Vilazodone Pharmacokinetics in Subjects With Mild to Moderate Renal Impairment

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Abstract

Objective: The objective of this study was to assess the pharmacokinetics of a single oral dose of vilazodone in healthy subjects with mild or moderate renal impairment compared with those having normal renal function.

Methods

n Vilazodone was administered to 44 healthy subjects with mild or moderate renal impairment and 44 healthy subjects with normal renal function. Vilazodone pharmacokinetic data were analyzed to determine the impact of renal impairment on vilazodone pharmacokinetics.

Results

n Mean (SD) terminal elimination half-life (t½) for vilazodone was 19.7 (13.5) hours in subjects with mild renal impairment, 22.1 (15.5) hours in subjects with moderate renal impairment, and 24.4 (12.8) hours in those with normal renal function. The mean (SD) body clearance (CL) of vilazodone was 1038 (203) mL/min.

Conclusions

n Vilazodone pharmacokinetics in subjects with mild to moderate renal impairment were comparable with those in subjects with normal renal function. These findings suggest that no dose adjustment of vilazodone would be required for subjects with mild to moderate renal impairment.

References

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Abstract

Vilazodone Cmax and AUC were not statistically different between normal renal function and subjects with mild to moderate renal impairment. The study was designed according to the ICH guidelines. The safety population included all subjects who had been exposed to vilazodone and had at least 1 postdose safety measure.

Methods

• Vilazodone concentrations in plasma and urine were determined by liquid chromatography with tandem mass spectrometry.

• Blood samples and urine were collected before and after dosing (blood, 0-144 hours; urine, 0-96 hours).

• The safety population included all subjects who had been exposed to vilazodone and had at least 1 postdose safety measure.

Results

Table 4. Blood Pressure and Pulse at Baseline and Change From Baseline 4 Hours After Dose

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mild Renal Impairment</th>
<th>Moderate Renal Impairment</th>
<th>Moderate/Healthy Match</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mm Hg</td>
<td>122.5 (114.0, 142.0)</td>
<td>126.5 (112.0, 156.0)</td>
<td>125.5 (113.0, 156.0)</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>78.3 (11.8)</td>
<td>74.4 (7.9)</td>
<td>71.8 (10.6)</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>78.3 (11.8)</td>
<td>74.4 (7.9)</td>
<td>71.8 (10.6)</td>
</tr>
</tbody>
</table>

Safety

• No adverse events were considered related to vilazodone.

• The only adverse event that occurred in at least 1 subject was mild stomach discomfort in 1 subject with moderate renal impairment.

Conclusions

• Vilazodone is a dual-acting potent and selective serotonin reuptake inhibitor and 5-HT1A partial agonist.

• The results of this study suggest that vilazodone pharmacokinetics are not substantially affected by mild to moderate renal impairment.

• Further studies are needed to evaluate the effect of more severe renal impairment on vilazodone pharmacokinetics.

References

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Objectives

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Methods

• All subjects provided written informed consent prior to enrolling in the study.
• To evaluate the safety and tolerability of vilazodone in subjects with mild to moderate renal impairment.

Study Subjects

• Vilazodone PK are similar in renally impaired and healthy subjects. Differences observed among groups are considered clinically not relevant and unlikely to require dosage adjustments.

Statistical Methods

• Differences in protein binding among the 3 groups, and total drug clearance was not affected.

Results

• Risk factors and drug interactions associated with vilazodone metabolism (CYP2D6, CYP3A4).

Conclusions

• The study included a screening period of at least 14 days (if UFL >1.5 μg/mL); a washout period of at least 14 days if other medications were being taken.

Introduction

• Data (on file) from phase 1 studies in healthy volunteers indicate vilazodone HCl is a dual-acting potent and selective serotonin reuptake inhibitor and receptor partial agonist in development for the treatment of major depressive disorder.

Safety

• Safety assessments were summarized, with no statistical comparisons performed.

Table 3. Pharmacokinetic Parameters of Vilazodone in Subjects With Mild to Moderate Renal Impairment Compared With Healthy Subjects

| Parameter       | Healthy Subjects (n = 8) | Mild Renal Impairment (n = 8) | Moderate Renal Impairment (n = 8) | p-Value
<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>t½, h</td>
<td>Median (range)</td>
<td>5.00 (4.00, 8.00)</td>
<td>5.00 (4.00, 8.00)</td>
<td>0.832</td>
</tr>
<tr>
<td>AUC0-∞, ng·h/mL</td>
<td>Median (range)</td>
<td>910 (358)</td>
<td>856 (290)</td>
<td>0.824</td>
</tr>
<tr>
<td>CLu/F, L/h</td>
<td>Mean (SD)</td>
<td>26.4 (10.7)</td>
<td>25.1 (9.5)</td>
<td>0.360</td>
</tr>
<tr>
<td>C – max, ng/mL</td>
<td>Median (range)</td>
<td>0.245 (0.032, 0.782)</td>
<td>0.199 (0.021, 0.479)</td>
<td>0.292</td>
</tr>
</tbody>
</table>

