Telaprevir is an inhibitor of the HCV NS3/4A protease. When used in combination with pegylated interferon and ribavirin, telaprevir has demonstrated a substantial increase in sustained virological response compared with pegylated interferon and ribavirin used alone. Telaprevir has good oral bioavailability, which is enhanced when administered with food. Telaprevir is extensively metabolized and primarily eliminated via faeces. No dose adjustment of telaprevir is needed in patients with mild to severe renal impairment or mild liver impairment. Telaprevir is a substrate and inhibitor of cytochrome P450 3A and P-glycoprotein and, thus, might interact with coadministered drugs that affect or are affected by these metabolic/transport pathways. This article reviews the pharmacokinetic and drug interaction profile of telaprevir.

Introduction

Globally, an estimated 170 million people (3% of the global population) are infected with HCV [1], a member of the Flaviviridae family of viruses that is classified into at least six major genotypes [2]. More than 50% of HCV infections become chronic, and this can lead to the development of liver fibrosis, cirrhosis and occasionally hepatocellular carcinoma [3]. Chronic HCV infection is the leading cause of liver failure requiring liver transplantation [4]. The introduction of blood screening diagnostic tests in the 1990s led to a rapid decrease in the incidence of HCV infection. Yet, the burden of pre-existing infections will increase over the coming decades [5].

Telaprevir is a covalent, reversible, selective, orally bioavailable inhibitor of the HCV NS3/4A serine protease. Telaprevir is a peptidomimetic inhibitor derived based on the conformation of the viral NS5A/5B substrate, in complex with the NS3/4A protease, using structure-based drug design techniques [6,7]. At doses of 750 mg administered orally every 8 h, telaprevir monotherapy for 14 days induced a median decline of more than 4 log units from baseline plasma HCV RNA levels in patients with chronic HCV genotype 1 infection [8]. Because of the development of resistance, telaprevir is not approved as monotherapy and must be used in combination with pegylated interferon (PEG-IFN) and ribavirin (RBV) [9–11].

Three Phase III clinical studies with telaprevir in combination with PEG-IFN/RBV have been completed [12–14]. Sustained virological response (SVR) in treatment-naive genotype 1 HCV-infected patients was assessed in the ADVANCE study comparing PEG-IFN-α2a and RBV alone for 48 weeks with telaprevir in combination with PEG-IFN/RBV administered for 12 weeks followed by PEG-IFN/RBV alone for an additional 12 or 36 weeks depending on initial on-treatment virological response. A higher proportion of patients achieved SVR with 12 weeks (79%) of telaprevir in combination with PEG-IFN/RBV compared with PEG-IFN/RBV alone (46%) [9,10].

In the ILLUMINATE study, a high proportion of treatment-naive patients with genotype 1 HCV treated with telaprevir for 12 weeks in combination with PEG-IFN/RBV achieved an extended rapid virological response (eRVR: undetectable HCV RNA at both weeks 4 and 12 after start of treatment; 65%) and SVR (74%). Patients achieving eRVR were randomized at weeks 20 to 24 (12 weeks of additional PEG-IFN/RBV) or week 48 (36 weeks of additional PEG-IFN/RBV) of total treatment duration. The trial showed that SVR rates were similar in the two arms indicating that the total duration of treatment could be reduced to 24 weeks in treatment-naive patients receiving telaprevir in combination with PEG-IFN/RBV if they achieve eRVR [9,10].

Finally, the REALIZE trial assessed the efficacy and safety of a telaprevir-based regimen in genotype 1 HCV-infected patients who had not responded to
a previous course of PEG-IFN/RBV therapy. SVR rates in the telaprevir arms compared with the PEG-IFN/RBV control arm, respectively, were 86% and 22% in prior relapsers, 59% and 15% in prior partial responders and 32% and 5% in prior null responders [9].

Safety results were consistent in all three Phase III trials. The most common adverse drug reactions to telaprevir (incidence at least 5% higher than in controls) were rash, pruritus, anaemia, nausea, haemorrhoids, diarrhoea, anorectal discomfort, dysgeusia, fatigue, vomiting and anal pruritus [9].

The present review summarizes the physicochemical properties of telaprevir and discusses, in detail, the pharmacokinetic and drug interaction profile of telaprevir obtained from in vitro studies and the extensive clinical pharmacology programme.

