PRODUCT MONOGRAPH

PrINCIVEK®

Telaprevir Tablets

375 mg

Antiviral Agent

Manufactured by:
Vertex Pharmaceuticals Incorporated

Distributed by:
Vertex Pharmaceuticals (Canada) Incorporated
275 Armand-Frappier Boulevard
Laval, Quebec
H7V 4A7

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PrINCIVEK®

Telaprevir tablets
375 mg

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	tablet 375 mg	None *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

INCIVEK (telaprevir), in combination with peginterferon alfa and ribavirin, is indicated for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease, including cirrhosis, who are treatment naïve or who have previously been treated with interferon-based treatment, including prior null responders, partial responders, and relapsers (see **CLINICAL TRIALS** for definitions of these terms).

The following points should be considered when initiating treatment with INCIVEK:

- INCIVEK **must not be administered as monotherapy** and must only be prescribed with both peginterferon alfa and ribavirin (see **WARNINGS AND PRECAUTIONS)**.

- INCIVEK efficacy has not been established for patients who have previously failed therapy with a treatment regimen that includes INCIVEK or other HCV NS3·4A protease inhibitors (see **WARNINGS AND PRECAUTIONS**).

- A high proportion of previous null responders (particularly those with cirrhosis) did not achieve a Sustained Virologic Response (SVR) and had telaprevir resistance-associated substitutions emerge on treatment with INCIVEK combination treatment (see **CLINICAL TRIALS**).

Geriatrics (≥ 65 years of age):
Clinical studies of INCIVEK did not include sufficient numbers of subjects aged 65 and over to

determine whether they respond differently from younger subjects. In general, caution should be exercised when administering INCIVEK in elderly patients, reflecting the greater frequency of anemia, decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy (see **WARNINGS AND PRECAUTIONS**).

Pediatrics (< 18 years of age):
The use of INCIVEK in pediatric patients is not recommended. No clinical data are available regarding the use of INCIVEK in children and adolescents younger than 18 years of age (see **WARNINGS AND PRECAUTIONS**).

CONTRAINDICATIONS

Contraindications to peginterferon alfa and ribavirin also apply to INCIVEK combination treatment. Refer also to the prescribing information for peginterferon alfa and ribavirin.

INCIVEK combination treatment is contraindicated in women who are pregnant or men whose female partners are pregnant (see **WARNINGS AND PRECAUTIONS, Pregnancy** and **Special Populations, Pregnant Women**).

Patients who are hypersensitive to telaprevir or to any ingredient in the formulation or component of the container. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING**.

INCIVEK is a strong inhibitor of CYP3A. INCIVEK 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) (Table 1). INCIVEK is also contraindicated when combined with drugs that strongly induce CYP3A and thus may lead to lower exposure and loss of efficacy of INCIVEK (see **DRUG INTERACTIONS** and **DETAILED PHARMACOLOGY**).

Table 1 - Drugs that are Contraindicated with INCIVEK

Drug Class	Drugs within Class that are Contraindicated with INCIVEK	Clinical Comments
Aldosterone antagonist	Eplerenone	Potential for hyperkalemia
Alpha 1-adrenoreceptor antagonist	Alfuzosin	Potential for hypotension or cardiac arrhythmia
Antiarrhythmics Class I Class III	 Quinidine, flecainide, propafenone Amiodarone	Potential for serious and/or life-threatening adverse reactions such as cardiac arrhythmias
Anticonvulsants	Carbamazepine, phenobarbital, phenytoin	Potential for lower exposure and loss of efficacy of telaprevir

Drug Class	Drugs within Class that are Contraindicated with INCIVEK	Clinical Comments
Antihistamines	Astemizole*, terfenadine*	Potential for serious and/or life-threatening adverse reactions such as cardiac arrhythmias
Antimycobacterials	Rifampin	Rifampin reduces telaprevir plasma concentrations significantly.
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Potential for acute ergot toxicity characterized by peripheral vasospasm or ischemia
GI motility agent	Cisapride*	Potential for serious cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, torsade de pointes, and QT prolongation.
Herbal products	St. John's Wort (*Hypericum perforatum*)	Plasma concentrations of telaprevir can be reduced by concomitant use of the herbal preparation St. John's Wort.
HMG-CoA reductase inhibitors	Lovastatin, simvastatin	Potential for myopathy including rhabdomyolysis
Neuroleptic	Pimozide	Potential for serious and/or life-threatening adverse reactions such as cardiac arrhythmias.
PDE5 inhibitor	Sildenafil [for treatment of pulmonary arterial hypertension], vardenafil	Potential for hypotension and/or cardiac arrhythmia
Sedatives/hypnotics	Orally administered midazolam*, triazolam	Prolonged or increased sedation or respiratory depression
Triptans	Eletriptan	Potential for coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation.

*Cisapride, astemizole and terfenadine are no longer marketed in Canada. Oral formulation of midazolam is not marketed in Canada.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
Serious Skin Reactions

Fatal and non-fatal serious skin reactions, including Toxic Epidermal Necrolysis (TEN), Stevens-Johnson Syndrome (SJS), and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have been reported in patients receiving INCIVEK combination treatment. Fatal cases have been reported in patients with progressive rash and systemic symptoms who continued to receive INCIVEK combination treatment after a serious skin reaction was identified.

For serious skin reactions, including rash with systemic symptoms or a progressive severe rash, INCIVEK, peginterferon alfa and ribavirin must be discontinued immediately. Discontinuing other medications known to be associated with serious skin reactions should also be considered. Patients should be promptly referred for urgent medical care.

Serious Skin Reactions/Rash

Fatal and non-fatal serious skin reactions, including Toxic Epidermal Necrolysis (TEN), Stevens-Johnson Syndrome (SJS), and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have been reported in patients receiving INCIVEK combination treatment. Fatal cases have been reported in patients with progressive rash and systemic symptoms who continued to receive INCIVEK combination treatment after a serious skin reaction was identified.

For serious skin reactions, including rash with systemic symptoms or a progressive severe rash, INCIVEK, peginterferon alfa and ribavirin must be discontinued immediately. Discontinuing other medications known to be associated with serious skin reactions should also be considered. Patients should be promptly referred for urgent medical care.

In clinical trials, serious skin reactions, including Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Stevens-Johnson Syndrome (SJS), were reported in less than 1% of subjects who received INCIVEK combination treatment compared to none who received peginterferon alfa and ribavirin alone. These serious skin reactions all required hospitalization and all patients recovered. 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).

TEN and Erythema Multiforme (EM) have been observed in post-marketing experience (see **ADVERSE DRUG REACTIONS, Post-Market Adverse Drug Reactions**).

Rash (all grades) occurred as an adverse drug reaction in the pooled placebo-controlled Phase 2 and 3 trials in 48.7% of subjects who received INCIVEK combination treatment compared to 28.0% of patients who received peginterferon alfa and ribavirin alone. Severe rash (involving more than 50% of body surface area) was reported in 4.8% of subjects who received INCIVEK combination treatment compared to 0.4% who received peginterferon alfa and ribavirin alone. The severe rash was pruritic and had a prominent eczematous component.

Patients with mild to moderate rashes should be followed for progression of rash. For additional information on mild to moderate rash, see **ADVERSE REACTIONS**. If rash progresses and becomes severe, INCIVEK should be discontinued. Peginterferon alfa and ribavirin may be continued. If improvement is not observed within 7 days of INCIVEK discontinuation, sequential or simultaneous interruption or discontinuation of ribavirin and/or peginterferon alfa should be considered. If medically indicated, earlier interruption or discontinuation of ribavirin and peginterferon alfa should be considered (see **SERIOUS BOXED WARNING**). Patients should be monitored until the rash has resolved. INCIVEK must not be restarted if discontinued due to rash. In clinical trials, rash was treated with oral antihistamines and/or topical corticosteroids; effectiveness of these measures has not been established. Treatment of rash with systemic corticosteroids is not recommended (see **DRUG INTERACTIONS**).

Pregnancy

INCIVEK must be used in combination with ribavirin and peginterferon alfa; therefore, 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. INCIVEK combination treatment should not be initiated unless a female patient has a negative pregnancy test immediately prior to initiation of treatment (see **CONTRAINDICATIONS,** and **WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women**).

If a female patient or a female partner of a male patient becomes pregnant during INCIVEK combination treatment, the patient should be apprised of the potential hazard of ribavirin to the fetus (see **WARNINGS AND PRECAUTIONS**, **Special Populations, Pregnant Women** and **CONSUMER INFORMATION**).

General

INCIVEK (telaprevir) **must not** be administered as monotherapy and must only be prescribed with both peginterferon alfa and ribavirin. Therefore, the prescribing information for peginterferon alfa and ribavirin must be consulted before starting treatment with INCIVEK.

There are no clinical data on re-treating patients who have failed an HCV NS3·4A protease inhibitor-based treatment, nor are there data on repeated courses of INCIVEK (see **DETAILED PHARMACOLOGY**).

See **CONTRAINDICATIONS**, Table 1 for a listing of drugs that are contraindicated for use with INCIVEK due to potentially life-threatening adverse events or potential loss of therapeutic effect to INCIVEK, and see **DRUG INTERACTIONS,** Table 4 for established and other potentially significant drug-drug interactions.

Carcinogenesis and Mutagenesis

Telaprevir has not been tested for its carcinogenic potential (see **TOXICOLOGY**).

Cardiovascular

Potential for QT Prolongation:

A study conducted in healthy subjects (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) (see **ACTION AND CLINICAL PHARMACOLOGY, ECG Evaluation**). Exposure at this dose was comparable to the exposure in HCV-infected patients dosed at 750 mg INCIVEK q8h plus peginterferon alfa and ribavirin. The potential clinical significance of these findings is uncertain.

Caution is recommended when prescribing INCIVEK concurrently with drugs known to induce QT prolongation and which are CYP3A substrates (such as erythromycin, ketoconazole, haloperidol, tacrolimus, and salmeterol). INCIVEK may increase concentrations of the co-administered drug and this may result in an increased risk of their associated cardiac adverse events. In the event that co-administration of such drugs with INCIVEK is judged strictly necessary, clinical monitoring, including ECG assessments, should be considered (see **DRUG INTERACTIONS**).

Use of INCIVEK should be avoided in patients with:

- Congenital QT prolongation, or a family history of congenital QT prolongation or sudden death. In the event that treatment with INCIVEK in such patients is judged clinically necessary, consideration should be given to monitoring, including ECG assessments.

INCIVEK 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) (see **DRUG INTERACTIONS**).

Monitoring and correction of electrolyte disturbances (e.g., hypokalemia, hypomagnesemia and

hypocalcemia) should be considered prior to initiation and during INCIVEK therapy.

Hematologic

Anemia:

Anemia has been reported with peginterferon alfa and ribavirin therapy. The addition of INCIVEK to peginterferon alfa and ribavirin is associated with an additional decrease in hemoglobin concentrations. In placebo-controlled Phase 2 and 3 clinical trials, the overall incidence and severity of anemia increased with INCIVEK combination treatment compared to peginterferon alfa and ribavirin alone. Hemoglobin values of <10 g/dL were observed in 33.7% of patients who received INCIVEK combination treatment and in 13.6% of patients who received peginterferon alfa and ribavirin. Hemoglobin values of <8.5 g/dL were observed in 8.3% of INCIVEK combination treatment patients compared to 2.3% of patients receiving peginterferon alfa and ribavirin alone (see **ADVERSE DRUG REACTIONS**).