Table 4. Blood Pressure and Pulse at Baseline and Change From Baseline 4 Hours After Dose

| Parameter       | Healthy Subjects (n = 8) | Mild Renal Impairment (n = 8) | Moderate Renal Impairment (n = 8) | p-Value
<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mm Hg</td>
<td>Median (range)</td>
<td>122.5 (114.0, 142.0)</td>
<td>126.5 (112.0, 156.0)</td>
<td>0.470</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>Median (range)</td>
<td>75.0 (58.0, 84.0)</td>
<td>75.0 (58.0, 84.0)</td>
<td>0.500</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>Median (range)</td>
<td>78.0 (65.0, 90.0)</td>
<td>78.0 (65.0, 90.0)</td>
<td>0.447</td>
</tr>
</tbody>
</table>

Table 5. Summary of Clinical Laboratory Parameters

| Parameter       | Healthy Subjects (n = 8) | Mild Renal Impairment (n = 8) | Moderate Renal Impairment (n = 8) | p-Value
<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT, IU/L</td>
<td>Median (range)</td>
<td>24.0 (0.0, 50.0)</td>
<td>26.0 (0.0, 50.0)</td>
<td>0.427</td>
</tr>
<tr>
<td>AST, IU/L</td>
<td>Median (range)</td>
<td>19.0 (0.0, 74.0)</td>
<td>21.0 (0.0, 74.0)</td>
<td>0.369</td>
</tr>
<tr>
<td>Bilirubin, mg/dL</td>
<td>Median (range)</td>
<td>0.3 (0.0, 1.2)</td>
<td>0.3 (0.0, 1.2)</td>
<td>0.509</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>Median (range)</td>
<td>0.7 (0.6, 1.0)</td>
<td>1.0 (0.6, 1.0)</td>
<td>0.087</td>
</tr>
</tbody>
</table>

Conclusions

• Vilazodone is well tolerated in subjects with mild or moderate renal impairment.

References

3. ZOCO clinical practice guidelines for the treatment of major depressive disorder, classification, and management of treatment-resistant depression. ACO; 2008 at the 10th World Congress.
Vilazodone Pharmacokinetics in Subjects With Mild to Moderate Renal Impairment

Harry Alcorn, Jr, PharmD, James Longstreth, PhD, Suzanne K. Swan, MD, Marijke H. Adams, PharmD, PhD, Carol R. Reed, MD


Abstract

Objective: Vilazodone (VLZ) is a selective serotonin reuptake inhibitor (SSRI) approved for the treatment of major depressive disorder. The study assessed the pharmacokinetics (PK) of VLZ in subjects with renal impairment.

Methods

Study Subjects

• Vilazodone was administered as a 20-mg tablet orally in a single dose to each investigational unit

Study Design

• Subjects were randomized to 3 groups

• The study included a washout period of 14 days prior to dosing

• The study included a washout period of 14 days prior to dosing

Results

Baselines Demographics

<table>
<thead>
<tr>
<th>Group</th>
<th>Age, Mean (SD), Years</th>
<th>Height, Mean (SD), cm</th>
<th>BMI, Mean (SD), kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>40.3 (5.9)</td>
<td>174.0 (8.1)</td>
<td>28.5 (5.7)</td>
</tr>
<tr>
<td>Moderate</td>
<td>40.0 (6.2)</td>
<td>173.0 (8.3)</td>
<td>28.2 (5.8)</td>
</tr>
<tr>
<td>Healthy Match</td>
<td>40.0 (5.9)</td>
<td>174.0 (8.1)</td>
<td>28.5 (5.7)</td>
</tr>
</tbody>
</table>

Safety

• Safety assessments included evaluation of adverse events (AEs), Laboratory Data (chemistry, hematology, and urinalysis), electrocardiography (ECG), and vital signs

Statistical Methods

• ANOVA was performed on the natural logarithms of AUC and Cmax

Conclusions

• Vilazodone PK was similar in subjects with mild or moderate renal impairment compared with healthy matched controls

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Methods

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Introduction

• Vilazodone (VLZ) is a dual-acting selective serotonin reuptake inhibitor and 5-HT1A antagonist

Objectives

• To determine the safety and efficacy of vilazodone in subjects with mild renal impairment

Results

Table 1. Demographics and Baseline Characteristics (Safety Population)

Safety

• No serious adverse events were considered to be related to vilazodone

Conclusions

• These findings suggest that no dose adjustment of vilazodone would be required for subjects with mild to moderate renal impairment

