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Pharmacokinetics of Different Dosing Strategies of Oral Posaconazole in Patients with Compromised Gastrointestinal Function and Who Are at High Risk for Invasive Fungal Infection

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The aim of this study was to assess different dosing strategies that may result in increased posaconazole bioavailability in patients with compromised gastrointestinal function and at high risk for invasive fungal infections. Patients undergoing chemotherapy and at risk for compromised gastrointestinal function received open-label posaconazole at 200 mg three times daily (TID) on days 1 to 8. Patients were randomized to one of three open-label dosing regimens of posaconazole on days 9 to 15: 200 mg TID, 400 mg twice daily (BID), or 400 mg TID. The plasma concentrations of interest on days 8 and 15 were 500 and 700 ng/ml, respectively; day 2 plasma concentrations of 250 and 350 ng/ml were chosen as levels that might result in steady-state concentrations of >500 and >700 ng/ml, respectively. A total of 75 patients enrolled; 52/75 (69%) completed the study, and 49/75 were included in the pharmacokinetic analyses. Mean plasma concentrations were 230, 346, and 637 ng/ml on days 2, 3, and 8, respectively. The day 15 values were 660, 930, and 671 ng/ml for 200 mg TID, 400 mg BID, and 400 mg TID, respectively. In 12 patients with a day 8 posaconazole concentration of <250 ng/ml, an overall benefit of the higher two doses was not apparent, suggesting that a subset of patients has low steady-state plasma concentrations. A change in dosing regimen on day 9 did not lead to higher exposures in these “poor absorbers” on day 15. Poor absorption may be enhanced with a high-fat meal, a nutritional supplement, or acidification.

Posaconazole (POS) is an extended-spectrum triazole antifungal approved as prophylaxis for invasive fungal disease (IFD) in high-risk patients (15). The pharmacokinetics (PK) of posaconazole have been extensively studied in healthy volunteers and patients at risk for IFD (1, 4, 10, 17). Several studies have demonstrated that the bioavailability of posaconazole is significantly enhanced when given with food, particularly a high-fat meal (5, 9), presumably because of an increase in dissolution. Patients at risk for IFD are often critically ill and may be unable to eat because of mucositis, severe nausea, neutropenic enterocolitis, or graft-versus-host disease (12, 14, 18). In these patients, absorption of posaconazole may be enhanced by dividing posaconazole doses or by administering the drug with a liquid nutritional supplement or acidic beverage (8, 9).

Health authorities have explored the potential for different dosing strategies of posaconazole oral suspension to increase plasma levels and have profiled the PK of these dosing strategies in a representative patient population with compromised gastrointestinal function and high risk of IFD. A secondary aim was to explore whether early measurement of posaconazole plasma concentrations (before steady state) accurately predicted steady-state plasma concentrations to determine whether early plasma levels can be used to guide therapy to reach a desired threshold value at steady state. There were two steady-state mean plasma concentration levels of interest. The first was 500 ng/ml, based on the MIC_{90} for most Aspergillus species (13). The second was 700 ng/ml in order to explore the feasibility of attaining a higher concentration of posaconazole because of its wide therapeutic index.

MATERIALS AND METHODS

Study design. This was a phase 4, open-label, randomized, multisite (conducted at seven centers in the United States and Europe), comparative study of the PK of posaconazole oral suspension conducted in accordance with Good Clinical Practice (ClinicalTrials.gov identifier: NCT00686543).

Eligible patients received oral posaconazole at 200 mg three times a day (TID) for 8 days (days 1 to 8). Patients were then randomized into one of three dosing groups for treatment during days 9 to 15: oral posaconazole 200 mg TID, 400 mg twice a day (BID), or 400 mg TID.

Patients were instructed to take posaconazole within 10 min after completion of a meal or oral nutritional supplement. A complete food intake review, including quantitative and qualitative dietary assessments, was performed on days 1 to 15, inclusive, to determine total daily calories consumed, fat content, and timing of meals relative to study drug dosing.