Hemoglobin levels decrease sharply during the first 4 weeks of treatment, with lowest values reached at the end of INCIVEK dosing. Hemoglobin values gradually returned to levels observed with peginterferon alfa and ribavirin alone after INCIVEK dosing completion. Hemoglobin should be monitored prior to and at least at weeks 2, 4, 8 and 12 during INCIVEK combination treatment and as clinically appropriate (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**).

In subjects receiving INCIVEK combination treatment, 2.7% discontinued INCIVEK alone, 0.9% discontinued INCIVEK combination treatment due to anemia compared to 0.5% receiving peginterferon alfa and ribavirin alone. In the same studies, there were 27.6% subjects undergoing a ribavirin dose modification (reduction, interruption or discontinuation) due to anemia as compared to 11.1% in the placebo group.

For the management of anemia, refer to the prescribing information for ribavirin for its dose reduction guidelines. If ribavirin is permanently discontinued for the management of anemia, INCIVEK must also be permanently discontinued, and must not be restarted, even at a reduced dose. If INCIVEK is discontinued for anemia, patients may continue treatment with peginterferon alfa and ribavirin. Ribavirin may be restarted per the dosing modification guidelines for ribavirin.

Hepatic/Biliary/Pancreatic

Hepatic:

INCIVEK is not recommended for use in patients with moderate or severe hepatic impairment (Child-Pugh B or C, score ≥ 7) or decompensated liver disease. No pharmacokinetic or safety data are available regarding the use of INCIVEK in HCV-infected patients with moderate or severe hepatic impairment (Child-Pugh B or C, score ≥ 7) or decompensated liver disease. No dose adjustment is necessary for patients with mild hepatic impairment (Child-Pugh A, score 5-6) (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics – Special Populations and Conditions**). Refer also to the prescribing information for peginterferon alfa and ribavirin.

Organ Transplant Patients:
The use of INCIVEK in organ transplant patients is not recommended because the safety and efficacy of INCIVEK in this patient population has not been established. A drug-drug interaction study in healthy subjects suggested a significant increase in serum drug exposure for cyclosporine and tacrolimus upon telaprevir co-administration (see **DRUG INTERACTIONS**).

Renal:
No dose adjustment is necessary for INCIVEK in HCV-infected patients with mild, moderate or severe renal impairment. The safety and efficacy of INCIVEK combination therapy has not been established in HCV-infected patients with a CrCl ≤ 50 mL/min (see **DOSAGE AND ADMINISTRATION**).

The pharmacokinetics of telaprevir were assessed after administration of a single 750 mg dose to HCV-negative subjects with severe renal impairment (CrCl < 30 mL/min). INCIVEK has not been studied in patients with end-stage renal disease (ESRD) or on hemodialysis (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations**). Refer also to the prescribing information for peginterferon alfa and ribavirin.

Special Populations
Pregnant Women:
Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. Ribavirin use is contraindicated in pregnant female patients or male patients whose female partners are pregnant (see **CONTRAINDICATIONS**). Refer also to the prescribing information for peginterferon alfa and ribavirin.

INCIVEK combination treatment should not be started unless a female patient has a negative pregnancy test immediately prior to initiation of treatment. Pregnancy testing must be performed monthly during INCIVEK combination treatment and for 6 months after all treatment has ended (see **WARNINGS AND PRECAUTIONS, Pregnancy** and **CONSUMER INFORMATION**).

Women of childbearing potential and their male partners, and male patients and their female partners of childbearing potential must not receive INCIVEK combination therapy unless they are using two effective forms of contraception during treatment with INCIVEK combination treatment and for the 6-month post-therapy period.

Hormonal contraceptives may not be a reliable form of contraception during INCIVEK dosing (see **DRUG INTERACTIONS**). Therefore, female patients of childbearing potential should use 2 additional non-hormonal methods of effective birth control during INCIVEK dosing and for 2 months after the last intake of INCIVEK. Examples of non-hormonal methods of contraception include a male condom with spermicidal jelly OR female condom with spermicidal jelly (a combination of a male condom and a female condom is not suitable), a diaphragm with spermicidal jelly, or a cervical cap with spermicidal jelly, or an intrauterine device (IUD).

As of 2 months after completion of INCIVEK treatment, hormonal contraceptives can again count

as one of the 2 required effective methods of birth control; however, specific prescribing information recommendations should be followed for the contraceptives.

Telaprevir treatment alone in mice and rats did not result in harm to the fetus. The highest doses tested produced exposures equal to 1.84- and 0.60-fold the exposures in humans at the recommended clinical dose, respectively. Telaprevir treatment alone had effects on fertility parameters in rats (see **TOXICOLOGY**). The no observed adverse effect level (NOAEL) for degenerative testicular toxicity was established at exposures 0.17-fold the human exposures at the recommended clinical dose. Potential effects on sperm (e.g., decreased % motile sperm and increased non-motile sperm count) were observed in a rat fertility study at exposures 0.30-fold the human exposures at the recommended clinical dose. Additional effects on fertility included minor increases in percent preimplantation loss, the percent of dams with nonviable embryos and percent of nonviable conceptuses per litter. These effects are likely associated with testicular toxicity in male rats but contributions of the female cannot be ruled out. Degenerative testicular toxicity was not observed in chronic toxicity studies in the dog. Furthermore, mean changes in proposed biomarkers of testicular toxicity among subjects who received telaprevir were comparable to placebo.

Nursing Women:
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. Refer also to the prescribing information for peginterferon alfa and ribavirin.

Pediatrics (< 18 years of age):
The use of INCIVEK in pediatric patients is not recommended. No clinical data are available regarding the use of INCIVEK in children and adolescents younger than 18 years of age.

Geriatrics (≥ 65 years of age):
Clinical studies of INCIVEK did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, caution should be exercised when administering INCIVEK in elderly patients, reflecting the greater frequency of anemia, decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Patients with Cirrhosis:
Treatment naïve and prior relapse subjects with cirrhosis may benefit from 48 weeks of treatment with peginterferon and ribavirin (see **DOSAGE AND ADMINISTRATION**).

A high proportion of previous null responders (particularly those with cirrhosis) did not achieve a SVR and had telaprevir resistance-associated substitutions emerge on treatment with INCIVEK combination treatment.

HIV Co-infection:
The safety and efficacy of INCIVEK have not been established in HCV/HIV co-infected patients. There are very limited safety and efficacy data to recommend the use of INCIVEK in this patient population. Due to the potential for loss of therapeutic effect of INCIVEK, telaprevir should not be used in patients receiving darunavir, fosamprenavir or lopinavir (see **DRUG INTERACTIONS**).

HBV Co-infection:
The safety and efficacy of INCIVEK has not been established in HCV/HBV co-infected patients.

Monitoring and Laboratory Tests
HCV-RNA levels should be monitored at weeks 4 and 12 and as clinically indicated. Use of a sensitive real-time RT-PCR assay for monitoring HCV-RNA levels during treatment is recommended. The assay should have a lower limit of HCV RNA quantification ≤ 25 IU/mL and a limit of HCV-RNA detection of approximately 10-15 IU/mL. For the purpose of assessing response-guided therapy eligibility, an "undetectable" HCV RNA result ("Target Not Detected") is required; a confirmed "detectable but below limit of quantification" HCV RNA result should not be considered equivalent to an "undetectable" HCV RNA result.

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 INCIVEK combination treatment.

These are recommended baseline values for initiation of INCIVEK combination treatment:
- Hemoglobin: ≥12 g/dL (females); ≥13 g/dL (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

Hematology evaluations (including white cell differential count) are recommended at weeks 2, 4, 8 and 12 and as clinically appropriate.

Chemistry evaluations (electrolytes, serum creatinine, uric acid, hepatic enzymes, bilirubin, TSH, serum cholesterol and LDL) are recommended as frequently as the hematology evaluations and as clinically indicated (see **ADVERSE REACTIONS**). Refer to the prescribing information for peginterferon alfa and ribavirin, including pregnancy testing requirements.

INCIVEK has been associated with increases in creatinine and uric acid and decreases in potassium (see **ADVERSE REACTIONS, Abnormal Hematologic and Clinical Chemistry Findings**).

ADVERSE REACTIONS

Adverse Drug Reaction (ADR) Overview

The safety assessment is based on the pooled data from the Phase 2 and 3 clinical trials comprising 1346 subjects who received 12 weeks of INCIVEK in combination with 24 or 48 weeks of peginterferon alfa and ribavirin.

INCIVEK must be administered with peginterferon alfa and ribavirin. Refer to their respective package inserts for their associated adverse reactions.

In subjects who received INCIVEK combination treatment, the most frequent adverse drug events (>20%) were fatigue, pruritus, nausea, headache, influenza-like illness, rash, anemia, insomnia, diarrhea, and pyrexia.

In subjects who received INCIVEK combination treatment, the most frequent adverse drug reactions (>10%) were pruritus, rash, nausea, anemia, diarrhea, vomiting, hemorrhoids, and proctalgia.

Serious adverse drug reactions occurred in 3.9% of subjects who received INCIVEK combination treatment compared to 0.7% of the subjects treated with peginterferon alfa and ribavirin. The most frequent serious adverse events occurring >0.5% in subjects treated with INCIVEK combination treatment were anemia and rash (see **WARNINGS AND PRECAUTIONS**).

10.4% of subjects discontinued INCIVEK due to adverse drug reactions. Rash, anemia, pruritus, nausea, and vomiting were the most frequent adverse drug reactions leading to discontinuation of INCIVEK.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The majority of the adverse drug reactions reported during treatment with INCIVEK combination treatment were mild in severity. In subjects who received INCIVEK combination treatment, the most common adverse drug reactions (≥10%) of all grades were pruritus, rash, nausea, anemia, diarrhea, vomiting, hemorrhoids, and proctalgia. 10.4% of subjects discontinued INCIVEK due to ADRs (in the pooled controlled trials: N = 1346).

ADRs to INCIVEK of all grades with a frequency of ≥1% are presented in Table 2.

Table 2 - Clinical Adverse Drug Reactions to INCIVEK Combination Treatment of All Grades Occurring in ≥1% of Treatment-Naïve and Previously Treated HCV-Infected Adult Subjects

Pooled Placebo-Controlled Studies 108, C216, 104, 104EU, and 106		
System Organ Class Preferred Term	**INCIVEK, peginterferon alfa, and ribavirin Combination Treatment N = 1346 (%)**	**Placebo/peginterferon alfa and ribavirin N = 764 (%)**
Blood and lymphatic system disorders		
Anemia	31.8	14.8
Endocrine disorders		
Hypothyroidism	1.9	0.4
Gastrointestinal disorders		
Nausea	39.5	29.2
Diarrhea	27.5	19.1
Vomiting	12.4	9.0
Hemorrhoids	12.2	2.6
Proctalgia	11.5	2.5
Anal pruritus	6.2	0.9
Rectal hemorrhage	3.8	0.7
Anal fissure	1.0	0
General disorders and administration site conditions		
Edema peripheral	2.3	0.4
Product taste abnormal	1.4	0.7
Infections and Infestations		
Oral candidiasis	2.2	0.7
Nervous system disorders		
Dysgeusia	9.5	4.2
Syncope	1.5	0.4
Skin and subcutaneous tissue disorders		
Pruritus	51.5	26.4
Rash	48.7	28.0
Eczema	6.0	3.0
Swelling face	1.9	0.7
Exfoliative rash	1.2	0.5

ADRs related to laboratory findings were thrombocytopenia, lymphopenia, hyperuricemia, hypokalemia, hyperbilirubinemia, and blood creatinine increased (see Table 3).

Rash

For severe rash, see **WARNINGS AND PRECAUTIONS**. In placebo-controlled Phase 2 and 3 trials, the overall incidence and severity of rash increased when INCIVEK was co-administered with peginterferon alfa and ribavirin. During INCIVEK treatment, rash adverse drug reactions (all grades) were reported in 48.7% of patients who received INCIVEK combination treatment and in 28.0% of patients who received peginterferon alfa and ribavirin.

