

Brand Name: Incivek™

Generic Name: telaprevir

Manufacturer¹: Vertex Pharmaceuticals, Inc.

Drug Class^{1,2,3,4,5}: Antiviral, Protease Inhibitor

Uses:

Labeled Uses^{1,2,3,4,5}: Treatment of genotype 1 chronic hepatitis C in combination with peginterferon alfa and ribavirin) in adult patients with compensated liver disease, including cirrhosis, who are treatment naive or who have been treated previously with interferon-based treatment, including null or partial responders, and treatment relapsers.

Mechanism of Action^{1,2,3,4,5}

Telaprevir reversibly binds to nonstructural protein 3/4A (NS 3/4A) serine protease, which is responsible for proteolytic cleavage of the hepatitis C virus (HCV) genotype 1 encoded polyprotein into the mature proteins NS4A, NS4B, NS5A and NS5B proteins, which are essential for viral replication. The binding of telaprevir inhibits HCV replication within host cells.

Pharmacokinetics^{1,2,3,4,5}:

Absorption:

T _{max}	4-5 hours
V _d	252 L
t _{1/2}	4-5hrs (single dose); 9-11 hrs (steady state)
Clearance	32.4 L/hr
Protein binding	59%-76% (% albumin decreases with increasing serum concentrations)
Bioavailability	Data not available

Metabolism: Primarily hepatic metabolism by hydrolysis, oxidation, reduction, and CYP3A4 to a less active (~30x) and inactive metabolites.

Elimination: Primarily through the feces (82%), but also exhaled air (9%) and urine (1%).

Efficacy:

Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, et. al. Telaprevir for retreatment of HCV infection. N Engl J Med. 2011 Jun 23;364(25):2417-28.

Study Design: Randomized, double-blind, placebo-controlled, phase 3 study

Description of Study: *Methods:* In this study, 622 patients were included at study centers in 17 countries including Europe, South American, North America, Israel, and Australia. Patients who met study criteria were randomly placed into one of three groups in a 2:2:1 ratio: T12PR48 group (266) initially received telaprevir for 12 weeks as well as peginterferon plus ribavirin for 48 weeks total; the lead-in T12PR48 group (264) received 4 weeks of peginterferon plus ribavirin, then 12 weeks of telaprevir was added to the peginterferon plus ribavirin with 48 weeks total treatment; PR48, or the control group (132), received only peginterferon plus ribavirin for 48 weeks. HCV RNA levels were measured at both screening and baseline, on day 3, and during weeks 1, 2, 4, 5, 6, 8, 10, 12, 14, 16, 20, 24, 26, and 48 of the treatment. Adverse events were assessed throughout the treatment period and during safety follow up assessments at 4 weeks after administration of the last dose of drug. Analysis in the study was based on intent-to-treat of all patients who were randomized and received at least one dose of a study drug.

Outcome Results: Patients in both telaprevir groups had a higher sustained virologic response compared to the control group: those who had a previous relapse (83% in T12PR48, 88% in the lead-in T12PR48 group, and 24% in the control group) and those who did not have a prior response (41%, 41%, and 9 %, respectively) with $p < 0.001$ for all comparisons. A similar rate of sustained virology response was seen in each telaprevir group for patients who had a relapse or no response or a partial response previously. For the combined subgroup of patients who had either relapse or partial response the rate of sustained virologic response was significantly higher when compared to the control groups (78% compared to 21%, $p < 0.001$). Sustained virologic response for all groups were 64% in the T12PR48 group, 66% in the lean-in T12PR48 group, and 17% in the control group ($p < 0.001$). Relapse rates were lower in the telaprevir treatment groups compared to control in patients who had previous relapse, no response, or partial response to prior therapy. In the virologic failure and relapse groups, 73% were found to have emergence of variant strains with decreased sensitivity to telaprevir. However, 58% of patients who developed these variants were no longer detected at the end of the study. The most frequent adverse events reported in both telaprevir groups were fatigue, pruritus, rash, nausea, influenza-like illness, anemia and diarrhea, which occurred in more than 25% of patients. More serious adverse events like anemia, neutropenia, and leucopenia were reported more in the telaprevir groups (37%) compared to the control group (22%). In both telaprevir groups 4% of patients discontinued telaprevir while 1% of patients discontinued all drugs due to rash. However, no patients in the control group discontinued treatment because of rash.