Study patients. Patients were of either sex, any race, and aged ≥18 years, were undergoing chemotherapy for acute myelogenous leukemia, and had a high risk of poor enteral medication absorption, based on the effects of cytotoxic chemotherapy (evidenced by, but not limited to, mucositis, nausea, vomiting, and diarrhea, at baseline). Patients were at high risk for IFD based on anticipated or documented prolonged neutropenia (absolute neutrophil count < 500/mm³ [0.5 × 10⁹/liter]). Patients were free from significant disease (other than acute myelogenous leukemia), and their clinical laboratory safety test results (blood chemistries) were...
within normal limits or clinically acceptable to the investigator or sponsor. Female patients agreed to use an effective method of contraception and had a negative serum pregnancy test result at baseline or within 72 h before the start of study drug.

Patients were excluded if they had moderate or severe liver dysfunction at baseline, defined as aspartate aminotransferase or alanine aminotransferase levels greater than twice the upper limit of normal (ULN) or a total bilirubin level greater than twice the ULN. Female patients were excluded if they were pregnant, intending to become pregnant, or breastfeeding. Other exclusion criteria included systemic antifungal therapy (oral, intravenous, or inhaled) for the treatment of proven or probable IFDs within 30 days before enrolment and posaconazole for prophylaxis against IFDs during the 10 days before enrolment (patients who were receiving any other systemic antifungal for IFD prophylaxis were required to discontinue those therapies at enrollment). The following drugs were not allowed at any time during the study: omeprazole (or other proton pump inhibitors); cimetidine for stress ulcer prophylaxis or treatment; drugs known to interact with azole antifungals, including vinca alkaloids, sirolimus, efavirenz, and anthracyclines; drugs known to prolong QTc; and investigational products.

The severity of gastrointestinal tract dysfunction was graded according to the National Cancer Institute’s (NCI) Common Terminology Criteria for Adverse Events v3.0 scale (11).

PK analysis. Blood samples for PK analyses were taken at predetermined time points. Blood samples for the determination of mean posaconazole concentrations in plasma were collected on days 1, 2, 3, 8, and 15 (premorning dose and a 5-h postmorning dose). Blood samples for trough posaconazole plasma concentrations ($C_{\text{min}}$) were collected on days 6, 7, 13, and 14, as near to the premorning dose as possible. The plasma concentration-time profile of posaconazole is relatively flat at steady state because of observed slow elimination. Thus, a single plasma concentration value at any time point (i.e., trough or $C_{\text{max}}$) at steady state when multiplied by dosing interval estimates area under the concentration-time curve for posaconazole (G. Krishna and A. Sansone-Parsons).

### TABLE 1 Demographics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients ($n = 75$)</th>
<th>Days 9 to 15 (inclusive)$^a$</th>
<th>POS, 200 mg TID ($n = 21$)</th>
<th>POS, 400 mg BID ($n = 20$)</th>
<th>POS, 400 mg TID ($n = 20$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, no. (%) of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>39 (52)</td>
<td>11 (52)</td>
<td>9 (45)</td>
<td>11 (55)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>36 (48)</td>
<td>10 (48)</td>
<td>11 (55)</td>
<td>9 (45)</td>
<td></td>
</tr>
<tr>
<td>Race, no. of patients (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>68 (91)</td>
<td>17 (81)</td>
<td>18 (90)</td>
<td>20 (100)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>5 (7)</td>
<td>3 (14)</td>
<td>2 (10)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>2 (3)</td>
<td>1 (5)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Mean age, yr (SD)</td>
<td>53.5 (12.1)</td>
<td>55.0 (10.9)</td>
<td>54.7 (13.3)</td>
<td>51.1 (11.4)</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ BID, twice daily; POS, posaconazole; TID, three times daily.

