Erectile dysfunction (ED) is generally defined as a condition characterized by the inability to achieve or maintain firm erections sufficient for sexual intercourse. Although not life-threatening, ED causes considerable suffering to a large number of men and, therefore, represents a significant health concern. It is one of the inevitabilities of the aging process, threatening, ED causes considerable suffering to a large number of men and, therefore, represents a significant health concern. It is one of the inevitabilities of the aging process, and is frequently found in men with certain conditions such as hypertension, smoking, diabetes, hypotension, cardiovascular disease, or from injuries such as spinal cord damage.

Patients with ED may have some degree of renal impairment, as a consequence of age and/or comorbid illness. Although contribution of renal clearance to the total clearance of avanafil is not significant, renal impairment may affect the hepatic metabolism and the pharmacokinetics (PK) of avanafil.

The primary objective of this study was to compare the PK of avanafil in male subjects with mild and moderate renal impairment to those with normal renal function.

METHODS

- This was an open-label, multinational, 3-cohort, matched-control study.
- Data from 24 subjects, assigned according to renal function (4 per cohort) were included in the analysis.
- There were 3 cohorts in this study:
  - Cohort 1: Normal renal function (CLcr ≥ 80 mL/min).
  - Cohort 2: Mild renal impairment (CLcr ≥ 50 to < 80 mL/min).
  - Cohort 3: Moderate renal impairment (CLcr ≥ 30 to < 50 mL/min).

- Subjects in each of the 3 cohorts received a single 20 mg oral dose of avanafil following an overnight fast.

- Serial plasma samples drawn from predose through 24 hours postdose were quantified for plasma avanafil using a validated LC-MS/MS method.

- Noncompartmental analysis was performed on the plasma concentrations versus time profiles to derive the PK parameters of interest (maximum plasma concentration [Cmax], area under the curve from time 0 to the last measurable concentration [AUC0-t], area under the curve from time 0 to infinity [AUC0-∞], apparent elimination constant [kel], apparent elimination half-life [t1/2], apparent total body clearance [CL/F], and apparent volume of distribution [V/F]).

- Analysis of variance was performed on the ln-transformed Cmax, AUC0-t, and AUC0-∞, using the SAS® Proc Mixed procedure. Nonparametric comparisons of Cmax and AUC0-t values were conducted using the Wilcoxon® Professional (Version 5.0.1, Pharsight Corporation, Cary, North Carolina).

- The median and 95% confidence intervals (CI) of the differences between cohorts for Cmax and AUC0-t values were calculated using Hodges-Lehmann estimates. Significant differences in Cmax and AUC0-t values for the treatment comparisons were confirmed if the resulting p-value was < 0.05.

RESULTS

- The geometric mean plasma avanafil concentrations in subjects with normal renal function (Cohort 1), mild renal impairment (Cohort 2), and moderate renal impairment (Cohort 3) are presented in Figure 1.

- Plasma overall concentrations were similar in subjects with normal renal function (Cohort 1), mild renal impairment (Cohort 2), and moderate renal impairment (Cohort 3).

- The summaries of plasma avanafil PK parameters following the administration of a single oral dose of 200 mg avanafil in subjects with normal renal function, mild renal impairment, and moderate renal impairment are presented in Table 1.

- Peak and total exposure to avanafil, as measured by Cmax, AUC0-t, and AUC0-∞, were similar between subjects with mild or moderate renal impairment and normal renal function.

- CL/F, V/F, t1/2, and kel values of avanafil were comparable among the subjects with normal renal function and subjects with mild or moderate renal impairment.

- The statistical comparisons of plasma avanafil PK parameters between subjects with mild or moderate renal impairment and normal renal function versus normal renal function are summarized in Table 2.

- Based on geometric mean ratios, peak and total exposure to avanafil between subjects with mild or moderate renal impairment and normal renal function were similar to each other (the differences ranged from approximately 0.7 to 1.2).

- Based on geometric mean ratios, peak and total exposure to avanafil between subjects with mild or moderate renal impairment and normal renal function were comparable between the two cohorts (the differences ranged from approximately 0.6 to 1.0).

- The nonparametric statistical comparisons of plasma avanafil Cmax and AUC0-t values between subjects with mild or moderate renal impairment and normal renal function showed that the p-values were > 0.05.

CONCLUSIONS

Peak and total exposure to plasma avanafil was similar between the subjects with mild or moderate renal impairment and those with normal renal function. The Cmax and AUC0-t values were not affected by renal impairment, because no statistically meaningful differences in the PK of avanafil were observed among subjects with different degrees renal function, avanafil dose adjustments are not recommended for patients with mild or moderate renal impairment.

Table 1: Arithmetic and Geometric Mean Plasma Pharmacokinetic Parameters for Avanafil Following a Single 200 mg Dose of Avanafil

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th>Geometric LS Means</th>
<th>Mean Ratio (90% CI) a</th>
<th>Percentage Change (8)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax</td>
<td>7380 ± 1700</td>
<td>8960</td>
<td>1.05 (0.90 - 1.23)</td>
<td>6.7%</td>
<td>0.187</td>
</tr>
<tr>
<td>AUC0-t</td>
<td>2750 ± 610</td>
<td>3790</td>
<td>1.37 (1.01 - 1.85)</td>
<td>36.0%</td>
<td>0.024</td>
</tr>
<tr>
<td>AUC0-∞</td>
<td>7300 ± 1500</td>
<td>9400</td>
<td>1.21 (0.99 - 1.47)</td>
<td>27.0%</td>
<td>0.053</td>
</tr>
</tbody>
</table>

Table 2: Statistical Comparisons of Plasma Avanafil Pharmacokinetic Parameters: Mild Renal Impairment (Cohort 2) vs. Normal Renal Function (Cohort 1)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean Ratio (90% CI) a</th>
<th>Percentage Change (8)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax</td>
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<td>AUC0-∞</td>
<td>1.21 (0.99 - 1.47)</td>
<td>27.0%</td>
<td>0.053</td>
</tr>
</tbody>
</table>

Note: *p < 0.05 was considered statistically significant.