Limitations: The study was funded by Vertex Pharmaceuticals, which manufactures telaprevir creating a conflict of interest. The authors never address compliance of medications and if this was taken into consideration with study groups. They fail to mention other medications the patients were taking. Authors mention interleukin-28B, which has been shown to predict response of peginterferon and ribavirin for HCV patients. Patients were not screened and therefore randomization did not account for this, which could have affected the results of the primary outcome.

Conclusion: The study showed that telaprevir combined with peginterferon and ribavirin significantly enhanced the rates of sustained virologic response for HCV infected patients

who had received treatment previously compared to peginterferon and ribavirin alone. These rates differed depending on the patients' previous response. Virologic failure was lower in patients who had a previous relapse or partial response compared to patients who had no response to prior therapy. Adverse effects in this study were consistent with the safety in all phase 2 and 3 trials.

Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med. 2011 Jun 23;364(25):2405-16.

Study Design: International, randomized, double blind, placebo-controlled, phase 3 study

Description of Study: *Methods:* In this study 1095 patients were stratified by HCV genotype 1 subtype (a, b, or unknown) and their baseline viral load (<800,000 or > 800,000 IU/mL) and randomized to one of three study groups: The T12PR group received telaprevir with peginterferon alfa-2a and ribavirin for 12 weeks, then peginterferon and ribavirin alone for 12 weeks if HCV RNA levels were undetectable at weeks 4 and 12, or they received combo therapy for 36 weeks if HCV RNA was detectable at either time point; the T8PR group received telaprevir with peginterferon and ribavirin for 8 weeks and then placebo with peginterferon and ribavirin for 4 weeks, then 12 or 36 weeks of peginterferon and ribavirin according to the same HCV RNA criteria stated above; and the PR group who received placebo and peginterferon and ribavirin for 12 weeks and then 36 weeks of peginterferon and ribavirin. A stopping rule was enforced for patients who did not show an adequate response. Efficacy assessment was done by monitoring of HCV RNA, which were done at baseline and weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 28, 36, 40, and 48 as well as follow-up visits at 4 weeks and weeks 60 and 72. At these same times chemical and hematologic assessments were performed as well as 4 weeks after the last dose of study drug was given. Adverse event data was collected at each treatment visit and safety follow-up assessment. Sample size of 350 patients was estimated to have a 92% power to show a difference among the treatment groups. Analysis of efficacy and safety in the study was based on intent-to-treat of all patients who were randomized and received at least one dose of a study drug. *Outcome Results:* There was a higher proportion in the two groups receiving telaprevir of sustained virologic response compared to the control group. There were 75% in the T12PR group and 69% in the T8PR group, compared to 44% in the PR group ($p < 0.001$). At 72 weeks there were 73% of pts in the T12PR group, 67% in the T8PR group, and 44% in the PR control group that had undetectable HCV RNA ($p < 0.001$ for each comparison with PR group). In each respective group, 68%, 66%, and 9% had undetectable HCV RNA at week 4 while 58%, 57%, and 8% had undetectable HCV RNA at weeks 4 and 12. Some of the most common adverse effects experienced at greater than 25% were fatigue, pyrexia nausea, diarrhea, pruritus, rash, headache, anemia, and insomnia. The most common adverse effects leading to discontinuation were rash and anemia.

Limitations: The study protocol was designed in collaboration by one of the authors and Vertex Pharmaceuticals, which is the manufacturer of telaprevir. One of the employees of the sponsor also assisted in revisions of the drafts of the manuscript.