More than 90% of rashes were of mild or moderate severity. The rash reported during INCIVEK

combination treatment was assessed as a typically pruritic, eczematous rash, and involved less than 30% of body surface area. The most common time for a rash to begin was during the first 4 weeks, but rash can occur at any time during INCIVEK combination treatment.

Discontinuation of INCIVEK combination treatment is not required for mild and moderate rash. Patients experiencing mild to moderate rash should be monitored for signs of progression. In clinical trials, the majority of patients were administered antihistamines and topical corticosteroids. Improvement of rash occurs after INCIVEK dosing completion or discontinuation; however, rashes may take weeks for complete resolution.

In clinical trials, pruritus was most commonly reported in association with rash, but some cases occurred without rash. The majority of pruritus events were not severe, did not lead to treatment discontinuation, and resolved after dosing completion.

Anemia
In placebo-controlled Phase 2 and 3 trials, anemia (all grades) was reported as an adverse drug reaction in 31.8% of patients who received INCIVEK combination treatment and in 14.8% of patients who received peginterferon alfa and ribavirin. Ribavirin dose reductions were used for management of anemia. 21.6% of patients receiving INCIVEK combination treatment required ribavirin dose reduction for anemia compared to 9.4% of patients receiving peginterferon alfa and ribavirin alone. In placebo-controlled Phase 2 and 3 trials, 2.7% of patients discontinued INCIVEK alone due to anemia, and 0.9% of patients discontinued INCIVEK combination treatment due to anemia compared to 0.5% receiving peginterferon alfa and ribavirin (see **WARNINGS AND PRECAUTIONS**).

Anorectal signs and symptoms
In clinical trials, anorectal adverse drug reactions (all grades) were reported in 26.2% of patients who received INCIVEK combination treatment and in 5.4% of patients who received peginterferon alfa and ribavirin. The majority of these events (e.g., hemorrhoids, anorectal discomfort, anal pruritus, and rectal burning) were mild to moderate, very few led to treatment discontinuation and they resolved after completion of INCIVEK dosing.

Patients Co-infected with HIV-1
The safety profile of INCIVEK in combination with peginterferon alfa and ribavirin was assessed in a Phase 2 trial of genotype 1 chronic HCV/HIV-1 co-infected subjects (N=60), who were treatment-naïve for hepatitis C. Subjects were either not on antiretroviral therapy (CD4 count $\geq$ 500 cells/mm^3), or had stable controlled HIV (HIV RNA < 50 copies/mL, CD4 count $\geq$ 300 cells/mm^3) being treated with efavirenz in combination with tenofovir disoproxil fumarate and emtricitabine or atazanavir/ritonavir, tenofovir disoproxil fumarate and emtricitabine or lamivudine regimen.

The overall safety analysis of HIV/HCV co-infected subjects receiving T/PR for CHC with or without concurrent HAART administration appears consistent with what has been observed with mono-infected CHC subjects receiving T/PR regimens with the exception that subjects receiving

atazanavir/ritonavir in the INCIVEK combination treatment group and in the peginterferon alfa and ribavirin group experienced a transient increase in indirect bilirubin levels through week 2, returning to near baseline by week 12.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Adverse drug reactions occurring in less than 1% of patients receiving INCIVEK are listed below by body system:

Eye: Retinopathy
Gastrointestinal: Proctitis
Metabolism and nutrition: Gout
Skin and subcutaneous tissue: Drug reaction with eosinophilia and systemic symptoms, urticaria, Stevens-Johnson syndrome (<0.1%)

Abnormal Hematologic and Clinical Chemistry Findings

Selected DAIDS Grade 2 and above laboratory abnormalities that represent a worsening from baseline, and considered laboratory abnormality adverse drug reactions observed in HCV-infected subjects treated with INCIVEK combination treatment, are presented in Table 3.

Table 3 - Laboratory Abnormality Adverse Drug Reactions, DAIDS Grade ≥ 2 in HCV-Infected Subjects

Pooled Placebo-Controlled Studies 108, C216, 104, 104EU, and 106			
Laboratory Parameter	**DAIDS Toxicity Range***	**INCIVEK, peginterferon alfa, and ribavirin Combination Treatment (%)****	**Placebo/peginterferon alfa and ribavirin (%)**
CHEMISTRY			
Creatinine, increase			
Grade 2	1.4-1.8 x ULN	0.9	0.4
Grade 3	1.9-3.4 x ULN	0.2	0
Hyperbilirubinemia			
Grade 2	1.6 to 2.5 x ULN	13.6	6.8
Grade 3	2.6 to 5.0 x ULN	3.6	1.1
Grade 4	>5.0 x ULN	0.3	0.1
Hyperuricemia			
Grade 2	10.1-12.0 mg/dL	17.9	2.6
Grade 3	12.1-15.0 mg/dL	4.6	0.5
Grade 4	>15.0 mg/dL	1.1	0
Hypokalemia			
Grade 2	2.5-2.9 mEq/L	1.6	0.3
Grade 3	2.0-2.4 mEq/L	0	0
HEMATOLOGY			
Absolute Lymphocyte Count, decrease			
Grade 2	500-599/mm^3	13.1	5.6
Grade 3	350-499/mm^3	11.8	4.4

Pooled Placebo-Controlled Studies 108, C216, 104, 104EU, and 106			
Laboratory Parameter	**DAIDS Toxicity Range***	**INCIVEK, peginterferon alfa, and ribavirin Combination Treatment (%)****	**Placebo/peginterferon alfa and ribavirin (%)**
Grade 4	<350/mm^3	4.8	0.9
Hemoglobin, decrease			
Grade 2	9.0-9.9 g/dL or any decrease 3.5-4.4 g/dL	27.0	27.0
Grade 3	7.0-8.9 g/dL or any decrease ≥4.5 g/dL	51.1	24.0
Grade 4	<7.0 g/dL	1.1	0
Platelet Count, decrease			
Grade 2	50,000-99,999/mm^3	24.4	15.6
Grade 3	25,000-49,999/mm^3	2.8	0.9
Grade 4	<25,000/mm^3	0.2	0.1
LIPIDS			
Low-Density Lipoprotein, increase			
Grade 2	4.13-4.90 mmol/L 160-190 mg/dL	6.9	2.1
Grade 3	≥4.91 mmol/L ≥190 mg/dL	2.5	0.4
Total Cholesterol, increase			
Grade 2	6.20-7.77 mmol/L 240-300 mg/dL	15.4	1.6
Grade 3	>7.77 mmol/L >300 mg/dL	2.0	0.1
*The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 1.0 (December 2004) ** Incidence was calculated by number of subjects with available data for each parameter. ULN = Upper Limit of Normal			

Most laboratory values returned to levels observed with peginterferon alfa and ribavirin by week 24, except platelet counts, which remained at levels lower than observed with peginterferon alfa and ribavirin until week 48 (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**).

Increases in serum uric acid occurred very commonly during treatment with INCIVEK in combination with peginterferon alfa and ribavirin. After the end of INCIVEK treatment, uric acid values typically decreased over the following 8 weeks and were comparable to those observed in patients receiving peginterferon alfa and ribavirin alone.

Additional Clinical Trial Experience in Treatment-Naïve Subjects

Study C211
In the analysis of an additional study (Study C211), the safety profile of combination therapy with INCIVEK 1125 mg twice daily was similar to the safety profile for patients receiving combination treatment with INCIVEK 750 mg every 8 hours (q8h) (see **CLINICAL TRIALS**). No new safety findings were identified.

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified during post-approval use of INCIVEK. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: pancytopenia, hemolytic anemia, agranulocytosis

Cardiac disorders: cardiac failure, pulmonary edema, myocardial infarction

Gastrointestinal disorders: pancreatitis

Hepatobiliary disorders: acute hepatic failure

Muskculoskeletal and connective tissue disorders: rhabdomyolysis.

Renal and urinary disorders: pyelonephritis, renal failure, acute renal failure

Skin and Subcutaneous Tissue Disorders: Toxic Epidermal Necrolysis (TEN) and Erythema Multiforme (EM) (see **WARNINGS AND PRECAUTIONS, Serious Skin Reactions/Rash)**

Vascular disorders: disseminated intravascular coagulation

DRUG INTERACTIONS

Serious Drug Interactions

- **Aldosterone antagonists** (eplerenone): **CONTRAINDICATED** due to potential for hyperkalemia.
- **Alpha 1-adrenoreceptor antagonists** (alfuzosin): **CONTRAINDICATED** due to potential for hypotension or cardiac arrhythmia.
- **Antiarrhythmics** (quinidine, flecainide, propafenone, amiodarone): **CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.

- **Anticoagulants** (warfarin): Concentrations of warfarin may be altered when co-administered with telaprevir. It is recommended that the international normalized ratio (INR) be monitored when warfarin is co-administered with telaprevir.

- **Anticonvulsants** (carbamazepine, phenobarbital, phenytoin): **CONTRAINDICATED.** Potential for lower exposure and loss of efficacy of telaprevir.

- **Antihistamines** (astemizole*, terfenadine*): **CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.

- **Antimycobacterials** (rifampin): **CONTRAINDICATED.** Rifampin reduces telaprevir plasma concentrations significantly.

- **Ergot Derivatives** (dihydroergotamine, ergonovine, ergotamine, methylergonovine): **CONTRAINDICATED** due to potential for acute ergot toxicity characterized by peripheral vasospasm or ischemia.

- **GI (Gastrointestinal) Motility Agents** (cisapride*): **CONTRAINDICATED** due to potential for serious cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, torsade de pointes, and QT prolongation.

- **Herbal Products** (St. John's Wort): **CONTRAINDICATED.** Plasma concentrations of telaprevir can be reduced by concomitant use of the herbal preparation St. John's Wort. Herbal preparations containing St. John's Wort should therefore not be administered concomitantly with telaprevir.

- **HMG-CoA Reductase Inhibitors** (lovastatin, simvastatin): **CONTRAINDICATED** due to potential for myopathy including rhabdomyolysis.

- **Immunosuppressants** (cyclosporine, tacrolimus, sirolimus): Concentrations of immunosuppressants may be increased with telaprevir. The use of telaprevir in organ transplant patients has not been studied.

- **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.

- **Neuroleptics** (pimozide): **CONTRAINDICATED** due to potential for serious and/or life-threatening adverse reactions such as cardiac arrhythmias.

- **PDE5 Inhibitors: CONTRAINDICATED** due to potential for hypotension and/or

cardiac arrhythmia.
--sildenafil (only when used for the treatment of pulmonary arterial hypertension)
--vardenafil

- **Sedatives/Hypnotics** (orally administered midazolam*, triazolam): **CONTRAINDICATED** due to potential for increased sedation or respiratory depression.

- **Triptans** (eletriptan): **CONTRAINDICATED** due to potential for coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation.

*Product not marketed in Canada.

Overview

Potential for INCIVEK to Affect Other Drugs

INCIVEK is a strong inhibitor of CYP3A and an inhibitor of P-glycoprotein (P-gp), OATP1B1, and OATP2B1. Co-administration of INCIVEK with drugs that are primarily metabolized by CYP3A and/or substrates for P-gp, OATP1B1, and OATP2B1 transport may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and adverse reactions (see Table 4). **If dose adjustments of concomitant medications are made during INCIVEK treatment, they should be re-adjusted after administration of INCIVEK is completed.**

Potential for Other Drugs to Affect INCIVEK

INCIVEK is a substrate of CYP3A and P-gp; therefore, drugs that induce CYP3A and/or P-gp may decrease INCIVEK plasma concentrations and reduce the therapeutic effect of INCIVEK. Co-administration of INCIVEK with drugs that inhibit CYP3A and/or P-gp may increase INCIVEK plasma concentrations.