### Chemical and physical properties

Telaprevir (molecular weight 679.85 Da) is a single diastereomer with the S-configuration at position 21 (Figure 1). Telaprevir can epimerize at position 21 in vitro and in vivo to form a mixture with the corresponding R-diastereomer, which is approximately 30-fold less active than telaprevir against HCV. In vitro, the ratio of S:R epimers at equilibrium in human plasma is approximately 60:40. Telaprevir acts as a linear peptidomimetic NS3/4A protease inhibitor that possesses an α-ketoamide group serine trap, forming a covalent but reversible complex [7]. Telaprevir has a slow binding mechanism, presumably due to the conformational change required to form the tightly bound complex. This conformational change allows for the formation of the covalent bond between the NS3/4A protease and telaprevir. Once formed, the covalent complex dissociates slowly back to free enzyme and inhibitor. As such, the bound enzyme–inhibitor complex of telaprevir has a long dissociation half-life ($t_{1/2}$) of 58 min [6].

### Pharmacokinetics

#### Absorption

Telaprevir is orally available and probably absorbed in the small intestine; there is no evidence for absorption in the colon [9]. For single doses of 375 mg to 1,875 mg telaprevir in healthy volunteers, exposure increased more than proportionally to the dose. However, an increase in dose from 750 mg to 1,875 mg in a multiple-dose 5-day study in healthy volunteers resulted in a less than proportional increase in exposure. Exposure was similar for healthy volunteers and HCV-infected patients after single-dose administration. Steady state after multiple doses of telaprevir every 8 h in HCV-infected patients was reached after 3 to 7 days of administration. The mean accumulation index (ratio of the area under the concentration–time curve from 0–8 h [AUC$_{0–8}$] at steady state versus AUC$_{0–8}$ after a single dose) in healthy volunteers receiving 750 mg telaprevir every 8 h was about 2.2.

Telaprevir is a P-glycoprotein (P-gp) substrate with a permeability coefficient (Papp) ratio of 20.5, measured as Papp basolateral-to-apical/Papp apical-to-basolateral in human Caucasian colon adenocarcinoma monolayers. Thus, telaprevir absorption can be affected by other substrates or inhibitors/inducers of P-gp. Although telaprevir is not an inhibitor of P-gp at concentrations up to 10 mM in vitro, a subsequent clinical study showed a drug interaction with digoxin, suggesting that telaprevir might inhibit P-gp in vivo. The high concentrations of telaprevir in the gut or liver after dosing could explain the discrepancy between the in vitro and in vivo findings.

#### Food effect

Food effect studies were conducted to determine if telaprevir should be administered with food. In a preliminary study in healthy volunteers, using an early formulation of telaprevir, a lower exposure of telaprevir was observed in the fed state compared with the fasted state. With the tablet formulation used in pivotal clinical studies, the effect of various meal...
types on the absorption of telaprevir was evaluated in a study with 30 healthy volunteers who received a single 750 mg dose of telaprevir under fasting conditions, after a standard breakfast (533 kcal, 21 g fat), high-calorie high-fat breakfast (928 kcal, 56 g fat), low-calorie high-protein breakfast (260 kcal, 9 g fat) or low-calorie low-fat breakfast (249 kcal, 3.6 g fat). Compared with the standard breakfast, telaprevir AUC and peak plasma concentration (Cmax), respectively, decreased by 73% and 83% when administered under fasting conditions, 26% and 25% when administered after a low-calorie high-protein breakfast, and 39% and 38% when administered after a low-calorie low-fat breakfast. Compared with the standard breakfast, telaprevir given after a high-calorie high-fat breakfast resulted in a small increase of exposure by 20% compared with administration after a standard breakfast (Figure 2) [15]. In summary, telaprevir exposure was three- to fourfold higher when administered with food than when administered in a fasted state. Therefore, telaprevir should always be taken with food (not low fat).

**Distribution**

Following oral administration to rats and dogs, significantly higher concentrations of telaprevir were achieved in the liver as the target organ relative to concentrations in plasma: the liver-to-plasma ratio was 35 to 1 [6].

Approximately 59–76% of telaprevir was bound to human plasma proteins at concentrations ranging from 0.1–20 μM. Thus, telaprevir is considered to be moderately bound to human plasma proteins, mainly α1-acid glycoprotein (AAG) and human serum albumin (HSA). The protein binding was concentration dependent and decreased with increasing telaprevir concentrations at all concentrations of HSA or AAG. In addition, protein binding of telaprevir decreased with decreasing concentrations of HSA or AAG. Telaprevir was displaced from its binding sites in human plasma in the presence of warfarin. However, the binding of warfarin was not affected by telaprevir [16].

