Pharmacokinetics and Safety of an Oral, Immediate-Release (IR) Tablet Formulation of Lefamulin in Fed and Fasted Healthy Subjects

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INTRODUCTION & PURPOSE

Lefamulin is the first semi-synthetic pleuromutilin antibiotic for IV and oral use in humans. It is currently in Phase 3 trials for the treatment of CAP in adults. Lefamulin effectively and selectively inhibits bacterial translation by binding to the peptidyl transferase center (PTC) at two sites. It interacts via four H-bonds and other interactions resulting in an "induced fit" whereby nucleotides in the PTC shift and further tighten the binding pocket around lefamulin. Previous pharmacokinetic studies of lefamulin revealed that steady-state was reached after 2 days of oral administration every 12 hours, and the elimination half-life after oral administration was similar to that after intravenous (IV) administration (data on file, Nabriva Therapeutics). In addition, the exposure from 600 mg doses given as 3 x 200 mg capsules or as a 600 mg immediate-release (IR) tablet was equivalent to that of a 150 mg intravenous dose. In this study, we evaluated the safety and effect of food on the pharmacokinetics of a 600 mg IR tablet formulation of lefamulin compared with intravenous (150 mg) and lefamulin active pharmaceutical ingredient (API) in capsule (200 mg) formulations.

OBJECTIVES

Primary Objective: Evaluate the absolute bioavailability and pharmacokinetics of lefamulin 600 mg IR tablet formulation in comparison with lefamulin 150 mg IV formulation

Secondary Objectives: Evaluate the relative bioavailability and pharmacokinetics of lefamulin 600 mg IR tablet formulation in comparison to lefamulin 600 mg active pharmaceutical ingredient in capsules (3 x 200 mg capsules)

Evaluate the pharmacokinetics of lefamulin 600 mg IR tablet formulation administered in the fed state and 1 hour after high-fat, high-calorie breakfast

Evaluate the safety and tolerability of lefamulin administered as single oral and IV doses

METHODS

This was a single-centre, single-dose, open-label, randomised, 4-period crossover study conducted in 20 healthy subjects aged 18 to 55 years. All subjects received single doses of each of the following lefamulin treatments in random order at 4 study sessions and each treatment period was separated by at least 2 weeks.

Treatment A: 600 mg IR tablet administered orally in a fasted state

Treatment B: 600 mg active pharmaceutical ingredient (3 x 200 mg capsules) administered orally in a fasted state

Treatment C: 150 mg in 250 mL citrated-buffered saline administered as an IV infusion over 1 hour

Treatment D: 600 mg IR tablet administered orally in a fasted state 1 hour after a high-fat, high-calorie breakfast

RESULTS

The study demonstrated that the exposure to lefamulin after a single 150 mg IV infusion and after administration of 600 mg oral IR tablet in the fasted state met the criterion for bioequivalence with respect to AUC (Figure 1; Table 1).

Absorption of lefamulin was rapid after oral administration, with a similar T\text{max} compared to the 1h infusion (Table 1; Figure 1).

Relative bioavailability of the tablet administered in the fed and fasted state (AUC\text{total} 81.57% (CI\text{90}: 75.34, 88.31%)) was slightly below the range for bioequivalence range of 80 to 125% (Table 2).

The most common AEs reported were GI disorders, and the incidence was higher after dosing with Treatment A than Treatment C and D.

Co-administration of lefamulin tablets with food resulted in a decrease in GI-related AEs (2 versus 12 events).

All AEs reported were mild in severity, no subject required concomitant medication for treatment of an AE, no subjects were withdrawn due to an AE and all AEs resolved by study end. No clinically significant findings in any laboratory assessments, vital signs, ECGs or physical examinations were reported.

CONCLUSIONS

Lefamulin was generally well tolerated, regardless of route of administration

Single doses of 600 mg IR tablets in the fasted state were bioequivalent to a 150 mg intravenous infusion with respect to AUC

The bioavailability of the IR tablet after a high fat/high calorie meal was slightly lower than that in the fasted state and did not reach the threshold for bioequivalence

REFERENCES


ACKNOWLEDGMENTS

We thank the volunteers, investigators, and study personnel who made this study possible. Medical writing support was provided by Scott Newcomer, MS of Davenport Scientific Services, LLC. Funding for medical writing support was provided by Nabriva Therapeutics.

Table 1. Summary Pharmacokinetic and Safety

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage</th>
<th>Food Status</th>
<th>Pharmacokinetics</th>
<th>Safety (% of Total)</th>
<th>Geometric Mean Ratio</th>
<th>AUC\text{IR} Ratio of Oral 600 mg and IV 150 mg (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>600 mg</td>
<td>Fasted</td>
<td>T\text{max} (hours)</td>
<td>(0.5-5.0)</td>
<td>0.875</td>
<td>1.00 (1.0-2.0)</td>
</tr>
<tr>
<td>B</td>
<td>600 mg</td>
<td>Fasted</td>
<td>T\text{max} (hours)</td>
<td>(0.5-5.0)</td>
<td>0.875</td>
<td>1.00 (1.0-2.0)</td>
</tr>
<tr>
<td>C</td>
<td>150 mg</td>
<td>Fasted</td>
<td>T\text{max} (hours)</td>
<td>(0.5-5.0)</td>
<td>0.875</td>
<td>1.00 (1.0-2.0)</td>
</tr>
<tr>
<td>D</td>
<td>600 mg</td>
<td>Fed</td>
<td>T\text{max} (hours)</td>
<td>(0.5-5.0)</td>
<td>0.875</td>
<td>1.00 (1.0-2.0)</td>
</tr>
</tbody>
</table>

Table 2. Ratio of AUC\text{IR} of Oral and IV of Lefamulin in the Fasted and Fed State

<table>
<thead>
<tr>
<th>Test</th>
<th>Geometric Mean Ratio</th>
<th>AUC\text{IR} Ratio of Oral 600 mg and IV 150 mg (%)</th>
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<tbody>
<tr>
<td>A</td>
<td>Cl\text{Lower}</td>
<td>Cl\text{Upper}</td>
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<tr>
<td>B</td>
<td>Cl\text{Lower}</td>
<td>Cl\text{Upper}</td>
</tr>
<tr>
<td>C</td>
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<td>Cl\text{Upper}</td>
</tr>
</tbody>
</table>

Figure 1. Mean concentration time curves of treatment periods

Graphical and statistical analysis were performed using a non-parametric test. The lower and upper 90% confidence limits of the geometric mean ratio were calculated for each dose condition and for each parameter. AUC\text{IR} was derived by the trapezoidal rule. The non-parametric test was used to determine the significance of differences between treatments. ANOVA was used to compare treatments with standard deviation. The differences were considered statistically significant if the p-value was less than 0.05. The results were reported to the nearest whole number.

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