Conclusion: The results of the study show that in patients with HCV genotype 1 infection there is a significant increase in the rate of sustained virologic response in patients who take a combination of telaprevir with peginterferon and ribavirin for 8 to 12 weeks followed by 24 to 48 weeks of peginterferon and ribavirin. Also, more than half of the patients receiving telaprevir had undetectable HCV RNA at weeks 4 and 12 indicating an extended rapid virologic response. Relapse occurred rarely in these patient populations after 24 weeks of treatment. Telaprevir combined with peginterferon and ribavirin is associated with a higher incidence of adverse effects like rash, GI disorders, and anemia than dual therapy alone.

Sherman KE, Flamm SL, Afdhal NH, Nelson DR, Sulkowski MS, Everson GT, et. al. Response-guided telaprevir combination treatment for hepatitis C virus infection. N Engl J Med. 2011 Sep 15;365(11):1014-24.

Study Design: Multinational, open-labeled, randomized, phase 3, noninferiority study in which results were double-blinded until week 24 of the study

Description of Study: *Methods:* In this study 540 patients were enrolled from 74 sites in Belgium, the Netherlands, and the US (including Puerto Rico). All patients received triple combination therapy with telaprevir, peginterferon, and ribavirin for 12 weeks. Following that, patients were divided into groups based on response to the combination therapy. Patients who had undetectable HCV RNA levels at 4 and 12 weeks (extended rapid virologic response) were randomly assigned in a 1:1 ratio after week 20 to stop treatment (group T12PR24) or continue with only peginterferon and ribavirin through 48 weeks (group T12PR48). Patients who did not have an extended rapid virologic response were assigned to the T12PR48 group. After treatment patients were assessed for sustained virologic response at follow up, which was T12PR24 group was 48 weeks versus 24 weeks for the T12PR48 group. All patients that completed the follow-up period were evaluated for response to treatment. The sample size of 157 patients per study group was found to have an 80% power to exclude the noninferiority of the T12PR24 group compared to the T12PR48 group if the examined rate of sustained virologic response was 90%. This sample size allowed for a noninferiority comparison between these groups with a noninferiority margin of -10.5%. *Outcome Results:* Concerning the patients who were randomly assigned to one of the 2 groups, a sustained virologic response was seen in 92% of patients in the T12PR24 group compared to 88% in the T12PR48 groups (95% CI -2 to 11) indicating the study treatment of 24 weeks was noninferior to the control group of treatment for 48 weeks. At 72 weeks after beginning treatment the HCV RNA level was undetectable in 70% of all patients. There was an absolute difference of -0.5 percentage points between the T12PR24 group and the T12PR48 group in patients with an extended rapid virologic response. HCV RNA levels at baseline were not indicative of sustained virologic response as 90% of this patient subpopulation showed extended rapid virologic response. Concerning adverse effects, in the overall study population during the

treatment phase, 9% of patients had a serious adverse effect. The most common was anemia, found in 2% of all patients. Other common adverse events experienced were fatigue (68%), pruritus (51%), nausea (47%), anemia (39%), headache (38%), rash (37%), insomnia (34%), diarrhea (30%), and influenza-like illness (26%).

Limitations: The study was funded by Tribotec and Vertex Pharmaceuticals, the manufacturer of telaprevir. The principle investigator together with the sponsor developed the study design and protocol and a Vertex Pharmaceuticals employee supplied medical writing, editorial, and coordination services.

Conclusion: In this study patients who had an extended rapid virologic response in the 24 week treatment of dual peginterferon and ribavirin after a 12 week treatment of telaprevir was noninferior to a 48 week treatment of dual therapy following telaprevir for 12 weeks in those patients infected with HCV genotype 1 that have not received previous treatment. Development of resistant strains was associated with virologic failure and follow up showed that 55% of patients originally resistant did not maintain those resistant strains. Rates of adverse effects and discontinuation of study drugs were similar compared to other clinical trials including telaprevir in combination with peginterferon and ribavirin therapy. Also, the rate of anemia in this study was 39% and was comparable to the ADVANCE study (37%) which looked at 12 week treatment with telaprevir.