The apparent volume of distribution (V/F, where V and F stand for the volume and oral bioavailability, respectively) of telaprevir was estimated from population pharmacokinetic analyses of Phase II and Phase III studies to be about 252 l; inter-individual variability of V/F was estimated to be about 72% [9]. This suggests a large apparent volume of distribution with penetration of telaprevir into tissues beyond the systemic circulation and is consistent with whole-body autoradiography studies of 14C-telaprevir conducted in rats, which
demonstrated distribution of radioactivity into several body tissues.

Metabolism
Telaprevir is extensively metabolized in the liver, involving hydrolysis, oxidation and reduction. Multiple metabolites were detected in faeces, plasma and urine. After repeated oral administration, the R-dias-tereomer of telaprevir (30-fold less active), pyrazinoic acid and a metabolite that underwent reduction at the α-ketoamide bond of telaprevir (not active) were found to be the predominant metabolites of telaprevir. In vitro studies using recombinant human cytochrome P450 (CYP) isoforms indicated that CYP3A was the major CYP isoform responsible for telaprevir metabolism. However, non-CYP mediated metabolism probably has a role after multiple dosing of telaprevir.

Excretion
After single-dose administration of 750 mg of 14C-labelled telaprevir, elimination of telaprevir and its metabolites in the faeces was the predominant route of excretion (82%); there was moderate excretion by expired air (9%) and minimal renal excretion (1%) [9]. The excretion of radioactivity in expired air can probably be explained by transfer of the radiolabelled carbon atom to CO2.

Effect of intrinsic factors on telaprevir pharmacokinetics
Effect of hepatic impairment
Two studies of single- and multiple-dose (6 days) telaprevir have been conducted in volunteers uninfected with HCV with mild (Child–Pugh A) or moderate (Child–Pugh B) hepatic impairment. A total of 30 individuals were enrolled in these studies (10 healthy volunteers, 10 volunteers with mild hepatic impairment and 10 volunteers with moderate impairment). Telaprevir exposure (AUC0–infty) decreased by 15% in volunteers with mild impairment and by 46% in volunteers with moderate hepatic impairment. Similar reductions were found for Cmax (10% for mild and 49% for moderate hepatic impairment under steady-state conditions, respectively) [17]. The effect of severe hepatic impairment on the pharmacokinetics of telaprevir has not been studied. The exposure decrease in volunteers with mild hepatic impairment was of limited magnitude and not deemed clinically relevant. Furthermore, the accumulation ratio of telaprevir was similar, indicating that mild hepatic impairment did not increase accumulation of telaprevir in plasma.

Because hepatic metabolism plays a major role in the elimination of telaprevir, volunteers with moderately impaired hepatic function were expected to be deficient in their ability to metabolize telaprevir, leading to increased concentrations of telaprevir in these volunteers. However, Child–Pugh B volunteers had lower concentrations of telaprevir compared with healthy individuals. The mechanism of this reduction in exposure has not been established, but may be related to lower concentrations of plasma proteins (HSA and AAG) in individuals with hepatic impairment [18] or due to reduced absorption resulting from the altered physiological status in hepatically impaired individuals. Reduced plasma protein levels (AAG and HSA) in hepatically impaired individuals can, in principle, reduce total drug concentration without affecting the concentrations of unbound protein, as has been shown for tamsulosin [19].

The appropriate dose of telaprevir in individuals with moderate hepatic impairment depends on the mechanism leading to reduced exposure, which has not been determined. Studies have not been conducted in HCV patients with severe (Child–Pugh C) hepatic impairment. Additionally, coadministered medications (PEG-IFN/RBV) are contraindicated in patients with moderate to severe hepatic impairment [20,21]; therefore, telaprevir is not recommended in this population.

Effect of renal impairment
Although renal excretion has a minor role in the elimination of telaprevir, exposure to non-renally eliminated drugs can increase in patients with renal impairment due to indirect effects on metabolizing enzymes and transporters [22]. Therefore, the effect of severe renal impairment on telaprevir plasma concentrations was studied. A single dose of 750 mg telaprevir was administered to 12 volunteers with severe renal impairment and 12 healthy volunteers matched for age, race, sex and body mass index. The telaprevir AUC extrapolated to infinity (AUCinfty) and Cmax were 21% and 3% higher, respectively, in volunteers with severe renal impairment [23]. Although no dose adjustments of telaprevir in patients with renal impairment are needed, telaprevir must be used in combination with PEG-IFN/RBV, for which specific guidance for use in patients with reduced renal function should be considered [20,21]. Telaprevir has not been studied in patients with end-stage renal disease or those on haemodialysis.