References


Study Subjects

• 117 subjects were included in the study, with 10 in each of the 5 treatment groups

Statistical Methods

• Safety and efficacy analyses were performed using a modified intention-to-treat (mITT) population

Table 2. Vilazodone PK Parameters (PK Population)

• Vilazodone is a dual-acting selective serotonin reuptake inhibitor and 5-HT1A antagonist

Objectives

• To determine the safety and efficacy of vilazodone in subjects with mild renal impairment

Safety

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Harry Alcorn, Jr, PharmD, James Longstreth, PhD, Suzanne K. Swan, MD, Marjike H. Adams, PharmD, PhD, Carol R. Reed, MD


Presented at the 163rd Annual Meeting of the American Psychiatric Association, May 22–26, 2010, New Orleans, Louisiana

Supported by PGxHealth, LLC

Abstract

Background: Vilazodone HCl (VLZ) is a dual-acting selective serotonin reuptake inhibitor and 5-HT1A receptor partial agonist that exerts its effects at the serotonin transporter and at pre- and post-synaptic 5-HT1A receptors.1,2 The pharmacokinetics (PK) of vilazodone in subjects with renal impairment have not been evaluated. Objective: The objective of the study was to evaluate the PK of vilazodone in subjects with renal impairment compared with those having normal renal function.

Methods

Study Design: The study included a screening period, an inpatient treatment period (days –1 through 14), and a 14-day follow-up period. Subjects received VLZ for 10 days (10 to 40 mg once daily) followed by a washout period of 14 days. PK evaluations, and were matched with another subject who also completed PK evaluations and received placebo (24 subjects total). The study was double-blind. The PK parameters for each subject: plasma and urine concentrations were measured, Vilazodone concentrations in plasma and urine were determined by liquid chromatography and mass spectrometry. Concomitant substances: drugs affecting coagulation (eg, NSAIDs, aspirin >325 mg/day, warfarin, clopidogrel) were not allowed during the study, and the study: psychoactive medication, monoamine oxidase inhibitors, migraine drugs with ergot alkaloids were not allowed during the study. The study population included subjects who had normal renal function and those who had mild or moderate renal impairment. Safety and tolerability of vilazodone were compared with placebo in all subjects.

Results

In the renal group, only 0.2% and 4% of vilazodone and its metabolites were found in urine, respectively. The study population included subjects who had normal renal function and those who had mild or moderate renal impairment. Safety and tolerability of vilazodone were compared with placebo in all subjects. The pharmacokinetic parameters were obtained for each subject and were matched with another subject who also completed PK evaluations and received placebo (24 subjects total). The study was double-blind. The PK parameters for each subject: plasma and urine concentrations were measured, Vilazodone concentrations in plasma and urine were determined by liquid chromatography and mass spectrometry. Concomitant substances: drugs affecting coagulation (eg, NSAIDs, aspirin >325 mg/day, warfarin, clopidogrel) were not allowed during the study, and the study: psychoactive medication, monoamine oxidase inhibitors, migraine drugs with ergot alkaloids were not allowed during the study. The study population included subjects who had normal renal function and those who had mild or moderate renal impairment. Safety and tolerability of vilazodone were compared with placebo in all subjects.

Conclusions

Vilazodone is a well-tolerated and efficacious antidepressant with a favorable safety profile. Differences in renal function did not result in clinically meaningful changes in vilazodone pharmacokinetics. Vilazodone was extensively bound to plasma proteins, with mean free fraction of ~0.75%. Oral clearance was not affected by mild or moderate renal impairment, also supporting the assumption that renal impairment does not affect protein binding and that the renal clearance and therefore oral clearance of vilazodone is not altered. Differences in protein binding among the renal impairment and healthy groups overlapped with nearly identical median values, suggesting there were no substantial differences in protein binding among the renal impairment and healthy groups. Differences in renal function did not result in clinically meaningful changes in vilazodone pharmacokinetics. Vilazodone was extensively bound to plasma proteins, with mean free fraction of ~0.75%. Oral clearance was not affected by mild or moderate renal impairment, also supporting the assumption that renal impairment does not affect protein binding and that the renal clearance and therefore oral clearance of vilazodone is not altered. Differences in protein binding among the renal impairment and healthy groups overlapped with nearly identical median values, suggesting there were no substantial differences in protein binding among the renal impairment and healthy groups. Differences in renal function did not result in clinically meaningful changes in vilazodone pharmacokinetics. Vilazodone was extensively bound to plasma proteins, with mean free fraction of ~0.75%. Oral clearance was not affected by mild or moderate renal impairment, also supporting the assumption that renal impairment does not affect protein binding and that the renal clearance and therefore oral clearance of vilazodone is not altered. Differences in protein binding among the renal impairment and healthy groups overlapped with nearly identical median values, suggesting there were no substantial differences in protein binding among the renal impairment and healthy groups.

