A Comparative, Randomized, Single-Dose, 2-Way Crossover Bioavailability Study of a Ramipril Oral Solution versus Tablet in Healthy Adult Volunteers

Marie-Chantal Bonhomme, Nadia Cardillo Marrico, Mike Di Spirito, Elliot M. Offman, Stephen P. Smith and M. Kevan Cassidy

Celerion, Montreal, Canada; Belfast, Northern Ireland; Rosemont Pharmaceuticals Ltd, Leeds, UK.

BACKGROUND

Ramipril is a potent, long-acting, angiotensin-converting enzyme (ACE) inhibitor and its effect on hypertension appears to result in loss of both tissue and circulating ACE activity, thereby reducing angiotensin II formation in tissue and plasma. Ramipril tablet is included in the treatment of hypertension; cardiovascular prevention for reducing cardiovascular risk and reducing and maintaining dose vary upon indication and range from 2.5 to 10 mg per day administered as a single dose or in two or equally divided doses. Following oral administration, ramipril is rapidly absorbed from the gastrointestinal tract with an absolute bioavailability of 50 to 65%. Cleavage of the enteric group, primarily by enterocytes in the liver, converts ramipril to its active diacid metabolite, ramiprilat. The parent drug is almost completely metabolized to ramiprilat, which has about 6 times the ACE inhibitory activity of the parent ramipril, and to the diketopiperazine enteric, the diketopiperazine acid, and the diketopiperazine ester, the diketopiperazine acid, and the diketopiperazine acid, all of which are inactive metabolites. An oral solution was developed with the intention of improving treatment compliance in patients who struggle swallowing solid oral dosage forms. In addition, the oral solution allows for individualized dosing, improving dose adjustment to achieve target blood pressure.

OBJECTIVE

The primary objective of this study was to assess the single-dose relative bioavailability of a 2.5 mg/mL ramipril oral solution and a marketed reference 2.5 mg ramipril tablet, under fasting conditions.

METHODS

• This was an open-label, randomized, 2-way crossover, 2-sequence, single-dose comparative bioavailability study.

• A total of 36 healthy adult subjects (26 males and 4 females) were enrolled in the study and randomized to study treatments.

• In each study period, subjects received a single 2.5 mg oral dose of one of the following treatments following an overnight fast.
  - Test: 2.5 mg/5 mL ramipril oral solution
  - Reference: marketed 2.5 mg ramipril tablet

• The washout period was 20 days between doses which covered more than 5 times the mean half-life of the metabolite ramiprilat.

• Serial blood samples drawn from subjects through 72 hours postdose were quantified for plasma ramipril (up to 12 hours) and ramiprilat using a validated LC-MS/MS method with a lower limit of quantification of 0.100 ng/mL, for both analytes.

• A noncompartmental analysis was performed on the plasma ramipril and ramiprilat concentrations to derive the pharmacokinetic (PK) parameters of interest using PK Analyst 3.2-931 (Celerion, Lincoln, Nebraska). The maximum plasma concentration (Cmax) was under the curve from time 0 to the last measurable concentration (AUC0-t), and the area under the curve from time 0 to infinity (AUC0-∞), time to reach Cmax (tmax), apparent elimination rate constant (t1/2), and other PK parameters were calculated for ramiprilat in plasma. Below limit of quantitation (BLQ) values were set to missing for statistical analyses when referenced by two measurable concentrations. Otherwise, BLQ values were set to zero.

• An analysis of variance was performed on the ln-transformed Cmax, AUC0-t, AUC0-∞, and Cmax values of the oral solution to the tablet formulation for ramipril should be within 80 - 125%.

• The dose administered for ramipril was presented for supportive information purposes.

• A non-parametric analysis was performed on ln(PLC) using SAS® version 9.1.3 (SAS Institute, Cary, North Carolina).

• Safety assessments included vital signs, clinical laboratory evaluations, 12-lead ECG and adverse event monitoring.

RESULTS

• Data from 35 subjects who completed the study were included in the PK and statistical analyses. All 36 subjects enrolled were included in the safety assessment. One subject withdrew from the study due to personal reasons.

• The arithmetic mean plasma ramipril and ramiprilat concentrations versus time plots following the administration of a 2.5 mg oral dose of the ramipril oral solution and tablet, under fasting conditions, are presented in Figures 1 and 2, respectively.

• A summary of plasma ramipril and ramiprilat PK parameters following the administration of a single 2.5 mg oral dose of the ramipril oral solution and tablet, under fasting conditions, is presented in Table 1.

• Results from the ANOVA bioequivalence assessment are presented in Table 2.

• Peak and total exposure to ramipril and ramiprilat were comparable between the oral solution and tablet. The geometric mean ratio of AUC0-t, AUC0-∞, Cmax, and t1/2 were comparable between the oral solution and tablet. The geometric mean ratio of AUC0-t, AUC0-∞, Cmax, and t1/2 were comparable between the oral solution and tablet.

• The geometric mean ratio of tmax was comparable between the oral solution and tablet.

CONCLUSIONS

The overall plasma ramipril and ramiprilat concentrations were comparable between the oral solution and tablet. The arithmetic mean plasma concentrations versus time plots of the study population receiving the oral solution exhibited adverse events possibly related to ramipril, consisting of reported headache, nausea, irritated area on the tongue and irritated throat.

Table 1 Summary of Plasma Pharmacokinetic Parameters for Ramipril and Ramipril Following a Single 2.5 mg Dose of Ramipril

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Mean Ratio [90% Confidence Interval]</th>
<th>Intrarun (CV %)</th>
<th>Interrun (CV %)</th>
<th>Mean Ratio [90% Confidence Interval]</th>
<th>Intrarun (CV %)</th>
<th>Interrun (CV %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramipril Oral Solution</td>
<td>Ramipril Tablet</td>
<td></td>
<td></td>
<td>Ramipril Oral Solution</td>
<td>Ramipril Tablet</td>
<td></td>
</tr>
<tr>
<td>Cmax (µg/mL)</td>
<td>1.16 [0.98-1.39]</td>
<td>9.2</td>
<td></td>
<td>1.20 [1.00-1.45]</td>
<td>7.1</td>
<td></td>
</tr>
<tr>
<td>AUC0-t (µg*hr/mL)</td>
<td>1.20 [1.00-1.45]</td>
<td>7.1</td>
<td></td>
<td>1.20 [1.00-1.45]</td>
<td>7.1</td>
<td></td>
</tr>
<tr>
<td>AUC0-∞ (µg*hr/mL)</td>
<td>1.20 [1.00-1.45]</td>
<td>7.1</td>
<td></td>
<td>1.20 [1.00-1.45]</td>
<td>7.1</td>
<td></td>
</tr>
<tr>
<td>t1/2 (hr)</td>
<td>0.560 [0.434-1.00]</td>
<td></td>
<td></td>
<td>0.697 [1.385-1.00]</td>
<td></td>
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</tr>
</tbody>
</table>

Figure 1 Arithmetic Mean Plasma Ramipril Concentrations versus Time

Figure 2 Arithmetic Mean Plasma Ramiprilat Concentrations versus Time