Drug-Drug Interactions

INCIVEK 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). INCIVEK is also contraindicated when combined with drugs that strongly induce CYP3A and thus may lead to lower exposure and loss of efficacy of INCIVEK (see **CONTRAINDICATIONS** and **DETAILED PHARMACOLOGY**).

Established and other potentially significant interactions are shown in Table 4. Table 4 provides effect of concentration of INCIVEK or concomitant drug with INCIVEK. These recommendations are based on either drug interaction studies (indicated with *) or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy. Most drug interaction studies have been performed with a telaprevir dose of 750 mg every 8 hours (q8h) of INCIVEK. Given that the 1125 mg twice-daily regimen results in

the same total daily dose with similar drug exposures of INCIVEK, the relative drug interactions are expected to be similar after multiple doses (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Table 4 - Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction (See DETAILED PHARMACOLOGY for Magnitude of Interaction.)

Concomitant Drug Class: Drug Name	**Effect on concentration of INCIVEK or Concomitant Drug**	**Clinical Comment**
ANALGESICS		
alfentanil fentanyl	↑ alfentanil ↑ fentanyl	Careful monitoring of therapeutic and adverse effects (including respiratory depression) is recommended when telaprevir is co-administered with alfentanil or fentanyl, including extended-release transdermal or transmucosal preparations of fentanyl.
ANTIARRHYTHMICS		
lidocaine (systemic)	↑ lidocaine	Telaprevir may increase the concentrations of systemically administered lidocaine. Caution is warranted and clinical monitoring is recommended when co-administered with telaprevir.
digoxin*	↑ digoxin	Concentrations of digoxin were increased when co-administered with telaprevir. The lowest dose of digoxin should be initially prescribed. The serum digoxin concentrations should be monitored and used for titration of digoxin dose to obtain the desired clinical effect.
ANTIBACTERIALS		
clarithromycin erythromycin telithromycin	↑ telaprevir ↑ antibacterials	Concentrations of both telaprevir and the antibacterial may be increased during co-administration. Caution is warranted and clinical monitoring is recommended when co-administered with telaprevir. QT interval prolongation and Torsade de Pointes have been reported with clarithromycin and erythromycin. QT interval prolongation has been reported with telithromycin.
ANTICOAGULANT		
warfarin	↑ or ↓ warfarin	Concentrations of warfarin may be altered when co-administered with telaprevir. It is recommended that the international normalized ratio (INR) be monitored when warfarin is co-administered with telaprevir.
ANTICONVULSANTS		
carbamazepine* phenobarbital phenytoin*	↓ telaprevir ↔ carbamazepine ↑ phenytoin ↑ or ↓ phenobarbital	Co-administration of telaprevir with the anticonvulsants carbamazepine and phenytoin were shown to significantly decrease telaprevir concentrations (see **DETAILED PHARMACOLOGY**). Co-administration of telaprevir with the anticonvulsants carbamazepine, phenobarbital and phenytoin may result in sub-optimal levels of telaprevir and lead to loss of virologic response. Concomitant use of telaprevir with carbamazepine, phenobarbital, or phenytoin is contraindicated (see **CONTRAINDICATIONS**).

Concomitant Drug Class: Drug Name	Effect on concentration of INCIVEK or Concomitant Drug	Clinical Comment
ANTIDEPRESSANTS		
escitalopram*	↔ telaprevir ↓ escitalopram	Concentrations of escitalopram were decreased when co-administered with telaprevir. Selective serotonin reuptake inhibitors such as escitalopram have a wide therapeutic index, but doses may need to be adjusted when combined with telaprevir.
trazodone	↑ trazodone	Concomitant use of trazodone and telaprevir may increase plasma concentrations of trazodone which may lead to adverse events such as nausea, dizziness, hypotension and syncope. If trazodone is used with telaprevir, the combination should be used with caution and a lower dose of trazodone should be considered.
ANTIFUNGALS		
ketoconazole* itraconazole posaconazole voriconazole	↑ ketoconazole ↑ telaprevir ↑ itraconazole ↑ posaconazole ↑ or ↓ voriconazole	Ketoconazole increases the plasma concentrations of telaprevir. Concomitant systemic use of itraconazole or posaconazole with telaprevir may increase plasma concentration of telaprevir. Plasma concentrations of itraconazole, ketoconazole, or posaconazole may be increased in the presence of telaprevir. When co-administration is required, high doses of itraconazole or ketoconazole (> 200 mg/day) are not recommended. Caution is warranted and clinical monitoring is recommended for itraconazole, posaconazole and voriconazole. QT interval prolongation and Torsade de Pointes have been reported with voriconazole and posaconazole. QT interval prolongation has been reported with ketoconazole. Due to multiple enzymes involved with voriconazole metabolism, it is difficult to predict the interaction with telaprevir. Voriconazole should not be administered to patients receiving telaprevir unless an assessment of the benefit/risk ratio justifies its use.
ANTI GOUT		
colchicines	↑ colchicine	Patients with renal or hepatic impairment should not be given colchicine with telaprevir, due to the risk of colchicine toxicity. A reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with normal renal or hepatic function. <u>Treatment of gout flares: co-administration of colchicine in patients on telaprevir:</u> 0.6 mg (1 tablet) for 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Not to be repeated before 3 days. <u>If used for prophylaxis of gout flares: co-administration of colchicine in patients on telaprevir:</u> If the original regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg once a day. If the original regimen was 0.6

Concomitant Drug Class: Drug Name	Effect on concentration of INCIVEK or Concomitant Drug	Clinical Comment
		mg once a day, the regimen should be adjusted to 0.3 mg once every other day. Treatment of familial Mediterranean fever (FMF): co-administration of colchicine in patients on telaprevir: Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).
ANTIMYCOBACTERIAL		
rifabutin	↓ telaprevir ↑ rifabutin	Concentrations of telaprevir may be decreased, while rifabutin concentrations may be increased during co-administration. Telaprevir may be less effective due to decreased concentrations. The concomitant use of rifabutin and telaprevir is not recommended.
BENZODIAZEPINES		
alprazolam* diazepam	↑ alprazolam ↑ diazepam	Concomitant use of alprazolam and telaprevir increase exposure to alprazolam. Clinical monitoring is warranted. Diazepam exposure may be increased when co-administered with telaprevir. Caution should be used and dose reduction for diazepam should be considered.
parenterally administered midazolam*	↑ midazolam	Concomitant use of parenterally administered midazolam with telaprevir increased exposure to midazolam. Co-administration should be done in a setting which ensures clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dose reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered.
zolpidem (non-benzodiazepine sedative)* buspirone (non-benzodiazepine sedative)	↓ zolpidem ↑ buspirone	Exposure to zolpidem was decreased when co-administered with telaprevir. Clinical monitoring and dose titration of zolpidem is recommended to achieve the desired clinical response. Buspirone exposure may be increased when co-administered with telaprevir. Caution should be used and dose reduction of buspirone should be considered.
CALCIUM CHANNEL BLOCKERS		
amlodipine* diltiazem felodipine nicardipine nifedipine nisoldipine verapamil	↑amlodipine ↑calcium channel blockers	Exposure to amlodipine was increased when co-administered with telaprevir. Caution should be used and dose reduction for amlodipine should be considered. Clinical monitoring is recommended. Concentrations of other calcium channel blockers may be increased when telaprevir is co-administered. Caution is warranted and clinical monitoring of patients is recommended.
CORTICOSTEROIDS		

Concomitant Drug Class: Drug Name	Effect on concentration of INCIVEK or Concomitant Drug	Clinical Comment
Systemic dexamethasone	↓ telaprevir	Systemic dexamethasone induces CYP3A and can thereby decrease telaprevir plasma concentrations. This may result in loss of therapeutic effect of telaprevir. Therefore this combination should be used with caution or alternatives should be considered.
Inhaled/Nasal fluticasone budesonide	↑ fluticasone ↑ budesonide	Concomitant use of inhaled fluticasone or budesonide and telaprevir may increase plasma concentrations of fluticasone or budesonide resulting in significantly reduced serum cortisol concentrations. Co-administration of fluticasone or budesonide and telaprevir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.
ENDOTHELIN RECEPTOR ANTAGONIST		
bosentan	↑ bosentan	<u>Co-administration of bosentan in patients on INCIVEK:</u> In patients who have been receiving INCIVEK for at least 10 days, start bosentan at 62.5 mg once daily or every other day based upon individual tolerability. <u>Co-administration of INCIVEK in patients on bosentan:</u> Discontinue use of bosentan at least 36 hours prior to initiation of INCIVEK. After at least 10 days following the initiation of INCIVEK, resume bosentan at 62.5 mg once daily or every other day based upon individual tolerability.
HIV-ANTIVIRAL AGENTS: HIV-PROTEASE INHIBITORS (PIs)		
atazanavir/ritonavir*	↓ telaprevir ↑ atazanavir	In a drug interaction study in healthy subjects where telaprevir was co-administered with atazanavir/ritonavir, the steady-state telaprevir exposure was reduced, while the steady-state atazanavir exposure was increased.
darunavir/ritonavir*	↓ telaprevir ↓ darunavir	In a drug interaction study in healthy subjects where telaprevir was co-administered with darunavir/ritonavir, the steady-state exposure to telaprevir and darunavir was reduced. Telaprevir should not be used in patients receiving darunavir.
fosamprenavir/ritonavir*	↓ telaprevir ↓ amprenavir	In a drug interaction study in healthy subjects where telaprevir was co-administered with fosamprenavir/ritonavir, the steady-state exposure to telaprevir and amprenavir exposure was reduced. Telaprevir should not be used in patients receiving fosamprenavir.
lopinavir/ritonavir*	↓ telaprevir ↔ lopinavir	In a drug interaction study in healthy subjects where telaprevir was co-administered with lopinavir/ritonavir, the steady-state telaprevir exposure was reduced, while the steady-state exposure to lopinavir was not affected. Telaprevir should not be used in patients receiving lopinavir.
HIV-ANTIVIRAL AGENTS: NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)		
efavirenz*	↓ telaprevir ↓ efavirenz	In a drug interaction study in healthy subjects where telaprevir was co-administered with efavirenz, the steady-state exposure to efavirenz and telaprevir was reduced. When telaprevir was co-administered at a dose of 1125 mg q8h, the reduced exposure to telaprevir was partially offset.
HIV-ANTIVIRAL AGENTS: NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs)		
tenofovir disoproxil	↔ telaprevir	In a drug interaction study in healthy subjects, co-administration of