FIG 1 Patient disposition. * The patient did not wish to continue in the study for reasons unrelated to study treatment. †, Noncompliance with the study protocol. BID, twice daily; TID, three times daily.
unpublished data). The mean concentration value for a patient was calculated as the mean of predose and 5-h postdose concentration values. The average concentration was calculated by calculating average of mean concentration values for all patients.

Plasma posaconazole concentrations were determined using a validated liquid chromatography tandem mass spectrometric method (16). The lower limit of quantitation was 5.00 ng/ml, the calibration range was 5.00 to 5,000 ng/ml, the precision (coefficient of variation [CV]) was 2.6 to 5.3%, and the accuracy was −1.8 to 2.0%. The plasma concentrations of interest on days 8 and 15 were 500 and 700 ng/ml. Day 2 plasma concentrations of 250 ng/ml (and 350 ng/ml) were chosen as levels that might result in steady-state concentrations of >500 ng/ml (and >700 ng/ml). The level of 250 ng/ml was based on the results of a PK study of posaconazole, which showed that the ratio of steady-state maximum plasma concentration compared to the plasma concentration on the first day of dosing was approximately 2 (6). The level of 350 ng/ml was based on a simulation that predicted the day 2 plasma concentration should be 350 ng/ml in order to reach a steady-state concentration of 700 ng/ml (2).

Mean plasma concentration inter- and intrapatient CVs were estimated using a mixed model with the natural logarithm of the trough concentration as the dependent variable, treatment, day, and treatment-by-day interaction as fixed effects and the patient as a random effect.

Safety analysis. Safety variables assessed included adverse events (AEs), including breakthrough IFD and premature discontinuation due to AEs, serious AEs (SAEs), clinical laboratory tests, and vital signs. An assessment of each patient’s gastrointestinal tract compromise was performed at baseline (day −1) and on days 1 to 15, inclusive.

Statistical analysis. The original study protocol stated that the primary PK parameter was mean plasma concentration, defined as the mean of the 0-h (trough, premorning dose) and the 5-h (postmorning dose) concentrations, on days 2, 8, and 15. However, a decision was made to focus on day 3 data instead of day 2 data. The rationale for this change is explained in the PK section in the Results.

Mean plasma concentrations were tabulated, and descriptive statistics and graphics were used to summarize the data. The percentage of patients with day 8 mean plasma concentrations above and below 250 and 350 ng/ml and with day 15 mean plasma concentrations above and below 500 and 700 ng/ml were to be tabulated to evaluate whether an increased dose of posaconazole could result in an increased mean plasma concentration. The percentage of patients with day 3 mean plasma concentrations above and below 250 and 350 ng/ml and with day 8 mean plasma concentrations above and below 500 and 700 ng/ml was to be tabulated to evaluate whether day 3 mean plasma concentrations were predictive of steady-state mean plasma concentration. Any correlation

FIG 2 Correlation between mean posaconazole plasma concentrations on days 2 and 8 (A) and days 3 and 8 (B) after multiple dosing of oral suspension (200 mg TID) (balanced data set, n = 49). \( R^2 \), coefficient of determination. BID, twice daily; TID, three times daily.

FIG 3 Mean posaconazole plasma concentrations on days 2, 3, 8, and 15 after multiple dosing of oral suspension (200 mg TID, 400 mg BID, and 400 mg TID) (balanced data set, n = 49). Boxes represent the 25th, 50th, and 75th percentiles; whiskers represent the 5th and 95th percentiles; and circles represent outliers. BID, twice daily; TID, three times daily.
between days 3 and 8 plasma concentration values were to be explored through graphic and descriptive statistics. Steady state was determined by visual inspection of $C_{\text{min}}$ data from days 6, 7, and 8 and days 13, 14, and 15.

**RESULTS**

A total of 75 patients were enrolled into the study: 36 women and 39 men, predominantly white (68/75 [91%]), with a mean age of 53.5 years (Table 1). The patient disposition is summarized in Fig. 1; 52/75 patients (69%) completed the study.

