Selected Properties of Telaprevir

Other names	TVR, Incivek®
Manufacturer	Vertex Pharmaceuticals Incorporated
Pharmacology/ Mechanism of Action	Telaprevir is a direct-acting antiviral agent (DAA) against the hepatitis C virus. This agent is a specific inhibitor of the HCV NS3·4A protease which is essential for viral replication. The slow binding mechanism for the interaction of telaprevir with the HCVNS3•4A protease occurs in 2 steps, with formation of a weaker complex followed by rearrangement to the tightly bound form (covalent complex).
Activity	Telaprevir inhibits genotype 2 HCV NS3 serine protease with similar potency to genotype 1a or 1b HCV proteases while its activity against genotype 3 and 4 HCV proteases is reduced. The approved indication for telaprevir is for HCV genotype 1 infection only.
Resistance – genotypic	<u>*In Vitro* Studies</u> Variants V36A/M, T54A/S, R155K/T, and A156S conferred lower levels of in vitro resistance to telaprevir (3- to 25-fold increase in telaprevir IC50), and the A156V/T and V36M+R155K variants conferred higher levels of in vitro resistance to telaprevir (>25-fold increase in telaprevir IC50). All telaprevir-resistant variants studied remained fully sensitive to interferon-alfa and ribavirin. <u>Clinical Virology Studies</u> Predominant telaprevir-resistant variants at baseline (pre-treatment) were rare (V36M, T54A and R155K <1% and T54S 2.7%). Predominant baseline resistance to telaprevir did not preclude subjects from achieving an SVR with a telaprevir, peginterferon-alfa, and ribavirin regimen. Sequence analyses of HCV in subjects treated with telaprevir who had on-treatment virologic failure or relapse identified amino acid substitutions at 4 positions in the NS3-4A protease region, consistent with the mechanism of action for telaprevir (V36A/M, T54A/S, R155K/T, and A156S/T/V). On-treatment virologic failure during telaprevir treatment was predominantly associated with higher-level resistant variants, and relapse was predominantly associated with lower-level resistant variants or wild-type virus. Subjects with HCV genotype 1a predominately had V36M and R155K single and combination variants, while subjects with HCV genotype 1b predominately had V36A, T54A/S, and A156S/T/V variants. This difference is likely due to the higher genetic barrier for the V36M and R155K substitutions for genotype 1b than genotype 1a. Among subjects treated with telaprevir, on-treatment virologic failure was more frequent in subjects with genotype 1a than with genotype 1b and more frequent in prior null responders than in other populations (treatment naïve, prior relapsers, prior partial responders). Follow-up analyses of telaprevir-treated subjects who did not achieve an SVR show that the population of wild-type virus increased and the population of telaprevir-resistant variants became undetectable over time after the end of telaprevir treatment.
Resistance – phenotypic	

 Prepared by Marie-Hélène Irvine, Pharm.D. Updated by A. Tseng, Pharm.D., AAHIVP, Toronto, ON. Please note: This chart summarizes selected properties based on current available data. Please consult a health professional whenever beginning, stopping or modifying drug therapy.

<table>
<tr><td>Cross-Resistance</td><td>There is some overlap between telaprevir and boceprevir primary resistance-associated variants:

<table><tr><th>Telaprevir</th><th>Boceprevir</th></tr><tr><td>V36A/M</td><td>V36M</td></tr><tr><td>T54A/S</td><td>T54A</td></tr><tr><td>R155K/T</td><td>R155K</td></tr><tr><td>A156T/V</td><td>A156T</td></tr></table></td></tr>
<tr><td>Oral Bioavailability</td><td>Orally available, most likely absorbed in the small intestine, with no evidence for absorption in the colon.