Contraindications^{1,2,3,4}:

Combination Therapy: Contraindications to peginterferon and ribavirin also apply to telaprevir due to combination treatment.

Pregnancy Women who are or may become pregnant should not take telaprevir due to its use in combination with ribavirin. Ribavirin may cause fetal harm and death when administered during pregnancy. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug treatment, the patient should be apprised of the potential hazard to a fetus. Use should also be avoided in men whose female partners are pregnant.

CYP interactions: Telaprevir is an inhibitor of CYP3A4. When taken in combination with drugs which are highly dependent on CYP3A for clearance, this may lead to elevated drug plasma concentrations that can be associated with serious and/or life-threatening events (e.g. narrow therapeutic index). Similarly, when used in combination with drugs that strongly induce CYP3A may lead to lower exposure and loss of efficacy of telaprevir.

Precautions^{1,2,3,4}:

Serious Skin Reactions: Reactions such as Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) and Stevens-Johnson syndrome. These were reported in less than 1% of patients. These reported reactions required hospitalization, however all patients recovered. Immediately discontinue telaprevir, peginterferon alfa, and ribavirin if serious skin rash occurs (rash, fever, facial edema, and evidence of internal organ involvement).

Rash: Rash has developed in 56% of patients. A severe rash (generalized or with vesicles or bullae or ulcerations other than SJS), has been reported in 4% of patients. Patients with a mild to moderate rash should be observed for worsening of rash or systemic involvement. If severe rash develops, discontinuation of telaprevir is recommended (may continue peginterferon and ribavirin). If there is no improvement within 7 days, consider discontinuation of peginterferon and ribavirin. Telaprevir dose reduction or re-initiation is not recommended. Treatment of rash with oral antihistamines and/or topical (not oral) corticosteroids may provide relief.

Anemia: There have been reports that when used with peginterferon and ribavirin, telaprevir further decreases in hemoglobin concentrations. Hemoglobin values ≤ 10 g/dL were observed in 36% of subjects who received telaprevir combination treatment compared to 17% of subjects who received peginterferon and ribavirin. Obtain a baseline CBC and monitor in weeks 2, 4, 8, and 12. Management may require dose reduction of ribavirin or discontinuation of telaprevir (telaprevir dose reductions not recommended); if ribavirin is discontinued, telaprevir must also be discontinued and must not be restarted.

General: Telaprevir must not be administered as monotherapy and must only be prescribed with both peginterferon and ribavirin.

Hepatic Impairment: Not recommended for patients with moderate or severe hepatic impairment (Child-Pugh B or C, score of 7 or greater) or decompensated liver disease.

Pregnancy: Telaprevir must be used in combination with peginterferon and ribavirin and as such the contraindications/ warnings applicable to those drugs apply to combination therapy. Ribavirin may cause fetal birth defects and/or death. Avoid pregnancy in both female patients and also in female partners of male patients. Hormonal contraceptives may be continued, but may not be effective during treatment with telaprevir and for up to two weeks following cessation of therapy.

Lactation: Excretion in the breast milk is unknown and telaprevir's use in breast feeding is not recommended.

Adverse Effects^{1,2,3,4}:

Occurring in >10% of patients

Central nervous system:

Fatigue (56%)

Dermatologic:

Rash (56%)

Pruritus (47%)

Endocrine and Metabolic:

Hyperuricemia (73%) (<12.1 mg/dL: 66%; ≥ 12.1 mg/dL: 7%)

Gastrointestinal:

Nausea (39%)

Diarrhea (26%)

Vomiting (13%)

Hemorrhoids (12%)

Anorectal pain/discomfort (11%)

Hematologic:

Anemia (36%)

Lymphocytopenia (15%)

Hepatic:

Hyperbilirubinemia (41%) (<2.6 x ULN: 37%; ≥2.6 x ULN: 4%)

Occurring in >1% to <10% of patients:

Gastrointestinal:

Dysgeusia (10%)

Anal pruritus (6%)

Hematologic:

Neutropenia (12%)

Leukopenia (8%)

Thrombocytopenia (3%)

Drug Interactions^{1,2,3,4}:

Atazanavir: Atazanavir may decrease the serum concentration of Telaprevir, while telaprevir may increase the serum concentration of Atazanavir.