**PK results.** PK analyses were conducted on the balanced data set, which included all patients with no missing PK data on days 3, 8, and 15 (49 patients).

Although the original protocol specified that day 2 plasma concentrations would be used for comparisons to day 8 and day 15 levels, it was decided to focus on day 3 data instead of day 2 data. Day 3 plasma concentrations (after four doses of posaconazole) were found to better predict day 8 plasma concentrations (Fig. 2).

The mean CV% values for posaconazole plasma concentrations on days 3, 8, and 15 are presented in Fig. 3. Despite the risk of compromised absorption of posaconazole in the study population, the observed mean plasma concentrations on day 3 and day 8 exceeded the PK levels of interest of 250 and 500 ng/ml, respectively, and approached 350 and 700 ng/ml. The mean posaconazole plasma concentrations (90% CI) on day 8 were 660 ng/ml (487 to 834 ng/ml), 930 ng/ml (617 to 1,243 ng/ml), and 671 ng/ml (530 to 811 ng/ml) for 200 mg TID, 400 mg BID, and 400 mg TID, respectively. It should be noted that patients were not stratified into dose groups according to their day 8 plasma concentrations and that prerandomization levels may have influenced postrandomization results. In spite of all patients receiving posaconazole at 200 mg TID on days 1 to 8 (inclusive), the mean plasma concentrations on day 8 were higher for patients randomly assigned to the 400-mg BID group (849 ng/ml) compared to the 200 mg TID group (620 ng/ml) or the 400-mg TID group (473 ng/ml). Table 2 shows the mean increases in plasma concentrations from days 8 to 15.

A total of 30/49 patients (61%) achieved a mean posaconazole plasma concentration of 250 ng/ml on day 3; of these 30 patients, 73% (22/30) achieved a mean concentration of 500 ng/ml on day 8. In contrast, 17/19 patients (89%) who did not achieve a mean posaconazole concentration of 250 ng/ml on day 3 also failed to achieve a mean concentration of 500 ng/ml on day 8 (Fig. 4).

On day 8, 37/49 patients (76%) achieved plasma concentrations above 250 ng/ml; among patients who did not achieve a mean plasma concentration of 250 ng/ml on day 8, 9 of 12 patients (75%) did not achieve a mean plasma concentration of 500 ng/ml on day 15 (Fig. 5). Table 3 shows the numbers and percentages of patients achieving mean plasma concentrations of 250 and 350 ng/ml on days 3 and 8 and 500 and 700 ng/ml on days 8 and 15. Interpatient CVs measured before and after patient randomization were comparable at 50.4 and 51.8%, respectively. Intrapatient CVs were low and comparable before and after randomization (7.2 and 5.9%, respectively), indicating that patients had consistent posaconazole levels at the end of each of these phases.

**PK/pharmacodynamics (dietary intake).** The majority of patients had a partial daily food intake and a moderate daily fat intake during the prerandomization and postrandomization periods. Despite a protocol requirement, neither food intake nor fat intake was maximal to promote posaconazole absorption; this may reflect the fact that a considerable proportion of patients reported nausea, vomiting, and/or diarrhea during the study. The dietary differences and symptoms reported by patients were sub-

**TABLE 2** Mean posaconazole plasma concentrations on days 8 and 15

<table>
<thead>
<tr>
<th>POS dose group (days 9 to 15)</th>
<th>No. of patients</th>
<th>Mean plasma concn (ng/ml)</th>
<th>Change in mean (ng/ml) from day 8 to day 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 mg TID</td>
<td>19</td>
<td>620</td>
<td>660</td>
</tr>
<tr>
<td>400 mg BID</td>
<td>14</td>
<td>849</td>
<td>930</td>
</tr>
<tr>
<td>400 mg TID</td>
<td>16</td>
<td>473</td>
<td>671</td>
</tr>
</tbody>
</table>

BID, twice daily; POS, posaconazole; TID, three times daily. All patients received 200 mg posaconazole TID on days 1 to 8, inclusive.