Exposure to telaprevir is higher during co-administration of peginterferon alfa and ribavirin than after administration of telapreviralone.</td></tr>
<tr><td>Effect of Food</td><td>The systemic exposure (AUC) to telaprevir was decreased by about 73% when telaprevir was administered under fasting conditions compared to when telaprevir was administered following a standard fat meal (533 kcal, 21 g fat). The telaprevir exposure was decreased by about 39% with a low-fat meal (249 kcal, 3.6 g fat), while exposure was increased by about 20% with a high-fat meal (928 kcal, 56 g fat), compared to telaprevir administration with a standard fat meal. Therefore, telaprevir should always be taken with food (not low fat; ~ 20g fat content).</td></tr>
<tr><td>Protein Binding</td><td>Telaprevir is approximately 59% to 76% bound to human plasma proteins. Telaprevir binds primarily to alpha 1-acid glycoprotein and albumin and the binding is concentration dependent, decreasing with increasing concentrations of telaprevir.</td></tr>
<tr><td>Vd</td><td>Typical apparent volume of distribution is estimated to be 252 L with an inter-individual variability of 72%.</td></tr>
<tr><td>Tmax</td><td>In clinical studies in healthy subjects in which a single 750-mg dose of telaprevir was administered after a regular breakfast, the median time of maximum concentration (tmax) ranged from 4.0 to 5.0 hours.</td></tr>
<tr><td>Serum T ½</td><td>In clinical studies in healthy subjects in which a single 750-mg dose of telaprevir was administered after a regular breakfast, the mean half-life (t1/2) ranged from 4.0 to 4.7 hours. At steady state, the effective half-life is about 9 to 11 hours.</td></tr>
<tr><td>Drug Concentrations</td><td>Drug concentrations in adult health subjects and in subjects with chronic hepatitis C are displayed below:

<table><tr><th></th><th>Healthy Volunteers (n=39)</th><th>CHC treatment-naïve patients (n=641)</th><th>CHC treatment-experienced patients (n=191)</th></tr><tr><td>C_{max} (ng/mL)</td><td>3040 (662)</td><td>3260 (946)</td><td>3990 (1120)</td></tr><tr><td>C_{min} (ng/mL)</td><td>1960 (548)</td><td>2690 (827)</td><td>3340 (1170)</td></tr><tr><td>AUC_{8h} (ng*h/mL)</td><td>19,900 (4710)</td><td>24,400 (7180)</td><td>30,100 (8720)</td></tr></table></td></tr>
<tr><td>Minimum target trough concentrations (for wildtype virus)</td><td>In an HCV subtype 1b replicon assay, the telaprevir IC50 value against wild-type HCV was 0.354 µM, similar to a subtype 1a infectious virus assay IC50 of 0.28 µM.</td></tr>
</table>

CSF (% of serum)	
Metabolism	Telaprevir is extensively metabolized in the liver, involving hydrolysis, oxidation, and reduction. CYP3A4 is the major CYP isoform responsible for telaprevir metabolism. However, non-CYP mediated metabolism likely plays a role after multiple dosing of telaprevir.
Excretion	82% of dose recovered in feces 9% of dose recovered in expired air 1% of dose recovered in urine (within 96 hours following administration of a single radiolabeled dose of telaprevir 750 mg) Apparent total clearance (Cl/F) is estimated to be 32.4 L/h with an inter-individual variability of 27.2%.
Dosing – Adult	Telaprevir must not be administered as monotherapy and must only be prescribed with both peginterferon alfa and ribavirin. The recommended dose of telaprevir is 750 mg (two 375-mg tablets) taken orally 3 times a day (7-9 hours apart) with food (not low fat). The total daily dose is 6 tablets (2250 mg). <u>If taken with efavirenz (not currently approved for use in HIV patients)</u> 1125 mg orally 3 times a day every 7-9 hours with food (not low fat) <u>1125 mg BID dosing (investigational):</u> Results of a Phase 3 study showed that 74% (274/369) of treatment-naïve HCV subjects who received twice-daily (BID) telaprevir in combination with pegylated-interferon and ribavirin achieved a viral cure (SVR12), compared to 73% (270/371) of people who received telaprevir at the standard dose of 750 mg every 8 hours. The study met its primary endpoint of non-inferiority. Fourteen percent (103/740) of people in the study were cirrhotic at study entry, and 52% (53/103) of them achieved a viral cure. Adverse events were generally similar between treatment arms and consistent with the safety profile described in the U.S. prescribing information for telaprevir and included rash, anemia and pruritis (itchiness).[Buti et al. 2012] The effectiveness of telaprevir 1125 mg Q12h was assessed in 118 treatment naïve and previously treated patients with genotype 1 chronic HCV infection. Most of these patients had compensated cirrhosis with a non-favorable IL28B genotype allele. Of 103 evaluable patients, 56.3% were treatment naïve/relapsers and 43.6% were treatment failures. In the treatment-naïve/relapser group, 94.8% were HCV RNA undetectable or <43 IU/mL at week 4 and undetectable at week 12 (eRVR=32/55). 30 of these subjects have reached week 24 and remain undetectable; 10 subjects have reached 12 weeks of follow-up and all are SVR12. In the treatment failure group, 51.1% were HCV RNA undetectable or <43 IU/mL and undetectable at week 12; 19 have reached week 24 and remain undetectable. 6 subjects in this group who stopped therapy early have achieved SVR12. 17/22 patients who failed therapy had F3/4. These interim results suggest that q12h dosing was associated with similar rates of RVR, eRVR and SVR as would be expected with q8h dosing.[Pockros et al. 2012] <u>Treatment Duration</u> The recommended duration of treatment with telaprevir is 12 weeks in combination with peginterferon alfa and ribavirin:

	<table><tr><th colspan="4">Treatment-Naïve and Prior Relapse Patients</th></tr><tr><th>HCV-RNA</th><th>Triple Therapy (telaprevir, peginterferon alfa and ribavirin)</th><th>Dual Therapy (peginterferon alfa and ribavirin)</th><th>Total Treatment Duration</th></tr><tr><td>Undetectable at Weeks 4 and 12</td><td>First 12 weeks</td><td>Additional 12 weeks</td><td>24 weeks</td></tr><tr><td>Detectable (1000 IU/mL or less) at Weeks 4 and/or 12</td><td>First 12 weeks</td><td>Additional 36 weeks</td><td>48 weeks</td></tr><tr><th colspan="4">Prior Partial and Null Responder Patients</th></tr><tr><td></td><td>Triple Therapy (telaprevir, peginterferon alfa and ribavirin)</td><td>Dual Therapy (peginterferon alfa and ribavirin)</td><td>Total Treatment Duration</td></tr><tr><td>All Patients</td><td>First 12 weeks</td><td>Additional 36 weeks</td><td>48 weeks</td></tr></table> <u>Treatment Failures</u> Patients with inadequate viral response are unlikely to achieve SVR, and may develop treatment emergent resistance substitutions. Discontinuation of therapy is recommended in all patients with (1) HCV-RNA levels of greater than or equal to 1000 IU/mL at Treatment Week 4 or 12; or (2) confirmed detectable HCV-RNA levels at Treatment Week 24. <table><tr><th>HCV-RNA</th><th>Action</th></tr><tr><td>Week 4 or Week 12: Greater than 1000 IU/mL</td><td>Discontinue telaprevir and peginterferon alfa and ribavirin</td></tr><tr><td>Week 24: Detectable</td><td>Discontinue peginterferon alfa and ribavirin</td></tr></table> <u>Missed Doses</u> If a dose is missed within 4 hours of the scheduled time, it should be taken as soon as possible with food. If more than 4 hours has passed since the dose should have been taken, this dose should be skipped, and the usual dosing schedule resumed.
Dosing – Pediatric	The use of telaprevir in pediatric patients is not recommended. No clinical data are available regarding the use of telaprevir in children and adolescents younger than 18 years of age.
Adjust in Liver Dysfunction	Dose modification of telaprevir is not required when administered to subjects with mild hepatic impairment (Child-Pugh A, score 5- 6). Telaprevir is not recommended for use in patients with moderate or severe hepatic impairment (Child-Pugh B or C, score ≥ 7) or decompensated liver disease. • Steady-state exposure to telaprevir was reduced by 15% in HCV-negative subjects with mild hepatic impairment (Child-Pugh Class A) compared to healthy subjects. • Steady-state exposure to telaprevir was reduced by 46% in HCV-negative subjects with moderate hepatic impairment (Child-Pugh Class B) compared to healthy subjects. No pharmacokinetic or safety data are available regarding the use of telaprevir in HCV-infected patients with moderate or severe hepatic impairment (Child-Pugh B or C, score ≥ 7) or decompensated liver disease. • The pharmacokinetics of telaprevir In HCV-negative subjects with severe