Bepridil [Off Market]: Telaprevir may increase plasma concentrations and enhance the adverse/toxic effect of Bepridil

Bosentan: Bosentan may decrease the serum concentration of Telaprevir through induction of CYP3A4. Telaprevir may increase the serum concentration of Bosentan through inhibition of CYP3A4.

Carbamazepine: May decrease the serum concentration of Telaprevir. Telaprevir may increase the serum concentration of Carbamazepine through CYP3A4 inhibition.

Clarithromycin: Both clarithromycin and telaprevir are inhibitors and substrates of CYP3A4 which can lead to increase in plasma concentrations of both.

Clozapine: Increased risk of QT prolongation.

Contraceptives (estrogens and progestins): Telaprevir may decrease the serum concentration. Hormonal contraceptives may be less effective during telaprevir therapy and for up to 2 weeks after discontinuation.

Corticosteroids: May decrease the serum concentration of Telaprevir. Telaprevir may increase the serum concentration of corticosteroids through CYP3A4 inhibition.

Cyclosporine: Telaprevir is a CYP3A4 inhibitor and p-glycoprotein inhibitor which may lead to increased plasma concentrations of cyclosporine.

CYP3A4 Inducers: these may increase the metabolism of substrates and decrease telaprevir plasma concentrations. Examples of inducers include:

Fosamprenavir, fosphenytoin, phenobarbital, phenytoin, rifabutin, rifampin, and St Johns Wort

CYP3A4 Inhibitors: These may decrease metabolism of substrates and increase telaprevir plasma concentrations. Examples of inhibitors include:

Deferasirox, itraconazole, ketoconazole, posaconazole, telithromycin, and voriconazole

CYP3A4 Substrates: Telaprevir may decrease the metabolism and increase plasma concentrations. Examples of substrates include:

Alfuzosin, almotriptan, alosetron, alprazolam, amiodarone, amlodipine, aripiprazole, atorvastatin, avanafil, axitinib, bortezomib, brentuximab vedotin, brinzolamide, budesonide (nasal, systemic, or oral inhalation), carbamazepine, ciclesonide, cisapride, clarithromycin, clozapine, colchicine, conivaptan, corticosteroids (systemic and oral inhaled), crizotinib, cyclosporine, dasatinib, desipramine, dienogest, dronedarone, dutasteride, dihydroergotamine, domperidone, eplerenone, ergot derivatives, erythromycin, everolimus, fentanyl, fesoterodine, fluticasone (nasal and oral inhalation), fosamprenavir, fosphenytoin, Guanfacine, halofantrine, ifosfamide, iloperidone, ivacaftor, ixabepilone, lapatinib, lidocaine, lovastatin, lumefantrine, lurasidone, maraviroc, methylprednisolone, midazolam, mifepristone, nilotinib, nisoldipine, paricalcitol, pazopanib, pimecrolimus, pimozide, prednisone, propafenone, ranolazine, red yeast rice, rifabutin, rivaroxaban, romidepsin, ruxolitinib, salmeterol, saxagliptin, sildenafil, silodosin, simvastatin, sorafenib, sirolimus, tacrolimus, tadalafil, tamsulosin, telithromycin, ticagrelor, tolterodine, tolvaptan, toremifene, traZODone, triazolam, vardenafil, vemurafenib, vilazodone, zuclopenthixol, and zolpidem

Darunavir: Decreased darunavir and telaprevir plasma concentrations and diminished therapeutic effect.

Desogestrel: Telaprevir may decrease contraceptive effectiveness.

Digoxin: Telaprevir may increase the serum concentration of Digoxin. Mechanism is unclear, but may be due to inhibition of p-glycoprotein.