Concomitant Drug Class: Drug Name	Effect on concentration of INCIVEK or Concomitant Drug	Clinical Comment
fumarate*	↑ tenofovir	telaprevir and tenofovir led to an increase in tenofovir exposure. Increased clinical and laboratory monitoring are warranted. The increase in the exposure to tenofovir was less when a combination of tenofovir and efavirenz was co-administered with telaprevir administered at doses of 1125 mg q8h.
HMG-CoA REDUCTASE INHIBITORS		
atorvastatin* fluvastatin pravastatin rosuvastatin	↑ statin	Plasma concentrations of atorvastatin are markedly increased when co-administered with telaprevir. Avoid concomitant administration of telaprevir and atorvastatin. Concomitant use of telaprevir with lovastatin and simvastatin is contraindicated (see **CONTRAINDICATIONS**). For rosuvastatin and pravastatin, the drug interaction potential is unknown; therefore, caution should be used. Fluvastatin is unlikely to interact with telaprevir.
HORMONAL CONTRACEPTIVES/ESTROGEN		
ethinyl estradiol* norethindrone*	↓ ethinyl estradiol ↔ norethindrone	Exposure to ethinyl estradiol was decreased when co-administered with telaprevir. Alternative methods of non-hormonal contraception should be used when hormonal contraceptives are co-administered with telaprevir (see **WARNINGS AND PRECAUTIONS**, and **CONSUMER INFORMATION**). Patients using estrogens as hormone replacement therapy should be clinically monitored for signs of estrogen deficiency.
IMMUNOSUPPRESSANTS		
cyclosporine* sirolimus tacrolimus*	↑ cyclosporine ↑ sirolimus ↑ tacrolimus	Plasma concentrations of cyclosporine and tacrolimus are markedly increased when co-administered with telaprevir. Plasma concentration of sirolimus may be increased when co-administered with telaprevir, though this has not been studied. Tacrolimus may prolong the QT interval. The use of telaprevir in organ transplant patients has not been studied, and therefore, is not recommended (see **WARNINGS AND PRECAUTIONS**).
INHALED BETA AGONIST		
salmeterol	↑ salmeterol	Concurrent administration of salmeterol and telaprevir is not recommended. Concentrations of salmeterol may be increased with telaprevir. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
INSULIN SECRETAGOGUES		
repaglinide	↑ repaglinide	Caution is warranted and clinical monitoring is recommended.
NARCOTIC ANALGESIC		

Concomitant Drug Class: Drug Name	Effect on concentration of INCIVEK or Concomitant Drug	Clinical Comment
methadone*	↓ R-methadone	Concentrations of methadone were reduced when co-administered with telaprevir. No adjustment of methadone dose is required when initiating co-administration of telaprevir. However, clinical monitoring is recommended as the dose of methadone during maintenance therapy may need to be adjusted in some patients. QT interval prolongation and Torsade de Pointes have been reported with methadone.
PDE5 INHIBITORS		
sildenafil tadalafil	↑ PDE5 inhibitors	Concentrations of PDE-5 inhibitors may be increased when co-administered with telaprevir. For the treatment of erectile dysfunction, sildenafil at a single dose not exceeding 25 mg in 48 hours, or tadalafil at a single dose not exceeding 10 mg dose in 72 hours can be used with increased monitoring for PDE-5 inhibitor-associated adverse events. Caution is warranted and clinical monitoring is recommended. Co-administration of vardenafil and telaprevir is contraindicated (see **CONTRAINDICATIONS**). Co-administration of sildenafil in the treatment of pulmonary arterial hypertension and telaprevir is contraindicated (see **CONTRAINDICATIONS**). Co-administration of tadalafil and telaprevir in the treatment of pulmonary arterial hypertension is not recommended.
*****These interactions have been studied. See **DETAILED PHARMACOLOGY**. The direction of the arrow (↑ = *increase,* ↓ = *decrease,* ↔ = *no change*) indicates the direction of the change in PK.		

In addition to the drugs included in Table 4 the interaction between INCIVEK and the following drugs was evaluated in clinical studies and no dose adjustment is needed for any drug (see **DETAILED PHARMACOLOGY**): esomeprazole, raltegravir, or buprenorphine.

QTc Prolonging Drugs

Drugs that cause QTc prolongation should be administered with caution in patients receiving INCIVEK. Drugs that have been associated with QTc interval prolongation and/or torsade de pointes include, but are not limited to, the following: antipsychotics (e.g., haloperidol); antidepressants (e.g., fluoxetine); opioids (e.g., methadone); macrolide antibiotics (e.g., erythromycin); quinolone antibiotics (e.g., moxifloxacin); antimalarials (e.g., quinine); azole antifungals (e.g., ketoconazole); beta-2 adrenoceptor agonists (e.g., salmeterol). See Table 1 for contraindicated antiarrhythmic drugs.

INCIVEK is a substrate for CYP3A4. The potential for prolongation of the QT/QTc interval may be increased if INCIVEK is administered in the presence of CYP3A4 inhibitors, such as ritonavir, ketoconazole, and erythromycin. INCIVEK is also an inhibitor of CYP3A4 and is anticipated to increase the exposure of drugs that also prolong the QTc interval, such as erythromycin,

ketoconazole, haloperidol, salmeterol, and vardenafil. Caution should be observed if these drugs are to be used concomitantly with INCIVEK.

Caution should be observed when using INCIVEK with drugs that can disrupt electrolyte levels, including, but not limited to, the following: loop, thiazide, and related diuretics; laxatives and enemas; amphotericin B.

The above lists of potentially interacting drugs are not comprehensive. Current information sources should be consulted for newly approved drugs that prolong the QTc interval, as well as for older drugs for which these effects have recently been established (see **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, Cardiovascular** and **ACTION AND CLINICAL PHARMACOLOGY**, **ECG Evaluation**).

Drug-Food Interactions

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). Therefore, INCIVEK should always be taken with food (not low fat) (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Drug-Herb Interactions

St. John's Wort (*Hypericum perforatum*)

Concomitant use of INCIVEK and St. John's Wort (*Hypericum perforatum*), or products containing St. John's Wort, is contraindicated (see **CONTRAINDICATIONS**, Table 1). Co-administration of telaprevir with St. John's Wort can substantially decrease telaprevir concentrations and may result in sub-optimal levels of telaprevir and lead to loss of virologic response.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

INCIVEK (telaprevir) **must not** be administered as monotherapy and must only be prescribed with both peginterferon alfa and ribavirin. For specific dosage instructions for peginterferon alfa and ribavirin, refer to the appropriate Product Monograph.

Renal Impairment

No dose adjustment is recommended for INCIVEK in HCV-infected patients with mild, moderate or severe renal impairment. The safety and efficacy of INCIVEK combination therapy has not been established in HCV-infected subjects with a CrCl ≤ 50 mL/minute (see **WARNINGS AND PRECAUTIONS, Renal** and **ACTION AND CLINICAL PHARMACOLOGY,**

Pharmacokinetics).

Hepatic Impairment
INCIVEK is not recommended for use in patients with moderate or severe hepatic impairment (Child-Pugh B or C, score ≥ 7) or decompensated liver disease. No dose adjustment of INCIVEK is necessary for patients with mild hepatic impairment (Child-Pugh A, score 5-6) (see **WARNINGS AND PRECAUTIONS, Hepatic** and **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Patients with Cirrhosis
Patients with cirrhosis may benefit from 48 weeks of treatment with peginterferon and ribavirin (see **WARNINGS AND PRECAUTIONS, Special Populations**).

Recommended Dose and Dosage Adjustment
The recommended dose of INCIVEK tablets is 1125 mg (three 375-mg tablets) taken orally 2 times a day (10-14 hours apart) with food (not low fat) (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics** and **DETAILED PHARMACOLOGY, Pharmacokinetics**). The total daily dose is 6 tablets (2250 mg).

The dose of INCIVEK must not be reduced to prevent treatment failure. Refer to the respective prescribing information for dose modification of peginterferon alfa and ribavirin (see **WARNINGS AND PRECAUTIONS**).

Duration of Treatment
The recommended duration of treatment with INCIVEK is 12 weeks in combination with peginterferon alfa and ribavirin. HCV-RNA levels should be monitored at weeks 4 and 12 to determine combination treatment duration and assess for treatment futility (Tables 5 and 6).

For the purpose of assessing response-guided therapy eligibility at weeks 4 and 12 (see Table 5), an "undetectable" HCV-RNA (Target Not Detected) result is required; a confirmed "detectable but below limit of quantification" HCV-RNA result should not be considered equivalent to an "undetectable" HCV-RNA (Target Not Detected) result (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).**

Treatment-naïve patients with cirrhosis who have undetectable HCV RNA (Target Not Detected) at weeks 4 and 12 of INCIVEK combination treatment may benefit from an additional 36 weeks of peginterferon alfa and ribavirin (48 weeks total) (see **CLINICAL TRIALS).**

Table 5 - Recommended Treatment Duration (See also Table 6 for Treatment Futility Rules)

Treatment-Naïve and Prior Relapse Patients

HCV RNA[a]	**Triple Therapy** INCIVEK, peginterferon alfa and ribavirin	**Dual Therapy** peginterferon alfa and ribavirin	**Total Treatment Duration**
Undetectable at Weeks 4 and 12	First 12 weeks	Additional 12 weeks	24 weeks
Detectable (1000 IU/mL or less) at Weeks 4 and/or 12	First 12 weeks	Additional 36 weeks	48 weeks
Prior Partial and Null Responder Patients			
	Triple Therapy INCIVEK, peginterferon alfa and ribavirin	**Dual Therapy** peginterferon alfa and ribavirin	**Total Treatment Duration**
All Patients	First 12 weeks	Additional 36 weeks	48 weeks

[a]In clinical trials, HCV RNA in plasma was measured using a COBAS® TaqMan® assay with a lower limit of quantification of 25 IU/mL and a limit of detection of 10 IU/mL. See **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests** for a description of HCV-RNA assay recommendations.

Discontinuation of Dosing

Patients with inadequate viral response are unlikely to achieve SVR, and may develop treatment-emergent resistance substitutions (see **MICROBIOLOGY**). Discontinuation of therapy is recommended in all patients with (1) HCV-RNA levels of greater than 1000 IU/mL at Treatment Week 4 or 12; or (2) confirmed detectable HCV-RNA levels at Treatment Week 24 (see Table 6).

Table 6 - Treatment Futility Rules: All Patients

HCV RNA	Action
Week 4 or Week 12: Greater than 1000 IU/mL	Discontinue INCIVEK and peginterferon alfa and ribavirin (INCIVEK treatment complete at 12 weeks)
Week 24: Detectable	Discontinue peginterferon alfa and ribavirin

If peginterferon alfa or ribavirin is discontinued for any reason, INCIVEK must also be discontinued.

If INCIVEK treatment is discontinued due to adverse drug reactions or due to lack of virologic response, INCIVEK treatment should not be reinitiated. See **WARNINGS AND PRECAUTIONS** for guidance on stopping INCIVEK for management of adverse events.

There are no data on re-treating patients who have failed a course of HCV NS3·4A protease inhibitor-based treatment, such as INCIVEK, or on re-treatment with INCIVEK (see **MICROBIOLOGY**). Re-initiation of treatment or re-treatment is not recommended.

Refer to the prescribing information of peginterferon alfa and ribavirin for recommendations for treatment interruption, discontinuation, or resumption of these drugs (see **WARNINGS AND PRECAUTIONS**).

Missed Dose

If a dose is missed within 6 hours of the scheduled time, it should be taken as soon as possible with food. If more than 6 hours has passed since the dose should have been taken, this dose should be skipped, and the usual dosing schedule resumed.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

Administration of activated charcoal may also be used to aid in the removal of unabsorbed active substance. General supportive measures are recommended.

The highest documented dose administered is 1875 mg every 8 hours for 4 days in healthy subjects with INCIVEK alone. In that study, the following common adverse events were reported more frequently with the 1875 mg q8h regimen compared to the 750 mg q8h regimen: nausea, headache, diarrhea, decreased appetite, dysgeusia, and vomiting.

No specific antidote is available for overdose with INCIVEK. Treatment of overdose with INCIVEK consists of general supportive measures including monitoring of vital signs, electrocardiograms, and observation of the clinical status of the patient.

It is not known whether telaprevir is dialyzable by peritoneal or hemodialysis.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Telaprevir is a direct-acting antiviral agent (DAA) against the hepatitis C virus. INCIVEK (telaprevir) is a specific inhibitor of the HCV NS3·4A protease which is essential for viral replication.