	hepatic impairment (Child- Pugh Class C) were not studied. • The use of telaprevir in organ transplant patients is not recommended because the safety and efficacy of telaprevir in this patient population has not been established.
Adjust in Renal Failure/ Dialysis	No dose adjustment is necessary for telaprevir in HCV-infected patients with mild, moderate or severe renal impairment. • After administration of a single dose of 750 mg to HCV-negative subjects with severe renal impairment (CrCl < 30 mL/min), the mean telaprevir Cmax and AUC were increased by 10% and 21%, respectively, compared to healthy subjects. • The safety and efficacy of telaprevir combination therapy has not been established in HCV-infected subjects with a CrCl ≤ 50 mL/min • Telaprevir has not been studied in patients with end-stage renal disease (ESRD) or on hemodialysis • It is not known whether telaprevir is dialyzable by peritoneal or hemodialysis.
Toxicity	<u>Common:</u> The most frequent adverse effects when used in combination with peginterferon alfa and ribavirin include: >10-20%: fatigue, pruritus, nausea, headache, influenza-like illness, rash, anemia, insomnia, diarrhea, vomiting, pyrexia, hemorrhoids, and proctalgia **WARNING: Serious Skin Reactions (Boxed Warning)** **Fatal and non-fatal serious skin reactions, including Stevens Johnson Syndrome (SJS), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), and Toxic Epidermal Necrolysis (TEN), have been reported in patients treated with telaprevir combination treatment. Fatal cases have been reported in patients with progressive rash and systemic symptoms who continued to receive telaprevir combination treatment after a serious skin reaction was identified.** **For serious skin reactions, including rash with systemic symptoms or a progressive severe rash, telaprevir, peginterferon alfa, and ribavirin must be discontinued immediately. Discontinuing other medications known to be associated with serious skin reactions should be considered. Patients should be promptly referred for urgent medical care.** • The presenting signs of DRESS may include rash, fever, facial edema, and evidence of internal organ involvement (e.g., hepatitis, nephritis). Eosinophilia may or may not be present. The presenting signs of SJS may include fever, target lesions, and mucosal erosions or ulcerations (e.g., conjunctivae, lips). **Telaprevir must not be restarted if discontinued due to rash (discontinuation of telaprevir combination treatment is not required for mild and moderate rash).** <u>Serious:</u> The most frequent serious adverse events were rash (see above Boxed Warning) anemia and rash • Anemia: In placebo-controlled Phase 2 and 3 clinical trials, the overall incidence and severity of anemia increased with telaprevir combination treatment compared to peginterferon alfa and ribavirin alone. Hemoglobin values of <100 g/L were observed in 33.7% of patients who received telaprevir combination treatment and in 13.6% of patients who received peginterferon

	alfa and ribavirin. Hemoglobin levels decrease sharply during the first 4 weeks of treatment, with lowest values reached at the end of telaprevir dosing. Hemoglobin values gradually improve after telaprevir dosing completion. Potential for QT Prolongation: A study conducted in healthy volunteers (n=41) showed a modest effect of telaprevir at a dose of 1875 mg q8h on the QTcF interval with a placebo-adjusted maximum mean increase of 8.0 msec (90% CI: 5.1-10.9). Exposure at this dose was comparable to the exposure in HCV-infected patients dosed at 750 mg telaprevir q8h plus peginterferon alfa and ribavirin. The potential clinical significance of these findings is uncertain. Use of telaprevir should be avoided in patients with congenital QT prolongation, or a family history of congenital QT prolongation or sudden death. Telaprevir should be used with caution in patients with a history of acquired QT prolongation; clinically relevant bradycardia (persistent heart rate <50 bpm); a history of arrhythmias (especially ventricular arrhythmias or atrial fibrillation); a history of heart failure with reduced left-ventricular ejection fraction; myocardial ischemia or infarction; cardiomyopathy; conduction system disease; or a requirement for drugs known to prolong the QT interval without CYP3A4 involvement by telaprevir (e.g., methadone).
Pregnancy & Lactation	U.S. FDA's Pregnancy Category: Category B (All Trimesters) Because telaprevir is to be taken in combination with peginterferon alfa and ribavirin, the warnings applicable to those drugs are also applicable to combination treatment. Refer also to the prescribing information for peginterferon alfa and ribavirin. Ribavirin may cause birth defects and/or death of the exposed fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients—both during treatment and for 6 months after the completion of all treatment. Telaprevir combination treatment should not be initiated unless a female patient has a negative pregnancy test immediately prior to initiation of treatment. Telaprevir treatment alone in mice and rats did not result in harm to the fetus. Telaprevir treatment alone had effects on fertility parameters in rats. These effects are likely associated with testicular toxicity in male rats but contributions of the female cannot be ruled out. It is not known whether telaprevir is excreted in human breast milk. When administered to lactating rats, levels of telaprevir were higher in milk compared to those observed in plasma. Because of the potential for adverse reactions in nursing infants, nursing must be discontinued prior to initiation of treatment.
Drug Interactions ***** See separate Drug Interaction Table.	Telaprevir is an inhibitor of CYP3A and P-glycoprotein (P-gp). Co-administration of telaprevir with drugs that are primarily metabolized by CYP3A and/or substrates for P-gp may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and adverse reactions. Telaprevir inhibits renal drug transporters OCT2, MATE1, OATP1B1 and OATP1B3.(Kunze et al. 2012). Telaprevir is contraindicated when combined with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events (narrow therapeutic index). Telaprevir is also contraindicated when combined with drugs that strongly induce CYP3A and thus may lead to lower exposure and loss of efficacy of telaprevir: • Aldosterone antagonists (eplerenone) due to potential for hyperkalemia • Alpha 1-adrenoreceptor antagonists (alfuzosin) due to potential for hypotension or cardiac arrhythmia • Antiarrhythmics (quinidine, flecainide, propafenone, amiodarone) due to