Diltiazem: Increased diltiazem plasma concentrations. Diltiazem and telaprevir have not been specifically studied together, however coadministration of amlodipine, another calcium channel blocker, and telaprevir led to significantly increased amlodipine plasma concentrations in a pharmacokinetic study.

Drospirenone: Telaprevir may decrease contraceptive effectiveness.

Efavirenz: Efavirenz may decrease the serum concentration of Telaprevir. Telaprevir may decrease the serum concentration of Efavirenz.

Erythromycin: Erythromycin may increase the serum concentration of Telaprevir through CYP3A4 inhibition. Telaprevir may increase the serum concentration of Erythromycin through CYP3A4 inhibition.

Escitalopram: Telaprevir may decrease the serum concentration of Escitalopram.

Estradiol: Telaprevir may decrease contraceptive effectiveness.

Felodipine: Increased felodipine plasma concentrations. Felodipine and telaprevir have not been specifically studied together, however co-administration of amlodipine, another

calcium channel blocker, and telaprevir led to significantly increased amlodipine plasma concentrations in a pharmacokinetic study.

Flecainide: Telaprevir may enhance the adverse/toxic effect of Flecainide.

Fosamprenavir: Fosamprenavir may decrease the serum concentration of Telaprevir through induction of CYP3A4. Telaprevir may increase the serum concentration of Fosamprenavir through CYP3A4 inhibition.

Fosphenytoin: fosphenytoin is an inducer of CYP3A4 which can lead to increased telaprevir metabolism and decreased serum concentrations. Telaprevir can increase fosphenytoin concentrations through CYP3A4 inhibition.

Iloperidone: CYP3A4 Inhibitors may increase serum concentrations of iloperidone and its active metabolites. Specifically, concentrations of the metabolites P88 and P95 may be increased.

Itraconazole: Both itraconazole and telaprevir are CYP3A4 inhibitors which may increase the serum concentration of both drugs.

Ketoconazole: Ketoconazole may increase the serum concentration of Telaprevir through inhibition of CYP3A4. Telaprevir may increase the serum concentration of Ketoconazole through inhibition of CYP3A4.

Lidocaine (systemic): Telaprevir may enhance the adverse/toxic effect of Lidocaine. Mechanism not clear, but CYP3A4 inhibition by telaprevir is suspected.

Lopinavir: May decrease the serum concentration of Telaprevir. Mechanism unclear.

Methadone: Telaprevir inhibits CYP3A4 of which methadone is a substrate. This may decrease the serum concentration of Methadone.

Nicardipine: Increased nicardipine plasma concentrations. Nicardipine and telaprevir have not been specifically studied together, however co-administration of amlodipine, another calcium channel blocker, and telaprevir led to significantly increased amlodipine plasma concentrations in a pharmacokinetic study.

Nifedipine: Increased nifedipine plasma concentrations. Nifedipine and telaprevir have not been specifically studied together, however co-administration of amlodipine, another calcium channel blocker, and telaprevir led to significantly increased amlodipine plasma concentrations in a pharmacokinetic study.

P-glycoprotein/ABCB1 Inducers: May decrease the serum concentration of P-glycoprotein/ABCB1 Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.).

P-glycoprotein/ABCB1 Inhibitors: May increase the serum concentration of P-glycoprotein/ABCB1 Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). Some examples of inhibitors include:

Telaprevir and quinidine

P-glycoprotein/ABCB1 Substrates: P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of P-glycoprotein/ABCB1 Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). Examples include:

Colchicine, cyclosporine, dabigatran etexilate, everolimus, prucalopride, quinidine, rivaroxaban, silodosin, and topotecan

Phenobarbital: Phenobarbital may decrease the serum concentration of Telaprevir through induction of CYP3A4. Telaprevir may decrease the serum concentration of phenobarbital. Telaprevir may increase the serum concentration of phenobarbital.

