Versus-Host Disease Patient Populations

<table>
<thead>
<tr>
<th></th>
<th>Posaconazole</th>
<th>Fluconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent-to-treat pop.</td>
<td>301</td>
<td>299</td>
</tr>
<tr>
<td>All-treated sub.</td>
<td>291</td>
<td>288</td>
</tr>
</tbody>
</table>

**Intent-to-treat population:** all randomized subjects  
**All-treated subjects:** Intent-to-treat subset who received $\geq 1$ dose

ITT indicates intent-to-treat.  
### Posaconazole Prophylaxis in Allogeneic Hematopoietic Stem Cell Transplant Recipients With Graft-Versus-Host Disease

Cumulative Duration of Prophylaxis

<table>
<thead>
<tr>
<th></th>
<th>Posaconazole (n = 301)</th>
<th>Fluconazole (n = 299)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration of prophylaxis, days</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD(^1,2)</td>
<td>80 ± 43</td>
<td>77 ± 43</td>
</tr>
<tr>
<td>Median (range)(^1)</td>
<td>111 (1-138)</td>
<td>108 (1-130)</td>
</tr>
</tbody>
</table>

All-treated patients (intent-to-treat subset who received ≥1 dose): posaconazole (n = 291); fluconazole (n = 288).

Posaconazole Prophylaxis in Allogeneic Hematopoietic Stem Cell Transplant Recipients With Graft-Versus-Host Disease Results – Proven/Probable Invasive Fungal Infections

**Fixed Treatment Period***

- **All IFIs**
  - Posaconazole: 5% (n = 301)
  - Fluconazole: 2% (n = 299)
  - *P = .07*

- **Aspergillosis**
  - Posaconazole: 2% (n = 27)
  - Fluconazole: 7% (n = 21)
  - *P = .006*

- **All IFIs**
  - Posaconazole: 8% (n = 22)
  - Fluconazole: 2% (n = 7)
  - *P = .004*

- **Aspergillosis**
  - Posaconazole: 1% (n = 3)
  - Fluconazole: 17% (n = 17)
  - *P = .001*

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*Fixed-time period.
†On-treatment period.
Posaconazole Prophylaxis in Allogeneic Hematopoietic Stem Cell Transplant Recipients With Graft-Versus-Host Disease

Time From First Dose to Invasive Fungal Infection* – Fixed Treatment Period†

Probability of Onset of Infection (%)

Mean (days)

Fluconazole (88)
Posaconazole (102)

P = .048

Days From First Dose

*All-treated subset.
†Fixed-time period.
All non-invasive fungal infection events are considered censored; all subjects censored at the end of prophylaxis phase.
### Posaconazole Prophylaxis in Allogeneic Hematopoietic Stem Cell Transplant Recipients With Graft-Versus-Host Disease

#### All-Cause Mortality – Fixed Treatment Period*1

<table>
<thead>
<tr>
<th>Cause of death (Investigator assessment), n (%)</th>
<th>Posaconazole n = 301</th>
<th>Fluconazole n = 299</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total deaths</strong></td>
<td>76 (25)</td>
<td>84 (28)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>39 (13)§</td>
<td>37 (12)</td>
</tr>
<tr>
<td>Complications related to invasive fungal infection</td>
<td>4 (1)§</td>
<td>12 (4)§</td>
</tr>
<tr>
<td>Progression of underlying disease/graft-versus-host disease</td>
<td>31 (10)</td>
<td>33 (11)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (1)</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>

No significant difference in time to death (P = .847) between groups.2

---

*Fixed-time period.

†P = .01 by Chi-square test.

‡P = .046 by log-rank test.


Prophylaxis in Allogeneic Hematopoietic Stem Cell Transplant Recipients With Graft Versus Host Disease: Treatment-related Adverse Events (≥2%)

<table>
<thead>
<tr>
<th>Body System/Preferred Term</th>
<th>Patients, n (%)</th>
<th>Posaconazole (n = 301)</th>
<th>Fluconazole (n = 299)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects reporting any AE</td>
<td>107 (36)</td>
<td>115 (38)</td>
<td></td>
</tr>
<tr>
<td>Body as a whole – General disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>3 (1)</td>
<td>7 (2)</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>4 (1)</td>
<td>5 (2)</td>
<td></td>
</tr>
<tr>
<td>Drug level altered</td>
<td>5 (2)</td>
<td>2 (1)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (1)</td>
<td>6 (2)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>3 (1)</td>
<td>8 (3)</td>
<td></td>
</tr>
<tr>
<td>Weakness</td>
<td>3 (1)</td>
<td>5 (2)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disorders, general</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (1)</td>
<td>5 (2)</td>
<td></td>
</tr>
<tr>
<td>Central and peripheral nervous system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td>4 (1)</td>
<td>6 (2)</td>
<td></td>
</tr>
<tr>
<td>Disorders of the eye</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vision blurred</td>
<td>3 (1)</td>
<td>5 (2)</td>
<td></td>
</tr>
</tbody>
</table>

### Prophylaxis in Allogeneic Hematopoietic Stem Cell Recipients With Graft Versus Host Disease: Treatment-related Adverse Events (≥2%), continued

<table>
<thead>
<tr>
<th>Body System/Preferred Term</th>
<th>Posaconazole (n = 301)</th>
<th>Fluconazole (n = 299)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4 (1)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Constipation</td>
<td>1 (&lt;1)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (3)</td>
<td>12 (4)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>3 (1)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>22 (7)</td>
<td>28 (9)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13 (4)</td>
<td>15 (5)</td>
</tr>
<tr>
<td><strong>Liver and biliary system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubinemia</td>
<td>8 (3)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>GGT increased</td>
<td>9 (3)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Hepatic enzymes increased</td>
<td>8 (3)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>8 (3)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>9 (3)</td>
<td>4 (1)</td>
</tr>
</tbody>
</table>