Effect of extrinsic factors: effect of coadministered drugs on the pharmacokinetics of telaprevir
In vitro studies indicated that telaprevir is a substrate and inhibitor of CYP3A and a substrate of P-gp. A number of other drugs that are substrates, inhibitors or inducers of CYP3A might be coadministered in HCV-infected patients and a selection of these drugs has been tested in the interaction studies summarized below. Similarly, the
effect of telaprevir on P-gp has been tested with digoxin as a probe substrate. Refer to Table 1 for a summary of telaprevir drug interaction studies. Drug–drug interaction studies of telaprevir in combination with antiretroviral agents will be reported separately.

PEG-IFN and RBV

In patients with chronic HCV infection, coadministration with PEG-IFN increased telaprevir steady-state minimum plasma concentration (Cmin) by about 22%; the Cmax and AUC were increased by about 30–40% compared with patients who received telaprevir monotherapy. RBV coadministration did not affect telaprevir exposure. Similar telaprevir concentrations were obtained regardless of whether the coadministered treatment was PEG-Intron/Rebetol or Pegasys/Copegus. PEG-IFN or RBV levels were not affected by the coadministration of telaprevir [24].

Ketoconazole and ritonavir

To determine the effect of CYP3A inhibition on the exposure to telaprevir, drug interaction studies were conducted with the antifungal agent ketoconazole and the HIV protease inhibitor ritonavir, both potent inhibitors of CYP3A [25,26]. Single-dose ketoconazole (400 mg) or ritonavir (100 mg) administration resulted in increased telaprevir exposure when coadministered with a single 750 mg dose of telaprevir in healthy volunteers. Ketoconazole increased telaprevir AUC0–∞ approximately 1.6-fold [27] and ritonavir increased telaprevir AUC0–∞ approximately 2-fold [9]. These results are consistent with in vitro data showing that CYP3A is the primary CYP enzyme responsible for the metabolism of telaprevir. However, the interaction of telaprevir with ritonavir and ketoconazole diminished after administration of

<table>
<thead>
<tr>
<th>Coadministered drug</th>
<th>Dose/schedule</th>
<th>Telaprevir</th>
<th>Subjects, n</th>
<th>AUC0–∞, LSM ratio (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alprazolam (Study 019)</td>
<td>0.5 mg</td>
<td>750 mg every 8 h for 10 days</td>
<td>17</td>
<td>†, 1.35 (1.23–1.49) ND</td>
</tr>
<tr>
<td>Amlodipine (Study 018)</td>
<td>5 mg</td>
<td>750 mg every 8 h for 7 days</td>
<td>19</td>
<td>†, 2.79 (2.58–3.01) ND</td>
</tr>
<tr>
<td>Atorvastatin (Study 018)</td>
<td>20 mg</td>
<td>750 mg every 8 h for 7 days</td>
<td>19</td>
<td>†, 7.88 [6.84–9.07] ND</td>
</tr>
<tr>
<td>Cyclosporine A (Study 021)</td>
<td>100 mg/10 mg²</td>
<td>750 mg every 8 h for 11 days</td>
<td>9</td>
<td>†, 4.64* [3.90–5.51] ND</td>
</tr>
<tr>
<td>Digoxin (Study 011)</td>
<td>2 mg oral</td>
<td>750 mg every 8 h for 11 days</td>
<td>20</td>
<td>†, 1.85 (1.70–2.00) ND</td>
</tr>
<tr>
<td>Escitalopram (Study C133)</td>
<td>10 mg once daily for 7 days</td>
<td></td>
<td>13</td>
<td>4, 0.65 (0.60–0.70) ↔, 0.93 (0.89–0.97)</td>
</tr>
<tr>
<td>Esmolol (Study C130)</td>
<td>40 mg once daily for 6 days</td>
<td></td>
<td>24</td>
<td>ND ↔, 0.98 (0.91–1.05)</td>
</tr>
<tr>
<td>Ethyl estradiol (Study 007)</td>
<td>0.035 mg once daily with 0.5 mg NE once daily for 21 days</td>
<td></td>
<td>24</td>
<td>4, 0.72 (0.69–0.75) ↔, 0.99 (0.93–1.05)</td>
</tr>
<tr>
<td>Ketoconazole (Study 003)</td>
<td>400 mg</td>
<td>750 mg</td>
<td>17</td>
<td>ND †, 1.62 [1.45–1.81]</td>
</tr>
<tr>
<td>Midazolam (Study 011)</td>
<td>0.5 mg IV</td>
<td>750 mg every 8 h for 9 days</td>
<td>22</td>
<td>†, 3.40 (3.04–3.79) ND</td>
</tr>
<tr>
<td>Midazolam (Study 011)</td>
<td>2 mg oral</td>
<td>750 mg every 8 h for 11 days</td>
<td>21</td>
<td>†, 8.96 [7.75–10.35] ND</td>
</tr>
<tr>
<td>Norethindrone (Study 007)</td>
<td>0.5 mg once daily with 0.035 mg EE once daily for 21 days</td>
<td></td>
<td>24</td>
<td>†, 0.89 [0.86–0.93] ↔, 0.99 (0.93–1.05)</td>
</tr>
<tr>
<td>Rifampin (Study 016)</td>
<td>600 mg once daily for 8 days</td>
<td></td>
<td>16</td>
<td>ND ↓, 0.08 (0.07–0.11)</td>
</tr>
<tr>
<td>Ritonavir (Study 003)</td>
<td>100 mg</td>
<td>750 mg</td>
<td>14</td>
<td>ND †, 2.00 [1.72–2.33]</td>
</tr>
<tr>
<td>R-Methadone (Study C135)</td>
<td>40–120 mg once daily of methadone</td>
<td></td>
<td>15</td>
<td>↓, 0.71 [0.66–0.76] ND</td>
</tr>
<tr>
<td>S-Methadone (Study C135)</td>
<td>40–120 mg once daily of methadone</td>
<td></td>
<td>15</td>
<td>↓, 0.64 [0.58–0.70] ND</td>
</tr>
<tr>
<td>Tacrolimus (Study 021)</td>
<td>2 mg/0.5 mg²</td>
<td>750 mg every 8 h for 13 days</td>
<td>9</td>
<td>†, 70.3* [52.9–93.4] ND</td>
</tr>
<tr>
<td>Zolpidem (Study 019)</td>
<td>5 mg</td>
<td>750 mg (single dose) for 10 days</td>
<td>20</td>
<td>†, 1.14 [0.96–1.36] ND</td>
</tr>
<tr>
<td>Zolpidem (Study 019)</td>
<td>5 mg</td>
<td>750 mg every 8 h for 10 days</td>
<td>19</td>
<td>↓, 0.53 [0.45–0.64] ND</td>
</tr>
</tbody>
</table>