![FIG 4](https://example.com/f4.png) Mean posaconazole plasma concentrations across dose groups on days 3, 8, and 15 after multiple dosing of oral suspension (200 mg TID, 400 mg BID, and 400 mg TID), stratified by mean plasma concentration of 250 ng/ml on day 3 (balanced data set, n = 49). Although all patients received 200 mg posaconazole TID on days 1 through 8, the scatter plot identifies patients according to randomized dose group for ease of comparison. BID, twice daily; TID, three times daily.
tle, and the numbers were too small to make meaningful conclusions regarding their impact on posaconazole absorption.

Safety results. The multiple doses of posaconazole 200 mg TID, 400 mg BID, or 400 mg TID were comparable in terms of safety and tolerability. A total of 74 patients (99%) reported at least one AE during the study. The most common AEs were diarrhea and nausea, each occurring in more than 50% of patients. The most commonly reported treatment-related AEs were nausea (13/75 patients [17%]), diarrhea (10/75 patients [13%]), and rash (8/75 patients [11%]). Elevated transaminases were reported in five patients and were considered possibly or probably treatment related in two patients. Fifteen patients withdrew because of an AE; the most common reasons for discontinuation were gastrointestinal disorders (seven patients [9%]) and infections (five patients [7%]).

Sixteen patients (21%) reported an SAE during the study. Only one SAE was considered to be treatment related: elevated transaminases in a patient in the group treated with posaconazole at 400 mg TID. Four deaths occurred during the study; none was considered treatment related.

Table 4 displays gastrointestinal symptoms reported at baseline and during treatment. Nausea was the most common baseline abnormality with >25% of subjects reporting common toxicity criteria (CTC) grade 2 or 3 symptoms. Diarrhea and nausea appeared to worsen most during treatment. The percentage of patients reporting CTC grade 1 to 3 nausea increased from ~40% at baseline to ~75% during treatment. Similarly, CTC grade 1 to 3 diarrhea was reported in 19% at baseline and 59% of patients during treatment.

**DISCUSSION**

The primary aim of this study was to explore the potential for different dosing strategies of posaconazole oral suspension to increase plasma levels and to profile the PK of these dosing strategies in a representative patient population with compromised gastrointestinal function and at high risk for IFD. Our results show that the achievement of adequate plasma concentrations of posaconazole can be anticipated in many patients despite a risk of poor enteral medication absorption. In these patients, the observed

---

**TABLE 3** Patients achieving mean plasma concentrations of interest on days 3, 8, and 15

<table>
<thead>
<tr>
<th>Level of interest (ng/ml)</th>
<th>Day</th>
<th>No. (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;250</td>
<td>3</td>
<td>19 (39)</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>12 (24)</td>
</tr>
<tr>
<td>≥250</td>
<td>3</td>
<td>30 (61)</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>37 (76)</td>
</tr>
<tr>
<td>&lt;350</td>
<td>3</td>
<td>28 (57)</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>33 (67)</td>
</tr>
<tr>
<td>≥350</td>
<td>3</td>
<td>21 (43)</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>33 (67)</td>
</tr>
<tr>
<td>≥500</td>
<td>8</td>
<td>24 (49)</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>31 (63)</td>
</tr>
<tr>
<td>≥700</td>
<td>8</td>
<td>17 (35)</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>25 (51)</td>
</tr>
</tbody>
</table>

---

**TABLE 4** Summary of CTC grades for selected gastrointestinal symptoms at baseline and the worst reported grade during treatment (n = 75, all patients)*