Phenytoin: phenytoin may decrease the serum concentration of Telaprevir through induction of CYP3A4. Telaprevir may decrease the serum concentration of Phenytoin. Telaprevir may increase the serum concentration of Phenytoin.

Prasugrel: Telaprevir is a CYP3A4 Inhibitors and may decrease serum concentrations of the active metabolites of Prasugrel.

Rifabutin: rifabutin is both a substrate and inducer of CYP3A4. This may decrease the serum concentration of Telaprevir. Telaprevir may increase the serum concentration of Rifabutin.

Rifampin: Rifampin may decrease the serum concentration of Telaprevir.

Ritonavir: Ritonavir may either increase or decrease the serum concentration of Telaprevir.

Sirolimus: Telaprevir may increase the serum concentration of Sirolimus through CYP3A4 and p-glycoprotein inhibition.

Telithromycin: Both telaprevir and telithromycin are inhibitors and substrates of 3A4 and may increase the serum concentrations of each other.

Tenofovir: Tenofovir is a p-glycoprotein inducer and may decrease telaprevir plasma concentrations. Also, through an unknown mechanism, telaprevir can severely increase tenofovir plasma concentrations.

Tocilizumab: May decrease the serum concentration of CYP3A4 Substrates.

Warfarin: Telaprevir may increase or decrease the serum concentration of Warfarin.

Dosing/Administration^{1,2,3,4,5}:

Adult Dosing

Normal dose: 750mg (two 375mg tablets) by mouth 3 times daily (7 – 9 hours apart). Administer with food not low in fat (~20g of fat).

Recommended duration of treatment: Administer for 12 weeks with the combination of peginterferon and ribavirin. Monitor HCV-RNA levels at 4 and 12 weeks to determine the total duration needed and assess efficacy.

Pediatrics

Safety, efficacy, and pharmacokinetic profile of telaprevir has not been established in pediatric patients.

Elderly

Use caution in patients >65 as this age group has not sufficiently been tested. It's recommended that administration and monitoring of therapy with telaprevir included increased monitoring of hepatic function and of concomitant disease states and drug therapies.

Renal impairment

No dose adjustment required in patients with mild, moderate, or severe renal impairment. Not studied in patients with CrCl \leq 50 mL per min, end-stage renal disease (ESRD), or on hemodialysis

Hepatic impairment

No dosage adjustment required in patients with mild hepatic impairment (Child-Pugh A score, 5 – 6). Not recommended in patients with moderate to severe hepatic impairment (Child-Pugh B or C, score greater than or equal to 7) as no pharmacokinetic or safety data are available.

Use in special circumstances^{1,2,3,4,5}:

Pregnancy: *See Precautions*

Lactation: *See Precautions*

Co-Infection: The safety and efficacy of INCIVEK have not been established in patients co-infected with HCV/HIV or HCV/HBV

Solid Organ Transplant: The safety and efficacy has not been established in solid organ transplant patients

Overdosage¹: The highest documented dose administered is 1875 mg every 8 hours for 4 days in healthy patients with telaprevir alone. Common adverse events were more frequently experienced compared to the 750 mg q8h regimen. These include: nausea, headache, diarrhea, decreased appetite, dysgeusia, and vomiting. No specific antidote is available for treatment of overdose, therefore treatment consists of supportive care measures. It is unknown if telaprevir is dialyzable by peritoneal or hemodialysis.

Conclusion:

Telaprevir is efficacious when combined with peginterferon and ribavirin for the treatment of HCV genotype 1 infection. It demonstrated clinically significant efficacy when combined in traditional therapy of increase rate of undetectable HCV RNA levels and a sustained virologic response. Telaprevir is associated with an increased risk of more severe side effects than those seen with peginterferon and ribavirin alone. In conclusion, telaprevir used in conjunction with current therapy of peginterferon and ribavirin is clinically useful in the treatment of HCV genotype 1 in patients regardless of viral load, presence of fibrosis or cirrhosis, and previous response to dual therapy alone.

Recommended References:

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