*Single dose unless indicated otherwise. †The area under the concentration–time curve (AUC) is indicated as an increase (†), decrease (↓) or unchanged (↔). bDose on day 1/dose on day 8. cValues are dose-normalized. EE, ethinylestradiol; IV, intravenous; LSM, least square means; ND, not determined; NE, norethindrone.
multiple doses of telaprevir. Following administration of four doses of 1,250 mg telaprevir, a single dose of 400 mg ketoconazole resulted in an increase in the AUC of telaprevir of only 21% compared with administration of telaprevir 750 mg every 8 h alone [27]. As predose telaprevir concentrations before the administration of ketoconazole were also higher, the increased telaprevir concentrations were probably the result of the 67% higher dose of telaprevir (1,250 mg every 8 h instead of 750 mg every 8 h) than the effect of ketoconazole.

The AUC of ketoconazole (400 mg dose) increased by 46% when coadministered with 1,250 mg telaprevir compared with ketoconazole alone. Thus, concomitant systemic use of ketoconazole and telaprevir may moderately increase plasma concentrations of telaprevir. Because plasma concentrations of ketoconazole might be increased in the presence of telaprevir, high doses of ketoconazole (>200 mg/day) are not recommended when coadministration is required.

Furthermore, coadministration of 750 mg telaprevir every 12 h with low dose (100 mg) ritonavir every 12 h for 14 days resulted in 15% to 32% lower telaprevir exposure at steady state on day 14, as compared with multiple dosing with 750 mg telaprevir every 8 h alone. The concentrations of telaprevir 750 mg every 12 h on day 14 of dosing with ritonavir were lower than those on day 1 [28]. CYP3A and/or P-gp induction by ritonavir [29] or inhibition of CYP3A by telaprevir itself could explain these results. In conclusion, although other strong inhibitors of CYP3A can increase telaprevir exposure, the effect is likely to be greater initially than at steady state of telaprevir.

**Rifampin**

The antibiotic rifampin is a potent inducer of CYP3A [30]. Coadministration of telaprevir and rifampin resulted in markedly decreased telaprevir exposure: the AUC$_{0-\infty}$ was reduced by approximately 92% and C$_{max}$ was reduced by approximately 86% [27]. These results indicate that strong CYP3A inducers such as rifampin can decrease exposure to telaprevir and should not be coadministered with telaprevir.