Pharmacodynamics

ECG Evaluation

A double-blind, randomized, placebo- and active-controlled crossover study was performed to evaluate the effect of telaprevir on ECG parameters in 44 healthy subjects with 38 providing evaluable ECG data.

The healthy subjects received telaprevir at the following doses:

750 mg q8h on days 1 to 4 followed by a single 750 mg morning dose on day 5
1875 mg q8h on days 1 to 4 followed by a single 1875 mg morning dose on day 5

Plasma concentrations with the telaprevir 1875 mg q8h dose in this study (mean C_{max} = 4230 ng/mL) were comparable to those observed in HCV patients who received telaprevir 750 mg q8h in combination with peginterferon alfa 2a and ribavirin (Table 7). Plasma concentrations for the 750 mg q8h dose in healthy subjects were slightly lower than in the target patient population (Table 7).

On day 5 of dosing, telaprevir 1875 mg q8h was associated with statistically significant increases in the QTcF interval with a maximum mean increase of 8.0 msec (90% CI 5.1, 10.9) (see **CONTRAINDICATIONS**, **WARNINGS AND PRECAUTIONS**, **Cardiovascular**; and **DRUG INTERACTIONS**, **QTc Prolonging Drugs**). The potential clinical significance of these findings is uncertain.

Pharmacokinetics

The pharmacokinetic properties of telaprevir have been evaluated in healthy adult subjects and in subjects with chronic hepatitis C (Table 7).

Table 7 - INCIVEK pharmacokinetic parameters in adult healthy subjects and in subjects with chronic hepatitis C

INCIVEK PK parameters (750 mg q8h)	Healthy subjects (n=39)	CHC treatment-naïve subjects (n=641)	CHC treatment-experienced subjects (n=191)
C_{max} (ng/mL)	3040 (662)	3260 (946)	3990 (1120)
C_{min} (ng/mL)	1960 (548)	2690 (827)	3340 (1170)
AUC_{8h} (ng*h/mL)	19,900 (4710)	24,400 (7180)	30,100 (8720)

Telaprevir exposure was similar regardless of whether the total daily dose of 2250 mg was administered as 750 mg every 8 hours (q8h) or 1125 mg twice daily. Based upon population pharmacokinetic modeling of telaprevir steady-state exposures, the Geometric Mean Least Square Ratios (90% CI) of 1125 mg twice daily versus 750 mg every 8 hours (q8h) were 1.08 (1.02; 1.13) for $AUC_{24,ss}$, 0.878 (0.827; 0.930) for $C_{trough,ss}$, and 1.18 (1.12;1.24) for $C_{max,ss}$.

Absorption:

Absorption and Bioavailability

Telaprevir is orally available, most likely absorbed in the small intestine, with no evidence for absorption in the colon. Maximum plasma concentrations after a single dose of telaprevir are generally achieved after 4 to 5 hours. In vitro studies performed with human Caco-2 cells

indicated that telaprevir is a substrate of P-glycoprotein (P-gp). Exposure to telaprevir is higher during co-administration of peginterferon alfa and ribavirin than after administration of INCIVEK alone.

Effects of Food on Oral Absorption
The systemic exposure (AUC) to telaprevir was decreased by about 73% when telaprevir was administered under fasting conditions compared to administration with a standard fat meal (533 kcal, 21 g fat). In addition, the fat content of the meal significantly affects exposure to telaprevir. The telaprevir exposure was decreased by about 39% with a low-fat meal (249 kcal, 3.6 g fat) and about 26% with a low-calorie, high protein meal (260 kcal, 9 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. In the Phase 3 trials, INCIVEK was administered within 30 minutes of completing a meal or snack containing approximately 20 grams of fat. Therefore, INCIVEK should always be taken with food (not low-fat).

Distribution: 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. After oral administration, the typical apparent volume of distribution (Vd/F) was estimated to be 252 L, with an inter-individual variability of 72%.

Metabolism: Telaprevir is extensively metabolized in the liver, involving hydrolysis, oxidation, and reduction. Multiple metabolites were detected in feces, plasma, and urine. After repeated-oral administration, R-diastereomer 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 CYP3A4 was the major isoform for CYP-mediated telaprevir metabolism. *In vitro* studies using recombinant aldo-ketoreductases indicated that these and potentially other reductases are also responsible for the reduction of telaprevir. Other proteolytic enzymes are also involved in the hydrolysis of telaprevir. These non-CYP mediated pathways of metabolism likely play a major role after multiple dosing of telaprevir.

Excretion: Following administration of a single oral dose of 750 mg ^{14}C-telaprevir in healthy subjects, 90% of total radioactivity was recovered in feces, urine and expired air within 96 hours post-dose. The median recovery of the administered radioactive dose was approximately 82% in the feces, 9% in exhaled air and 1% in urine. The contribution of unchanged ^{14}C-telaprevir and the R-diastereomer of telaprevir towards total radioactivity recovered in feces was 31.9% and 18.8%, respectively. After oral administration, the apparent total clearance (Cl/F) was estimated to be 32.4 L/h with an inter-individual variability of 27.2%. The mean elimination half-life after single-dose oral administration of telaprevir 750 mg typically ranged from about 4.0 to 4.7 hours. At steady state, the effective half-life is about 9 to 11 hours.

Special Populations and Conditions
Gender: The effect of subject gender on telaprevir pharmacokinetics was evaluated using population pharmacokinetics of data from Phase 2 and 3 studies of telaprevir. No dose

adjustments are deemed necessary based on gender.

Race: Population pharmacokinetic analysis of telaprevir in HCV-infected subjects indicated that race had no apparent effect on the exposure to telaprevir.

Hepatic Insufficiency:
INCIVEK is not recommended in HCV-infected subjects with moderate or severe hepatic impairment. 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. The pharmacokinetics of telaprevir in HCV-negative subjects with severe hepatic impairment (Child-Pugh Class C) were not studied.

Dose modification of INCIVEK is not required when administered to subjects with mild hepatic impairment. 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.

In previously treated subjects with chronic HCV infection who had compensated liver disease and were treated with INCIVEK in combination with peginterferon alfa and ribavirin, subjects with cirrhosis had similar PK parameters compared to those without cirrhosis.

Renal Insufficiency: After administration of a single dose of 750 mg to HCV-negative subjects with severe renal impairment (CrCl < 30 mL/min), the mean telaprevir C_{max} and AUC were increased by 10% and 21%, respectively, compared to healthy subjects.

STORAGE AND STABILITY
Store at 25ºC; excursions permitted to 15-30ºC.

SPECIAL HANDLING INSTRUCTIONS

Disposal of unused/expired medicines:
The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established "collection systems" if available.

DOSAGE FORMS, COMPOSITION AND PACKAGING
Dosage form:
INCIVEK (telaprevir) is supplied as purple film-coated capsule-shaped tablets for oral administration. Each tablet is debossed with the characters "V 375" on one side.

Composition:
Each tablet contains 375 mg of telaprevir, colloidal silicon dioxide, croscarmellose sodium, D&C Red No. 40, dibasic calcium phosphate (anhydrous), FD&C Blue No. 2, hypromellose acetate

succinate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, sodium lauryl sulfate, sodium stearyl fumarate, talc, and titanium dioxide.

Packaging:
INCIVEK is packaged as follows:

- 28-day packer contains 4 weekly cartons of 7 blister strips each (6 tablets per blister strip): twice –daily dose.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

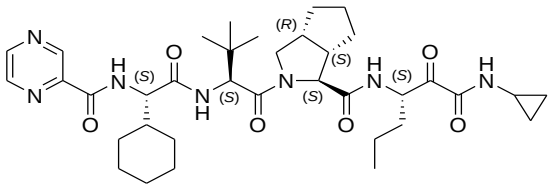
Drug Substance

Common name: telaprevir

Chemical name: (1*S*,3a*R*,6a*S*)-2-[(2*S*)-2-({(2*S*)-2-cyclohexyl-2-[(pyrazin-2-ylcarbonyl)amino]acetyl}amino)-3,3-dimethylbutanoyl]-*N*-[(3*S*)-1-(cyclopropylamino)-1,2-dioxohexan-3-yl]-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrole-1-carboxamide

Molecular formula and molecular mass: $C_{36}H_{53}N_7O_6$
MW 679.85

Structural formula:



Physicochemical properties: Telaprevir is a white to off-white powder that is practically insoluble in water (0.0047 mg/mL).

CLINICAL TRIALS

The efficacy and safety of INCIVEK in subjects with genotype 1 chronic hepatitis C was evaluated in four Phase 3 studies: three in treatment-naïve subjects and one in previously treated subjects (relapsers, partial responders, and null responders). Subjects in these studies had compensated liver disease, detectable HCV RNA, and liver histopathology consistent with chronic hepatitis C. Plasma HCV-RNA values were measured using the COBAS® TaqMan® HCV test (version 2.0), for use with the High Pure System. The primary endpoint was sustained virologic response (SVR). For Trials 108, 111, and C216, SVR was defined as less than 25 IU per mL at last observation within the SVR visit window (i.e., weeks 32-78 for subjects assigned to 24 weeks of treatment and weeks 56-78 for subjects assigned to 48 weeks of treatment) and is considered a virologic cure. For Trial C211, SVR was defined based on the HCV-RNA assessment in the window 12 weeks after the planned end of treatment, using the last measurement in the window. In addition, the limit of quantitation of 25 IU/mL was used to determine SVR (see Table 8).

Table 8 - Study Demographics and Trial Design

Study ID	Study Phase Type of Control Blind Population	Drugs Regimens	Assigned Regimen (Dosed/Completed Treatment)	Total Treatment Duration	Gender M/F Median Age (Range)
108	Phase 3 Randomized Placebo-controlled Double-Blind Parallel-group	Telaprevir (750 mg q8h) Peg-IFN-alfa-2a (180 µg/week) and RBV (1000 or 1200 mg/day, depending on body weight)	T8/PR (364/260) T12/PR (363/268) Pbo/PR48 (361/202)	24 or 48 weeks based on eRVR 24 or 48 weeks based on eRVR 48 weeks	636/452 49 (18; 69)
111	Phase 3 Randomized Active-controlled Open-label	Telaprevir (750 mg q8h) Peg-IFN-alfa-2a (180 µg/week) and RBV (1000 or 1200 mg/day, depending on body weight)	eRVR+ T12/PR24 (162/161) eRVR+ T12/PR48 (160/119) eRVR- T12/PR48 (118/79) Other (100/0)	eRVR+ and randomized to 24 or 48 weeks PR treatment arms eRVR- subjects assigned to PR48 treatment arm Discontinued before week 20	325/215 51 (19; 70)
C216	Phase 3 Randomized Placebo-controlled Blinded	Telaprevir (750 mg q8h) Peg-IFN-alfa-2a (180 µg/week) and RBV (1000 or 1200 mg/day, depending on body weight)	T12/PR48 (266/215) T12(DS)/PR48 (264/226) Pbo/PR48 (132/88)	48 weeks 48 weeks 48 weeks	460/202 51 (21; 70)
C211	Phase 3 Randomized Active-controlled Open-label	**Arm 1:** Telaprevir (750 mg q8h) three times a day Peg-IFN-alfa-2a (180 µg/week) and RBV (1000 or 1200 mg/day, depending on body weight) OR **Arm 2:** Telaprevir (1125 mg b.i.d.) twice a day Peg-IFN-alfa-2a (180 µg/week) and RBV (1000 or 1200 mg/day, depending on body weight).	T12 (q8h)/PR (371/112) T12 (b.i.d)/PR (369/101)	24 or 48 weeks based on RVR 24 or 48 weeks based on RVR	444/296 51 (18; 70)

Treatment-naïve Adults

Study 108 (ADVANCE)

Study 108 was a randomized, double-blind, parallel-group, placebo-controlled trial conducted in treatment-naïve subjects (had received no prior therapy for HCV, including interferon or pegylated interferon monotherapy). INCIVEK was given for the first 8 weeks of treatment (T8/PR regimen) or the first 12 weeks of treatment (T12/PR regimen) in combination with Peg-IFN-alfa-2a/RBV for either 24 or 48 weeks. Subjects who had undetectable HCV RNA (Target Not Detected) at weeks 4 and 12 (extended Rapid Virologic Response [eRVR]) received 24 weeks of Peg-IFN-alfa-2a/RBV treatment, and subjects who did not have undetectable HCV RNA at weeks 4 and 12 (no eRVR) received 48 weeks of Peg-IFN-alfa-2a/RBV treatment. The control regimen (Pbo/PR48) had a fixed treatment duration, with telaprevir-matching placebo for the first 12 weeks and Peg-IFN-alfa-2a/RBV for 48 weeks.