<table>
<thead>
<tr>
<th>CTC grade and symptom</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTC grade at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>64 (85.3)</td>
<td>6 (8.0)</td>
<td>3 (4.0)</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>43 (57.3)</td>
<td>11 (14.7)</td>
<td>18 (24.0)</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>66 (88.0)</td>
<td>4 (5.3)</td>
<td>3 (4.0)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>61 (81.3)</td>
<td>8 (10.7)</td>
<td>5 (6.7)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Worst reported CTC grade during treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>37 (49.3)</td>
<td>21 (28.0)</td>
<td>10 (13.3)</td>
<td>7 (9.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>18 (24.0)</td>
<td>20 (26.7)</td>
<td>30 (40.0)</td>
<td>6 (8.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>50 (66.7)</td>
<td>11 (14.7)</td>
<td>12 (16.0)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>31 (41.3)</td>
<td>18 (24.0)</td>
<td>18 (24.0)</td>
<td>8 (10.7)</td>
</tr>
</tbody>
</table>

* For missing values at baseline, postbaseline values were assessed as grade 0; missing postbaseline values were assessed as missing. No CTC grade 4 values were reported for any symptom. CTC, common toxicity criteria.
mean plasma concentrations on day 3 and day 8 exceeded the PK levels of interest of 250 and 500 ng/ml and approached the levels of 350 and 700 ng/ml, respectively.

Determination of a relationship between plasma concentrations of any antifungal agent and efficacy comes from a combination of experimental models of fungal infections, assessments of pharmacodynamics and PK in animals and in clinical settings and data. In a previously reported nonrandomized trial on posaconazole salvage treatment for invasive aspergillosis, a positive association between exposure and response was demonstrated (a quartile analysis showed 53 and 75% response rates for patients with average plasma concentrations of 411 and 1,250 ng/ml, respectively) (19). Based on these exposure-response analyses, a mean plasma level of interest of 500 ng/ml was chosen since this is also average plasma concentrations of 411 and 1,250 ng/ml, respectively. Analysis showed 53 and 75% response rates for patients with average plasma concentrations of 411 and 1,250 ng/ml, respectively) (19). Based on these exposure-response analyses, a mean plasma level of interest of 500 ng/ml was chosen since this is also the MIC_{50} of most Aspergillus species (13). An average plasma concentration of 700 ng/ml has previously been discussed as a target threshold for posaconazole (3, 7). Although this suggested level has not been further evaluated, a second plasma level of interest of 700 ng/ml was chosen in this trial to explore the feasibility of attaining a higher posaconazole plasma concentration since posaconazole has a wide therapeutic index.

A secondary aim of this study was to explore whether early measurement of posaconazole plasma concentrations (before steady state) accurately predicts steady-state plasma concentrations in order to determine whether early plasma levels can be used to guide therapy to reach a desired threshold value at steady state. The results of the present study suggest that in patients with gastrointestinal compromise, day 3 plasma concentrations are better than day 2 plasma concentrations in predicting day 8 plasma concentrations (R^2, 0.64 versus 0.46, respectively).

There appears to be a subset of patients who have low mean posaconazole plasma concentrations on days 3, 8, and 15; these patients likely represent “poor absorbers.” In general, the data indicate that although day 3 levels were predictive of steady-state plasma levels, patients who could be categorized as poor absorbers on day 3 (mean posaconazole concentration <250 ng/ml) tended to remain low absorbers throughout the study, regardless of dosing regimen change. For patients who were poor absorbers on day 8, a change in dosing regimen commencing on day 9 did not lead to higher exposures by day 15.

Adherence to dosing, dietary intake, or the presence of nausea, vomiting, or diarrhea did not clearly differentiate poor absorbers from patients who achieved the desired PK levels. It must be emphasized that absorption in these patients might be enhanced with a high-fat meal, liquid nutritional supplement or an acidic beverage (e.g., ginger ale) (9). Phenytoin and rifabutin should also be avoided because of potential drug interactions and leading to increased clearance of posaconazole (15).

In summary, achieving posaconazole steady-state plasma concentrations of ≥500 ng/ml can be anticipated in many patients with compromised gastrointestinal function. In these patients, day 3 plasma levels of posaconazole appear to be predictive of day 8 levels.

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