**Effect of telaprevir on the pharmacokinetics of coadministered drugs**

**Midazolam**

The effect of coadministration of telaprevir and the CYP3A substrate midazolam, a benzodiazepine, on pharmacokinetic properties was analysed in 24 healthy volunteers. Telaprevir significantly inhibited the CYP3A-mediated intestinal and hepatic metabolism of midazolam. The plasma AUC$_{0-24h}$ of midazolam after intravenous (IV) administration (that is, hepatic metabolism only) increased approximately 3.4-fold after coadministration with telaprevir and the t$_{1/2}$ of midazolam increased approximately 4-fold under these conditions [31].

The effect of telaprevir on orally administered midazolam (intestinal and hepatic metabolism) was more pronounced. The midazolam AUC$_{0-24h}$ increased nine-fold after coadministration of telaprevir. The ratio of 1-hydroxymidazolam to midazolam also decreased approximately 17-fold upon coadministration of telaprevir, indicating that the metabolism of midazolam was significantly reduced due to the inhibition of CYP3A. The midazolam elimination half-life increased approximately fourfold, similar to that observed following IV administration. The midazolam C$_{max}$ increased approximately threefold after coadministration with telaprevir suggesting that the absorption of midazolam was significantly increased due to the inhibition of CYP3A [31].

Similar increases in exposure to midazolam have been observed with other CYP3A inhibitors. Coadministration of 400 mg ketoconazole increased exposure (AUC$_{0-\infty}$) to 2 mg midazolam 10.3-fold at day 1 and 14-fold at steady state [32]. Coadministration of tipranavir/ritonavir led to a 26.9-fold increase of exposure to midazolam at single dose and a 10.3-fold increase at steady-state conditions [33]. Further, Schmitt et al. [34] observed a 12-fold increase in midazolam AUC$_{0-\infty}$ following coadministration of ritonavir-boosted saquinavir at steady state.

Telaprevir coadministration decreased the intestinal extraction ratio to a much greater extent than the hepatic extraction ratio, indicating a strong contribution of intestinal CYP3A inhibition to the increase in midazolam exposure. A similar result showing a greater effect on intestinal than on hepatic CYP3A activity was also found for tipranavir/ritonavir [33].

These results suggest that the dosage of drugs that are substrates of CYP3A might need to be reduced when coadministered with telaprevir, in particular for those medications with a narrow therapeutic index. Coadministration with some drugs including triazolam and oral midazolam is contraindicated [9].

**Zolpidem and alprazolam**

Zolpidem is a non-benzodiazepine hypnotic [35] and alprazolam is a benzodiazepine indicated for the management of anxiety disorder or the short-term relief of symptoms of anxiety [36]. Both substances are mainly metabolized by CYP3A [37–39].

Zolpidem exposure (AUC$_{0-\infty}$) in healthy individuals increased 14% when coadministered with a single dose of telaprevir, but was decreased by 47% when coadministered with multiple doses of telaprevir [40]. The mechanism of the effect of telaprevir on zolpidem pharmacokinetics is unknown. It might be necessary to
increase the dose of zolpidem in patients experiencing lack of pharmacological effect when zolpidem is coadministered with telaprevir.

The AUC\textsubscript{0–∞} of alprazolam increased by approximately 35% when alprazolam was coadministered with multiple doses of telaprevir. The C\textsubscript{max} of alprazolam was similar when alprazolam was given alone or coadministered with a multiple dose of telaprevir. This was accompanied by an increased mean t\textsubscript{1/2} from 13.4 h to 18.7 h. These results suggest that telaprevir inhibits the systemic metabolism of alprazolam. Dose adjustment of alprazolam might be required when coadministered with telaprevir [9].

Amlodipine and atorvastatin

Amlodipine is a calcium channel antagonist used to treat high blood pressure and angina or coronary artery disease. Atorvastatin is a statin widely used to lower high cholesterol and reduce the risk of heart attack and stroke. Amlodipine and atorvastatin are often used in combination and are available as a co-formulation [41,42]. Both substances are substrates of CYP3A [43–46].

Telaprevir significantly inhibited the metabolism of amlodipine and atorvastatin given as a combined formulation. AUC\textsubscript{0–∞} of amlodipine increased approximately 2.8-fold and the mean t\textsubscript{1/2} increased from 41 h to 95 h. The AUC\textsubscript{0–∞} of atorvastatin increased about eight-fold; the mean t\textsubscript{1/2} decreased from 9.4 h to 6.8 h [47]. A similar inhibition of atorvastatin metabolism was shown for a combination of tipranavir/ritonavir leading to a 9.4-fold increase in AUC\textsubscript{0–24 h} of atorvastatin under steady-state conditions [48].

The pharmacokinetic parameters of telaprevir during coadministration with amlodipine/atorvastatin were similar to the steady-state estimates obtained from other studies [47]. This suggests that adequate exposure of telaprevir was achieved in this study and there was no relevant effect of amlodipine or atorvastatin on telaprevir pharmacokinetics.