	potential for serious and/or life-threatening reactions such as cardiac arrhythmias • Antimycobacterials (rifampin) because it reduces telaprevir plasma concentrations significantly • Ergot Derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine) due to potential for acute ergot toxicity characterized by peripheral vasospasm or ischemia • St. John's Wort because it reduces telaprevir plasma concentrations • HMG-CoA Reductase Inhibitors (atorvastatin, lovastatin, simvastatin) due to potential for myopathy including rhabdomyolysis • Neuroleptics (pimozide) due to potential for serious and/or life-threatening adverse reactions such as cardiac arrhythmias secondary to increases in plasma concentrations of antiarrhythmics • PDE-5 Inhibitors due to potential for hypotension and/or cardiac arrhythmia (sildenafil: only when used for the treatment of pulmonary arterial hypertension) • Sedatives/Hypnotics (triazolam) due to potential for increased sedation or respiratory depression • Triptans (eletriptan) due to potential for coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation. The potential for prolongation of the QT/QTc interval may be increased if telaprevir is administered in the presence of CYP3A4 inhibitors, such as ritonavir, ketoconazole, and erythromycin. Caution should be observed if these drugs are to be used concomitantly with telaprevir. Caution should also be observed when using telaprevir with drugs that can disrupt electrolyte levels. <u>Other significant DIs:</u> • Anticoagulants (warfarin) → concentrations of warfarin may be altered when coadministered with telaprevir. Monitor the INR • Immunosuppressants (cyclosporine, tacrolimus, sirolimus) because concentrations of immunosuppressants may be increased with telaprevir • Long Acting Beta-Adrenoceptor Agonists (salmeterol): Concentrations of salmeterol may be increased with telaprevir. Concurrent administration of salmeterol and telaprevir is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia. <u>Antiretroviral Interactions:</u> Telaprevir concentrations are reduced by ritonavir-boosted fosamprenavir, darunavir, lopinavir, and, to a lesser extent, atazanavir. Efavirenz also reduces blood concentrations of telaprevir, an effect that can, in part, be offset by using a higher telaprevir dose (1125 mg q8h). Telaprevir use significantly reduces concentrations of darunavir and fosamprenavir. • Avoid coadministration with DRV/r, FPV/r, LPV/r • ATV/r is considered compatible with telaprevir • EFV is considered compatible with telaprevir but with a dose increase of telaprevir (see dosing recommendations in section above) • TDF is considered compatible with telaprevir • RAL is considered compatible with telaprevir
Baseline Assessment	The following laboratory evaluations (complete blood count with white blood cell differential counts, electrolytes, serum creatinine, liver function tests, TSH, uric acid, serum cholesterol and LDL) must be conducted in all patients prior to

	initiating telaprevir combination treatment. These are recommended baseline values for initiation of telaprevir combination treatment: - Hemoglobin: ≥120 g/L (females); ≥130 g/L (males) - Platelet count ≥ 90,000/mm^3 - Absolute neutrophil counts ≥1500/mm^3 - Adequately controlled thyroid function (TSH) - Calculated creatinine clearance ≥50 mL/min - Potassium ≥3.5 mmol/L
Routine Labs	- Hemoglobin at least every 4 weeks - Chemistry (electrolytes, serum creatinine, uric acid, hepatic enzymes, bilirubin, TSH, serum cholesterol, and LDL) as frequently as the hematology evaluations or as clinically indicated - Hematology (incl. white cell differential count) at week 2, 4, 8, and 12 or as clinically appropriate thereafter
Dosage Forms	375 mg purple film-coated capsule-shaped tablets. Each tablet is debossed with the characters “V 375” on one side.
Storage	Store at 25ºC; excursions permitted to 15-30ºC.

References:

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