The Effect of Mild and Moderate Hepatic Impairment on Telaprevir Pharmacokinetics

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Author Disclosures

**Drs. Adiwijaya and Garg** are employees and stock owners of Vertex Pharmaceuticals Incorporated.

**Dr. Chandorkar** was an employee of Vertex at the time this work was performed and is a current stock holder. He is currently employed by and holds stock in Cubist Pharmaceuticals.

**Dr. van Heeswijk** is an employee of Tibotec BVBA, Belgium.

**Dr. McNair** was an employee of Vertex at the time this work was performed. She is currently employed by Equipoise Consulting.

**Dr. Kwo** has received consulting fees from Abbott, Anadys, Bayer, Bristol Myers Squibb, Gilead, Merck, Novartis, Vertex; he also received fees for Non-CME/CE services directly from Bristol Myers Squibb, Gilead, Merck, and Roche; and contracted research funding from Abbott, Anadys, Bayer, Bristol Myers Squibb, Gilead, Merck, Novartis, Roche, and Vertex.

**Dr. Gordon** has received consulting fees from Achillion, Bristol-Myers Squibb, CVS Caremark, Gilead Pharmaceuticals, Merck, Salix Pharmaceuticals, Johnson and Johnson, and grant support from Abbott Pharmaceuticals, Anadys Pharmaceuticals, Bristol-Myers Squibb, Conatus, Eiger Biopharmaceuticals, Inc, Exalenz BioScience, Gilead Pharmaceuticals, GlaxoSmithKline, GlobeImmune, Intercept Pharmaceuticals, Merck, Roche Pharmaceuticals, Tibotec, Vertex Pharmaceuticals, Zymogenetics, and served as a speaker/teacher for Bayer, Gilead, Roche, Merck and Vertex.
Introduction

• Telaprevir (TVR) is an NS3/4A serine protease inhibitor of HCV\(^1,2\)
• TVR is metabolized by CYP3A and non-CYP pathways
• Based on animal data, biliary elimination is also likely
• Patients with HCV-related advanced fibrosis have varying degrees of liver impairment that may affect drug metabolism\(^3\)
  – The effects of mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment on TVR PK was examined in cirrhotic volunteers

Study Design

Three volunteer groups:
- Healthy, N=10
- Child-Pugh A (CPA), N=10
- Child-Pugh B (CPB), N=10

TVR 750 mg single dose

TVR 750 mg q8h

Day 1

Days 2-5

Day 6

24h PK sampling

Pre-dose PK samples

24h PK sampling

All TVR doses were administered with food
Safety

• Early discontinuation due to adverse events (AEs):

  Healthy volunteers
  ▪ rash, pruritus (n=1)
  ▪ edema (n=1)

  CPA volunteers
  ▪ erythema (n=1)
  ▪ pruritus, rash, erythema, (n=1)

• In CPB volunteers, no discontinuations or serious AEs related to study reported.
Median Plasma Concentrations of TVR after a Single Dose of 750 mg (Day 1)

GLS Mean Ratio (90% CI)

**CPA**
- $C_{\text{max}}$: 0.82 (0.62, 1.08)
- $AUC_{8h}$: 0.89 (0.66, 1.22)

**CPB**
- $C_{\text{max}}$: 0.59 (0.45, 0.78)
- $AUC_{8h}$: 0.63 (0.47, 0.86)
Telaprevir Plasma Concentration – Time Profiles on Day 6

Median Day 6 telaprevir conc (ng/ml)

GLS Mean Ratio (90% CI)

<table>
<thead>
<tr>
<th></th>
<th>CPA</th>
<th>CPB</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$</td>
<td>0.90 (0.72, 1.10)</td>
<td>0.51 (0.41, 0.63)</td>
</tr>
<tr>
<td>AUC$_{8\text{h}}$</td>
<td>0.85 (0.70, 1.02)</td>
<td>0.54 (0.43, 0.66)</td>
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Median Plasma Concentrations of TVR after a Single Dose of 750 mg (Day 1)

Median Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HV</th>
<th>CPB</th>
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<tbody>
<tr>
<td>$T_{1/2}$ (h)</td>
<td>4.45</td>
<td>6.97</td>
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<tr>
<td>$V_z/F$ (L)</td>
<td>375</td>
<td>592</td>
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<td>$CL/F$ (L/h)</td>
<td>60</td>
<td>65</td>
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Median Plasma Concentrations of TVR after Multiple Doses of 750 mg q8h

Median Parameters

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<th>Parameter</th>
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<td>$T_{1/2}$ (h)</td>
<td>6.45</td>
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<tr>
<td>$V_z/F$ (L)</td>
<td>163</td>
<td>319</td>
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<tr>
<td>CL/F (L/h)</td>
<td>23</td>
<td>37</td>
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</tbody>
</table>

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Possible Explanation for the Lowered Exposure in Hepatic Impairment

- Reduced binding to albumin and $\alpha_1$-acid glycoprotein (AAG)\(^1\) could increase the clearance and volume of distribution of TVR, leading to reduced total drug levels (without affecting the unbound levels of TVR).
- Lowered bioavailability due to poor absorption

Conclusions

• The effect of mild hepatic impairment on telaprevir PK was not clinically significant
  – No dose modification is required in Child-Pugh A patients¹

• Moderate hepatic impairment reduced the steady-state AUC of telaprevir by 46%
  – The appropriate dose of telaprevir in HCV-infected patients with moderate and severe hepatic impairment has not been determined; telaprevir is not recommended in these patients¹

¹INCIVEK™ U.S. Prescribing Information. Vertex Pharmaceuticals Incorporated.
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