On the basis of these results, the use of atorvastatin with telaprevir should be avoided, whereas amlodipine should be used with caution (dose reduction should be considered and clinical monitoring is recommended) when used with telaprevir [9].

Esomeprazole

Esomeprazole is an antidepressant of the selective serotonin reuptake inhibitor class commonly used in HCV-infected patients receiving PEG-IFN/RBV treatment [50]. In vivo studies demonstrated that esomeprazole is primarily metabolized by CYP3A, CYP2D6 and CYP2C19 [51].

Esomeprazole 10 mg at steady state did not influence the pharmacokinetics of telaprevir in healthy volunteers. However, in the presence of telaprevir, the C\textsubscript{max}, C\textsubscript{min} and AUC\textsubscript{0–24 h} of esomeprazole were decreased by 42%, 30% and 35%, respectively, compared to treatment with esomeprazole alone [52]. The exact mechanism of this interaction with esomeprazole is not known, as other CYP3A inhibitors such as ritonavir and ketoconazole did not show any interaction with citalopram/escitalopram [53,54].

Serotonin reuptake inhibitors such as escitalopram have a wide therapeutic index; however, doses might need to be adjusted for some patients when combined with telaprevir to maintain effective treatment.

Methadone and buprenorphine

Methadone is a synthetic opioid that is commonly administered in HCV patients for the treatment of opioid dependence. Methadone is mostly administered as a combination of its R- and S-isomers; the R-isomer is responsible for the desired opioid effects [55,56]. The primary inactive metabolite of methadone, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrroli dine, is predominantly generated by CYP3A, and to a lesser extent CYP2D6, and is mainly excreted in the urine [57]. However, more recent results from an in vivo study do not support a role for CYP3A in the N-demethylation of methadone [58].

HCV-negative volunteers on stable methadone maintenance therapy received telaprevir (750 mg every 8 h) for 7 days [59]. Telaprevir pharmacokinetics were comparable with previous pharmacokinetic studies, suggesting an absence of an effect of methadone on the pharmacokinetics of telaprevir. Telaprevir decreased
exposure (AUC0-24 h) to R-methadone by 29% when compared with methadone treatment alone. The S/R-methadone ratio of AUC0-24 h was comparable in the presence of telaprevir compared with methadone maintenance treatment alone, suggesting the lack of a stereospecific effect.

To investigate the mechanism for the reduction in methadone concentrations during coadministration of telaprevir, the protein binding of 3H-R-methadone was studied in plasma samples before and after the addition of telaprevir by equilibrium dialysis. The median unbound fraction of R-methadone was 7.9% before the addition of telaprevir and increased to 10% after addition of telaprevir. Although the median unbound fraction of 3H-R-methadone increased by 26% upon addition of telaprevir, the estimated unbound Cmin of R-methadone was comparable before and after addition of telaprevir [59].

The reduction in total R-methadone concentration during coadministration with telaprevir did not result in clinically significant changes in withdrawal symptoms. During coadministration of telaprevir and methadone fewer individuals experienced withdrawal symptoms, overall craving for heroin was lower or identical and the resting pupil diameter was smaller when compared with methadone administration alone. These findings are consistent with the observation that unbound (that is, effective) R-methadone concentrations were not affected by telaprevir and theoretical principles indicating that interactions via protein displacement generally have little clinical relevance [60].

Thus, no adjustment of methadone dose is required when initiating coadministration of telaprevir. However, clinical monitoring is recommended as the dose of methadone during maintenance therapy might need to be adjusted in some patients.

Buprenorphine is a semisynthetic opioid that is also used for the treatment of opioid dependence. Fourteen HCV-negative volunteers on stable buprenorphine/naloxone maintenance therapy received telaprevir (750 mg every 8 h) for 7 days [61]. The total exposure (AUC) of buprenorphine was not significantly affected, the Cmax was reduced by 20% and the Cmin was increased by 6%. The AUC of norbuprenorphine (active metabolite) was slightly (9%) lowered by telaprevir and the Cmax was reduced by 15% [61]. There were no discontinuations due to adverse events. The median resting pupil diameter measured 4 h after dosing showed larger decreases when telaprevir was coadministered compared with the baseline values (day -1) and was similar to the values recorded during follow up visits (days 14 and 38) when buprenorphine/naloxone was administered alone. These results suggest that buprenorphine exposure and pharmacodynamics were not affected significantly by telaprevir.