Demography and baseline characteristics are summarized in Table 9.

Table 10 shows the response rates for the T12/PR and Pbo/PR48 groups.

Study 111 (ILLUMINATE)

Study 111 was a randomized, open-label trial conducted in treatment-naïve subjects. The study was a non-inferiority trial designed to compare SVR rates in subjects achieving eRVR who were treated with INCIVEK for 12 weeks in combination with Peg-IFN-alfa-2a/RBV for either 24 weeks (T12/PR24 regimen) or 48 weeks (T12/PR48 regimen). The primary assessment was an evaluation of non-inferiority, using a margin of -10.5% of the 24-week regimen compared to the 48-week regimen in subjects with undetectable HCV RNA at weeks 4 and 12.

Demography and baseline characteristics are summarized in Table 9.

Previously Treated Adults

Study C216 (REALIZE)

Study C216 was a randomized, double-blind, placebo-controlled trial conducted in subjects who did not achieve SVR with prior treatment with Peg-IFN-alfa-2a/RBV or Peg-IFN-alfa-2b/RBV. The study enrolled prior relapsers (subjects with HCV RNA undetectable at end of treatment with a pegylated interferon-based regimen, but HCV RNA detectable within 24 weeks of treatment follow-up) and prior non-responders (subjects who did not have undetectable HCV- RNA levels during or at the end of a prior course of at least 12 weeks of treatment). The nonresponder population included 2 subgroups: prior partial responders (greater than or equal to 2-$\log_{10}$ reduction in HCV RNA at week 12, but not achieving HCV RNA undetectable at end of treatment with peginterferon alfa and ribavirin) and prior null responders (less than 2-$\log_{10}$ reduction in HCV RNA at week 12 of prior treatment with peginterferon alfa and ribavirin).

Subjects were randomized in a 2:2:1 ratio to one of two INCIVEK combination treatment groups (with and without a Peg-IFN-alfa-2a/RBV lead-in) or a control group. The T12/PR48 group received INCIVEK and Peg-IFN-alfa-2a/RBV for 12 weeks (without a lead-in), followed by placebo and Peg-IFN-alfa-2a/RBV for 4 weeks, followed by Peg-IFN-alfa-2a/RBV for 32 weeks. The T12(DS)/PR48 group had a lead-in (delayed start of INCIVEK) with placebo and Peg-IFN-alfa-2a/RBV for 4 weeks, followed by INCIVEK and Peg-IFN-alfa-2a/RBV for 12 weeks,

followed by Peg-IFN-alfa-2a/RBV for 32 weeks. The Pbo/PR48 group received placebo and Peg-IFN-alfa-2a/RBV for 16 weeks, followed by Peg-IFN-alfa-2a/RBV for 32 weeks.

Demography and baseline characteristics are summarized in Table 9.

The lead-in and immediate start regimens produced comparable SVR and no SVR rates, so data from these two groups were pooled (Table 13).

Table 9 - Demography and Baseline Characteristics: Study 108, Study 111, Study C216 and Study C211

Variable	Study 108 N=1088 n (%)	Study 111 N=540 n (%)	Study C216 N=662 n (%)	Study C211 N=740 n (%)
BMI, kg/m^2				
<25	430 (40)	177 (33)	216 (33)	304 (41)
≥25 to <30	404 (37)	188 (35)	273 (41)	280 (38)
≥30	250 (23)	174 (32)	172 (26)	153 (21)
Race				
Caucasian/White	958 (88)	427 (79)	615 (93)	680 (92)
Black	94 (9)	73 (14)	30 (5)	35 (5)
Asian	20 (2)	9 (2)	11 (2)	16 (2)
Other	16 (1)	31 (6)	6 (1)	9 (1)
Ethnicity				
Hispanic or Latino	117 (11)	54 (10)	72 (11)	90 (12)
Not Hispanic or Latino	971 (89)	473 (88)	590 (89)	649 (88)
Baseline HCV RNA, IU/mL				
<800000	249 (23)	95 (18)	76 (11)	111 (15)
≥800000	839 (77)	445 (82)	586 (89)	629 (85)
Result of most recent liver biopsy[a]				
No or minimal fibrosis	409 (38)	147 (27)	154 (23)	349 (47)
Portal fibrosis	448 (41)	244 (45)	192 (29)	180 (24)
Bridging fibrosis	163 (15)	88 (16)	147 (22)	107 (15)
Cirrhosis	68 (6)	61 (11)	169 (26)	103 (14)
HCV genotype				
1a	641 (59)	387 (72)	352 (54)	419 (57)
1b	439 (40)	147 (27)	300 (46)	317 (43)
1 (subtype unknown)	8 (1)	6 (1)		

[a] Measured by METAVIR fibrosis score F0-F4

Null and partial responders had higher baseline HCV RNA levels and more advanced liver disease (cirrhosis) than relapsers; other characteristics were similar across these populations.

STUDY RESULTS

Treatment-naïve Adults

Study 108 (ADVANCE)

Table 10 shows the response rates for the T12/PR and Pbo/PR48 groups. The SVR rate was significantly higher (P<0.0001) in the T12/PR group (79%) than in the Pbo/PR48 group (46%).

Table 10 - Response Rates: Study 108

Treatment Outcome	T12/PR N = 363 (%) n/N	Pbo/PR48 N = 361 (%) n/N
SVR	79 (285/363)	46 (166/361)
RVR (undetectable at Week 4)	68 (246/363)	9 (34/361)
SVR in RVR subjects	87 (215/246)	91 (31/34)
eRVR	58 (212/363)	8 (29/361)
SVR in eRVR subjects	92 (195/212)	93 (27/29)
No eRVR	42 (151/363)	92 (332/361)
SVR in no eRVR subjects	60 (90/151)	42 (139/332)
Outcome for Subjects without SVR		
On-treatment virologic failure[a]	7 (26/363)	29 (105/361)
Relapse[b]	4 (11/298)	24 (53/220)
Other[c]	11 (41/363)	10 (37/361)

[a] On-treatment failure includes subjects who met a protocol-defined virologic stopping rule and/or who had detectable HCV RNA at the end of treatment with viral breakthrough.
[b] Relapse was defined as having less than 25 IU/mL at last observation within the planned end of treatment visit window followed by detectable HCV RNA during follow-up.
[c] Other includes subjects with detectable HCV RNA at the time of their last trial drug but who did not have viral breakthrough, and subjects with a missing SVR assessment.

In the T8/PR group, the overall SVR rate was 72%. The eRVR rate was 57% and the SVR rate for eRVR subjects was 86%. The SVR rate for no eRVR subjects was 52%. More subjects in the T8/PR group experienced virologic failure after Week 12 while receiving peginterferon alfa and ribavirin alone, 7% compared to 4% in T12/PR group.

The rate of undetectable HCV RNA at treatment week four was higher for the T12/PR group (68%; 243/363) than for the Pbo/PR48 group (9%; 34/361). In the T12/PR group, 54% (195/363) of subjects completed 24 weeks.

SVR rates were higher (absolute difference of at least 22%) for the T12/PR group than for the Pbo/PR48 group across subgroups by sex, age, race, ethnicity, body mass index, HCV genotype subtype, baseline HCV RNA (less than 800,000, greater than or equal to 800,000 IU/mL), and extent of liver fibrosis. In subjects with either no/minimal or portal fibrosis, the SVR rates were higher for the T12/PR group (82%; 237/290) than for the Pbo/PR48 group (49%; 140/288) [95% CI (25.8, 40.4)]. Among subjects with advanced fibrosis (bridging fibrosis or cirrhosis), the SVR rates were higher for the T12/PR group (66%; 48/73) than for the Pbo/PR48 group (36%; 26/73) [95% CI (14.7, 45.6)]. However, there were small numbers of subjects enrolled in some key subgroups. In the T12/PR group:

- Twenty-one subjects had cirrhosis at baseline and the overall SVR in these subjects was 71% (15/21). Among subjects with cirrhosis, 43% (9/21) achieved an eRVR and were assigned to 24 weeks of treatment; of those, 78% (7/9) achieved SVR. In the Pbo/PR48 group, the SVR rate for subjects with cirrhosis was 38% (8/21).
- Twenty-six subjects were Black/African Americans. The overall SVR among Black/African American subjects was 62% (16/26). Among these subjects, 35% (9/26) achieved an eRVR and were assigned to 24 weeks of treatment; of those, 89% (8/9) achieved SVR. In the Pbo/PR48 group, the SVR rate for Black/African American subjects was 29% (8/28).

Table 11 shows SVR rates for subject subgroups.

Table 11: SVR rates for subject subgroups: Study 108

Subgroup	**T12/PR**	**Pbo/PR**
Men	78% (166/214)	46% (97/211)
>45 to ≤ 65 years of age	73% (157/214)	39% (85/216)
Caucasian	79% (258/325)	48% (153/318)
Black	62% (16/26)	29% (8/28)
Hispanic Latino	77% (27/35)	39% (15/38)
BMI ≥ 30 kg/m^2	73% (56/77)	44% (38/87)
Baseline HCV RNA ≥ 800,000 IU/mL	77% (215/281)	39% (109/279)
HCV genotype 1a	74% (157/213)	42% (88/208)
HCV genotype 1b	85% (127/149)	52% (78/151)
Baseline liver fibrosis		
No fibrosis, minimal fibrosis, or portal fibrosis	82% (237/290)	49% (140/288)
Bridging fibrosis	63% (33/52)	35% (18/52)
Cirrhosis	71% (15/21)	38% (8/21)

T12/PR: INCIVEK for 12 weeks with peginterferon alfa-2a and ribavirin for 24 or 48 weeks;
Pbo/PR: placebo for 12 weeks with peginterferon alfa-2a and ribavirin for 48 weeks

Study 111 (ILLUMINATE)

The SVR rate for all subjects enrolled in the trial was 74%. 72% (389/540) of subjects achieved undetectable HCV RNA at week 4 (rapid virologic response). A total of 352 (65%) subjects achieved eRVR and of those 322 (60%) were randomized to 24 weeks (T12/PR24, n=162) or 48 weeks (T12/PR48, n=160) of treatment. The SVR rates were similar at 92% (T12/PR24) and 90% (T12/PR48), respectively. Again, small numbers of subjects were enrolled in some key subgroups:

- Sixty-one (11%) of subjects had cirrhosis at baseline. Among subjects with cirrhosis, 30 (49%) achieved an eRVR: 18 were randomized to T12/PR24 and 12 to T12/PR48. The SVR rates were 61% (11/18) for the T12/PR24 group and 92% (11/12) for the T12/PR48 group.
- Blacks/African Americans comprised 14% (73/540) of study subjects. Thirty-four (47%) Black/African American subjects achieved an eRVR and were randomized to T12/PR24

or T12/PR48. The SVR rates were both 88% (15/17), compared to 92% (244/266) for Caucasians among randomized subjects.