**Prophylaxis in Allogeneic-HSCT Recipients With Graft-Versus-Host Disease: Treatment-related AEs (≥2%), continued**

<table>
<thead>
<tr>
<th>Body System/Preferred Term</th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Posaconazole (n = 301)</td>
</tr>
<tr>
<td>Metabolic and Nutritional Disorders</td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase increased</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Renal and urinary system disorders</td>
<td></td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Special senses, other</td>
<td></td>
</tr>
<tr>
<td>Taste perversion</td>
<td>3 (1)</td>
</tr>
</tbody>
</table>

Posaconazole is effective and safe for the prevention of invasive fungal infections in hematopoietic stem cell transplant recipients during the “at-risk” period for mould and yeast infections and reduces fungal-related mortality.
**Summary of Posaconazole Prophylaxis Studies**

- In acute myelogenous leukemia patients with neutropenia due to chemotherapy, posaconazole was
  - Significantly better than pooled standard azoles for prophylaxis for *Candida* and *Aspergillus* infections
  - Associated with a decrease in all cause mortality at day 100

- In hematopoietic stem cell transplant recipients with graft versus host disease, posaconazole was
  - Significantly better than fluconazole for prophylaxis for *Candida* and *Aspergillus* infections during the exposure period*
  - Associated with a reduction in invasive fungal infection-related mortality

- Posaconazole has a safety profile comparable to fluconazole

*On-treatment period.*
<table>
<thead>
<tr>
<th>Condition</th>
<th>Primary</th>
<th>Alternative</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous aspergillosis</td>
<td>...</td>
<td>Similar to invasive pulmonary aspergillosis</td>
<td>Surgical resection is indicated where feasible</td>
</tr>
<tr>
<td>Aspergillus peritonitis</td>
<td>...</td>
<td>Similar to invasive pulmonary aspergillosis</td>
<td>...</td>
</tr>
<tr>
<td>Empirical and preemptive anti-fungal therapy</td>
<td>For empirical antifungal therapy, L-AmB (3 mg/kg/day IV), caspofungin (70 mg/day 1 IV and 50 mg/day IV thereafter), itraconazole (200 mg every day IV or 200 mg BID), voriconazole (6 mg/kg IV every 12h for 1 day, followed by 3 mg/kg IV every 12 h; oral dosage is 200 mg every 12 h)</td>
<td>Preemptive therapy is a logical extension of empirical antifungal therapy in defining a high-risk population with evidence of invasive fungal infection (e.g., pulmonary infiltrate or positive galactomannan assay result)</td>
<td></td>
</tr>
<tr>
<td>Prophylaxis against invasive aspergillosis</td>
<td>Posaconazole (200 mg every 8h)</td>
<td>Itraconazole (200 mg every 12 h IV for 2 days, then 200 mg every day IV or itraconazole (200 mg PO every 12 h); caspofungin (50 mg/day)</td>
<td>Efficacy of posaconazole prophylaxis demonstrated in high-risk patients (patients with GVHD and neutropenic patients with AML and MDS)</td>
</tr>
<tr>
<td>Aspergillosis</td>
<td>No therapy or surgical resection</td>
<td>Itraconazole or voriconazole; similar to invasive pulmonary aspergillosis</td>
<td>The role of medical therapy in treatment of aspergillosis is uncertain; penetration into preexisting cavities may be minimal for AmB but is excellent for itraconazole</td>
</tr>
<tr>
<td>Chronic cavitary pulmonary aspergillosis</td>
<td>Itraconazole or voriconazole</td>
<td>Similar to invasive pulmonary aspergillosis</td>
<td>Innate immune defects demonstrated in most of these patients; long-term therapy may be needed; surgical resection may lead to significant complications; anecdotally responses to IFN-γ</td>
</tr>
<tr>
<td>Allergic bronchopulmonary aspergillosis</td>
<td>Itraconazole</td>
<td>Oral voriconazole (200 mg PO every 12 h or posaconazole (400 mg PO BID)</td>
<td>Corticosteroids are a cornerstone of therapy; itraconazole has a demonstrable corticosteroid-sparing effect</td>
</tr>
<tr>
<td>Allergic aspergillus sinusitis</td>
<td>None of itraconazole</td>
<td>Few data on other agents</td>
<td>...</td>
</tr>
</tbody>
</table>
Primary antifungal prophylaxis in leukemia patients

• **Induction chemotherapy of acute leukemia**
  - Fluconazole 50-400 mg qd iv/oral: CI
  - Itraconazole oral solution 2.5 mg/kg bid: CI
  - Posaconazole 200 mg tid oral: Al
  - Candins iv: insufficient data
  - Polyene iv: CI
  - Aerosolized liposomal amphotericin B in combination with oral fluconazole: BI
Primary antifungal prophylaxis in leukemia patients

• Allogeneic hematopoietic stem cell transplantation: GvHD phase
  Fluconazole 400 mg qd iv/oral: CI
  Itraconazole 200 mg IV followed by oral solution 200 mg bid: BI
  Posaconazole 200 mg tid oral: AI
  Candins iv: insufficient data
  Polyene iv: CI
  Voriconazole 200 mg bid oral: provisional AI
  Aerosolized liposomal amphotericin B plus fluconazole: insufficient data