Digoxin

In vitro studies using Caucasian colon adenocarcinoma cells suggested that telaprevir is a substrate of P-gp [9,62]. Thus, potential drug interactions between telaprevir and the P-gp substrate digoxin were evaluated in healthy male volunteers. Coadministration of telaprevir with a single oral dose of digoxin increased the AUC of digoxin approximately 2-fold and the Cmax of digoxin increased approximately 1.5-fold, indicating increased absorption of digoxin. These results suggest that telaprevir enhanced digoxin absorption either by intestinal P-gp inhibition or saturation due to high local concentrations of telaprevir in the gut. The renal clearance of digoxin appeared to be similar with and without telaprevir, indicating that there is a minimal, if any, effect of telaprevir on P-gp in the kidney [31].

The magnitude of the interaction of telaprevir with digoxin is comparable to other drugs, including ritonavir, that have been tested for P-gp interaction using digoxin as a probe drug [63–66].

When telaprevir and digoxin are coadministered, the lowest dose of digoxin should be initially prescribed. The serum digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect.

Cyclosporine and tacrolimus

Cyclosporine and tacrolimus are immunosuppressants used in the post-operative phase of liver or kidney transplantations and have narrow therapeutic ranges. Because telaprevir is an inhibitor of CYP3A and P-gp, the effect of telaprevir on cyclosporine and tacrolimus exposure was determined in a study in healthy volunteers [67]. Cyclosporine alone was administered as a single 100 mg dose with an 8-day washout period. Telaprevir was then administered as 750 mg every 8 h and cyclosporine was coadministered as two single doses of 10 mg each, with the first dose of telaprevir, and again when telaprevir had reached steady state. Tacrolimus was administered as a single 2 mg dose with a 14-day washout period. This was followed by coadministration of a single dose of 0.5 mg tacrolimus with telaprevir at steady state (750 mg every 8 h) [67].

Coadministration with steady-state telaprevir increased dose-normalized exposure (DN_AUC∞) to cyclosporine 4.6-fold and DN_AUC∞ to tacrolimus approximately 70-fold. Coadministration with telaprevir increased the mean (sd) t1/2 of cyclosporine from 12 h (1.67 h) to 42.1 h (11.3 h) and the mean (sd) t1/2 of tacrolimus from 40.7 h (5.83 h) to 196 h (159 h). The effects of a single dose and steady-state dosing of telaprevir on cyclosporine pharmacokinetics were similar.
The mechanism for the greater effect of telaprevir on the pharmacokinetics of tacrolimus compared with cyclosporine might be related to the lower bioavailability of tacrolimus compared with cyclosporine in healthy volunteers and the potential for increased oral bioavailability due to inhibition of CYP3A-mediated first-pass metabolism by telaprevir.

Telaprevir significantly increases the exposure of both cyclosporine and tacrolimus, consistent with observations from other potent CYP3A inhibitors [68,69]. Without an understanding of the adjustments required for dose and/or dosing frequency, co-administration of telaprevir with tacrolimus or cyclosporine can lead to serious or life-threatening adverse events. The safety and efficacy of telaprevir have not been established in patients undergoing solid organ transplants.

Hormonal contraceptives
Potential drug interactions between telaprevir and a hormonal contraceptive containing norethindrone (NE) and ethinylestradiol (EE) were evaluated. Healthy female volunteers received once-daily NE/EE alone for 21 days and once-daily NE/EE in combination with telaprevir for 21 days.

Coadministration of telaprevir and NE/EE had no significant effect on telaprevir or NE pharmacokinetic parameters; however, coadministration of telaprevir reduced EE C_{max} by 26% and EE AUC_{0–24 h} at steady state by 28% [70]. Considering the decrease observed in EE concentrations with concomitant telaprevir administration, individuals might experience reduced efficacy of hormonal contraceptives containing EE. In addition, telaprevir-based regimens must include RBV, which has teratogenic and/or embryocidal potential [20]. Therefore, two effective non-hormonal methods of contraception should be used during treatment with telaprevir and for up to two weeks following cessation of telaprevir. Patients using oestrogens as hormone replacement therapy should be clinically monitored for signs of oestrogen deficiency.

Conclusions
The pharmacokinetics of telaprevir have been extensively studied in numerous Phase I clinical studies, as well as in HCV-infected patients as part of the clinical development programme. It has been shown that telaprevir inhibits CYP3A and is metabolized by this isoenzyme. In addition, telaprevir can inhibit or saturate P-gp. To enhance its absorption, telaprevir should be taken with food (not low fat). The potential for interactions of telaprevir with a broad range of commonly coadministered drugs in the HCV-infected population are well characterized by the studies outlined in this article.

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