Objectives

Study Subjects

- Subjects were enrolled in 1 of 4 cohorts based on normal renal function or mild or moderate renal impairment and age (65 years or older), race (Caucasian or non-Caucasian), and stratification.
- Patients with mild or moderate renal impairment were stratified based on stage of renal function.

Safety

- Safety evaluations included assessment of adverse events (AEs), laboratory tests, physical examination, and vital signs.

Table 1: Vilazodone Concentration Data for Subjects With Normal Renal Function and Subjects With Mild and Moderate Renal Impairment

Table 2: Summary of Vital Signs and Laboratory Data for Subjects With Normal Renal Function and Subjects With Mild and Moderate Renal Impairment

Figure 1: Mean Vilazodone Concentration Profile, by Group (Linear Scale)

Figure 2: Vilazodone Mean and Median Plasma Concentration Over Time

References


Statistical Methods

- The PK data were log-transformed and analyzed by linear mixed effect models using the NLME software package.
- The PK parameters, CL/F, V/F, t1/2, and Cmax were used as the dependent variables.
- The PK parameters were analyzed for differences between groups, and the Cmax was compared across groups.
- The rate and extent of absorption were assessed using appropriate statistical methods.

Conclusion

Vilazodone is a well-tolerated and efficacious antidepressant with a favorable safety profile. Differences in renal function did not result in clinically meaningful changes in vilazodone pharmacokinetics. Vilazodone was extensively bound to plasma proteins, with mean free fraction of ~0.75%. Oral clearance was not affected by mild or moderate renal impairment, also supporting the assumption that renal impairment does not affect protein binding and that the renal clearance and therefore oral clearance of vilazodone is not altered. Differences in protein binding among the renal impairment and healthy groups overlapped with nearly identical median values, suggesting there were no substantial differences in protein binding among the renal impairment and healthy groups.

Conclusions

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Abstract

Objective: To determine the pharmacokinetics (PK) of vilazodone, a serotonin-1A receptor partial agonist and serotonin reuptake inhibitor, in subjects with mild to moderate renal impairment.

Methods

A total of 32 subjects (16 mild renal impairment, 16 moderate renal impairment, matched with 16 healthy subjects) were treated with a single 20-mg dose of vilazodone. Subjects were matched by age, sex, and body mass index. PK parameters were compared using paired or unpaired t-tests for normally distributed data, otherwise a Wilcoxon signed rank test was used.

Results

Baseline Demographics

<table>
<thead>
<tr>
<th>Group</th>
<th>Sex, n (%)</th>
<th>Age, years (range)</th>
<th>Weight, kg (mean ± SD)</th>
<th>Scr, µmol/L (median, range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy Match</td>
<td>8 (50%)</td>
<td>26–41 (26.4, 38.6)</td>
<td>18.7–38.6 (26.4, 38.6)</td>
<td>48.1–112.0 (74.0, 96.0)</td>
</tr>
<tr>
<td>Mild/healthy match</td>
<td>8 (50%)</td>
<td>26–41 (26.4, 37.6)</td>
<td>18.7–38.6 (26.4, 37.6)</td>
<td>48.1–112.0 (78.0, 107.0)</td>
</tr>
<tr>
<td>Moderate/healthy match</td>
<td>8 (50%)</td>
<td>26–41 (26.7, 33.7)</td>
<td>18.7–38.6 (26.7, 33.7)</td>
<td>48.1–112.0 (85.5, 102.0)</td>
</tr>
</tbody>
</table>

Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Healthy Match</th>
<th>Mild Renal Impairment</th>
<th>Moderate Renal Impairment</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-∞ (ng·h/mL)</td>
<td>372 (263, 541)</td>
<td>367 (279, 824)</td>
<td>383 (233, 600)</td>
<td>0.52</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>34.1 (28.4, 50.0)</td>
<td>29.6 (22.4, 59.2)</td>
<td>29.4 (15.8, 57.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>74.0 (55.0, 96.0)</td>
<td>78.0 (68.0, 107.0)</td>
<td>85.5 (72.0, 102.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Mean f, %</td>
<td>34.8 (6.9)</td>
<td>33.0 (12.0)</td>
<td>31.8 (14.5)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Safety

No subject discontinued because of a treatment-emergent adverse event (TEAE). The 90% CIs for the above PK parameters were outside the 0.80 to 1.25 range normally considered to indicate bioequivalence in a bioequivalence study.

Conclusions

The pharmacokinetics of vilazodone are similar in both renal impairment groups and healthy subjects, and there are no clinically significant differences between groups in PK parameters on the log scale or geometric means on the original scale. The use of herbal supplements and alcoholic beverages also was prohibited.

Supported by PGHealth, LLC

References