The SVR rate for Black/African American subjects was 62% (45/73).

Table 12 shows SVR rates by extent of liver fibrosis at baseline.

Table 12: SVR Rates by Extent of Liver Fibrosis at Baseline: Study 111

Subgroup	Subjects with undetectable HCV RNA at weeks 4 and 12		T12/PR All Subjects[a]
	T12/PR24	T12/PR48	
No fibrosis, minimal fibrosis, or portal fibrosis	96% (119/124)	91% (115/127)	77% (302/391)
Bridging fibrosis	95% (19/20)	86% (18/21)	74% (65/88)
Cirrhosis	61% (11/18)	92% (11/12)	51% (31/61)

T12/PR24: INCIVEK for 12 weeks with peginterferon alfa-2a and ribavirin for 24 weeks;
T12/PR48: INCIVEK for 12 weeks with peginterferon alfa-2a and ribavirin for 48 weeks
[a] All subjects includes the 322 subjects with undetectable HCV RNA at weeks 4 and 12 and the 218 other subjects treated in the study (118 who did not have undetectable HCV RNA at weeks 4 and 12 and 100 who discontinued the study before week 20, when randomization occurred)

Study C211(OPTIMIZE)

Study C211 was a randomized, open-label, Phase 3 trial in treatment-naïve subjects randomized to receive 12 weeks of either INCIVEK 750 mg every 8 hours [T12(q8h)/PR] or INCIVEK 1125 mg twice daily [T12 (twice daily.)/PR] in combination with peginterferon alfa-2a and ribavirin. The trial was designed to compare twice-daily dosing [T12(twice daily)/PR] versus q8h dosing [T12(q8h)/PR] of INCIVEK. At week 12, INCIVEK dosing ended and subjects continued on peginterferon alfa-2a and ribavirin treatment. The total treatment duration was determined based on the subjects' individual on-treatment viral response. If a subject achieved undetectable HCV RNA < 25 IU/mL (Target Not Detected) at week 4, the total treatment duration was 24 weeks. Otherwise, the total treatment duration was 48 weeks.

The 740 enrolled subjects had a median age of 51 years (range: 18 to 70); 60% of the subjects were male; 21% had a body mass index ≥ 30 kg/m^2; 5% were Black/African American; 2% were Asian; 85% had baseline HCV RNA levels ≥ 800,000 IU/mL; 15% had bridging fibrosis; 14% had cirrhosis; 57% had HCV genotype 1a; and 43% had HCV genotype 1b.

Table 13 shows the response rates for the T12 (twice daily)/PR group and the T12 (q8h)/PR group by treatment outcomes. The overall SVR rates were similar at 74% [T12 (twice daily)/PR; 274/369] and 73% [T12 (q8h)/PR; 270/371], respectively.

Table 13: Response Rates: Study C211

Treatment outcome	T12(twice daily)/PR N = 369 % (n/N)	T12(q8h)/PR N = 371 % (n/N)
SVR	74% (274/369)	73% (270/371)
RVR (undetectable at week 4)[a]	69% (256/369)	67% (250/371)
SVR in RVR subjects	86% (221/256)	85% (213/250)
eRVR	66% (244/369)	63% (234/371)
SVR in eRVR subjects	89% (218/244)	89% (209/234)
No eRVR	34% (125/369)	37% (137/371)
SVR in no eRVR subjects	45% (56/125)	45% (61/137)
Outcome for Subjects without SVR		
On-treatment virologic failure[b]	10% (38/369)	10% (36/371)
Relapse[c]	8% (23/300)	6% (19/293)
Other[d]	9% (34/369)	12% (46/371)

[a] Subjects with planned total treatment duration of 24 weeks.

[b] On-treatment-virologic failure includes subjects who met a protocol-defined virologic stopping rule and/or who had detectable HCV RNA at the time of their last dose of study drug and had viral breakthrough.

[c] Relapse was defined as having less than 25 IU/mL at the planned end of treatment followed by HCV RNA $\geq$ 25 IU/mL at the last observation within the SVR follow-up visit window.

[d] Other includes subjects with detectable HCV RNA at the planned end of treatment but who did not have viral breakthrough, and subjects with a missing SVR assessment during planned follow-up.

SVR rates were similar for the T12 (twice daily)/PR and T12 (q8h)/PR groups across subgroups determined by sex, age, race, ethnicity, body mass index, HCV genotype subtype, IL28B genotype, baseline HCV RNA (less than 800,000, greater than or equal to 800,000 IU/mL), and extent of liver fibrosis. However, there were small numbers of subjects who were Black/African American (35) or who had cirrhosis (see Table 14). The overall SVR among Black/African American subjects was 50% (10/20) in the T12 (twice daily)/PR group and 60% (9/15) in the T12 (q8h)/PR group. Forty-six percent (16/35) of these subjects were assigned to 24 weeks of treatment and of those 88% (14/16) achieved SVR.

Table 14 shows SVR rates by extent of liver fibrosis at baseline.

Table 14: SVR Rates by Extent of Liver Fibrosis at Baseline: Trial C211

Subgroup	T12(twice daily)/PR N = 369 SVR % (n/N)	T12(q8h)/PR N = 371 SVR % (n/N)
Baseline liver fibrosis		
No fibrosis or minimal fibrosis	80% (138/172)	79% (140/177)
Portal fibrosis	79% (75/95)	80% (68/85)
Bridging fibrosis	67% (32/48)	64% (38/59)
Cirrhosis	54% (29/54)	49% (24/49)

HIV-1 Co-infected patients:
INCIVEK in combination with peginterferon alfa and ribavirin was assessed in a Phase 2 trial of genotype 1 chronic HCV/HIV-1 co-infected subjects (N=60), who were either not on HIV antiretroviral therapy or who were being treated with either efavirenz, in combination with tenofovir disoproxil fumarate and emtricitabine or atazanavir/ritonavir, tenofovir disoproxil fumarate and emtricitabine or lamivudine regimen (see **ADVERSE REACTIONS**).

Previously Treated Adults

Study C216 (REALIZE)

Table 15 shows the response rates for the T12/PR48 and Pbo/PR48 groups. Compared to the T12/PR48 group, the lead-in T12(DS)/PR48 group did not provide any clinically meaningful difference in SVR rates.

For the prior relapse population, SVR rates were significantly higher (P<0.001) in the T12/PR48 group (86%) than in the Pbo/PR48 group (22%). For the prior partial responder population, SVR rates were significantly higher (P<0.001) in the T12/PR48 group (59%) than in the Pbo/PR48 group (15%). For the prior null responder population, SVR rates were significantly higher (P<0.001) in the T12/PR48 group (32%) than in the Pbo/PR48 group (5%).

Table 15 - Response Rates: Study C216

Treatment Outcome	All T12/PR48[a] % (n/N)	Pbo/PR48 % (n/N)
SVR rate		
Prior relapsers	86 (246/286)	22 (15/68)
Prior partial responders	59 (57/97)	15 (4/27)
Prior null responders	32 (47/147)	5 (2/37)
Treatment Outcomes for Subjects Without SVR		

Treatment Outcome	All T12/PR48[a] % (n/N)	Pbo/PR48 % (n/N)
On-treatment virologic failure[b]		
Prior relapsers	1 (3/286)	26 (18/68)
Prior partial responders	18 (17/97)	70 (19/27)
Prior null responders	52 (76/147)	84 (31/37)
Relapse[c]		
Prior relapsers	3 (8/254)	63 (27/43)
Prior partial responders	20 (14/71)	0 (0/4)
Prior null responders	24 (15/62)	50 (2/4)

[a] Lead-in and immediate start T12/PR regimens pooled

[b] On-treatment virologic failure includes subjects who met a protocol-defined virologic stopping rule or who had detectable HCV RNA at the time of their last dose of INCIVEK and subjects who had viral breakthrough on peginterferon alfa/ribavirin.

[c] Relapse rates are calculated with a denominator of subjects with undetectable HCV RNA (Target Not Detected) at the end of treatment

Among prior relapsers, 76% (218/286) achieved an eRVR and of those 95% (208/218) achieved an SVR. In earlier clinical trials, 78% (52/67) of prior relapsers achieved an eRVR and were treated with 24 weeks of peginterferon alfa and ribavirin (T12/PR24); of those, 94% (49/52) achieved an SVR.

For all populations in the study (prior relapsers, prior partial responders, and prior null responders), SVR rates were higher for the T12/PR group than for the Pbo/PR48 group across subgroups by sex, age, ethnicity, body mass index, HCV genotype subtype, baseline HCV-RNA level, and extent of liver fibrosis.

Twenty-six percent (139/530) of INCIVEK-treated subjects had cirrhosis at baseline. SVR rates among cirrhotic subjects who received INCIVEK combination treatment compared to Pbo/PR48 were: 84% (48/57) compared to 7% (1/15) for prior relapsers, 34% (11/32) compared to 20% (1/5) for prior partial responders, and 14% (7/50) compared to 10% (1/10) for prior null responders.

Four percent (19/530) of treatment experienced subjects who received INCIVEK combination treatment were Black/African Americans; the SVR rate for these subjects was 63% (12/19) compared to 66% (328/498) for Caucasians.

Table 16 shows SVR rates by extent of liver fibrosis.

Table 16: SVR Rates by Extent of Liver Fibrosis at Baseline: Study C216		
Extent of liver fibrosis	**All T12/PR48[a]**	**Pbo/PR48**
Prior relapsers		
No or minimal fibrosis or portal fibrosis	87% (145/167)	32% (12/38)
Bridging fibrosis	85% (53/62)	13% (2/15)

Cirrhosis	84% (48/57)	7% (1/15)
Prior partial responders		
No or minimal fibrosis or portal fibrosis	77% (36/47)	18% (3/17)
Bridging fibrosis	56% (10/18)	0 (0/5)
Cirrhosis	34% (11/32)	20% (1/5)
Prior null responders		
No or minimal fibrosis or portal fibrosis	41% (24/59)	6% (1/18)
Bridging fibrosis	42% (16/38)	0 (0/9)
Cirrhosis	14% (7/50)	10% (1/10)

[a] Lead-in and immediate start T12/PR regimens pooled.
T12/PR48: INCIVEK for 12 weeks followed by placebo for 4 weeks, in combination with peginterferon alfa-2a and ribavirin for 48 weeks; Pbo/PR48: placebo for 16 weeks in combination with peginterferon alfa-2a and ribavirin for 48 weeks

DETAILED PHARMACOLOGY

Pharmacodynamics

Safety Pharmacology

Telaprevir inhibited hERG currents in stably transfected HEK293 (N=4) with an IC_{25} value of 54.95 μM (nominal concentrations).

In canine Purkinje fibres (N=4/treatment), telaprevir increased action potential duration at 90% of repolarisation (APD90) by 8% ($P<0.05$) at a nominal concentration of 50 μM when compared to the vehicle-treated group.

In a placebo-controlled crossover study in free-moving, conscious telemetry dogs (N=4), telaprevir was not associated with effects on blood pressure, heart rate, or ECG intervals when tested at single doses of 25, 75, and 250 mg/kg administered by oral gavage.

Results of a thorough QTc study in healthy subjects demonstrated a modest effect of a telaprevir dose (1875 mg q8h) on the QTcF interval with a placebo-adjusted maximum mean increase of 8.0 ms (90% CI: 5.1; 10.9).

Telaprevir had no significant effect on mean respiratory rate or tidal volume and no effect on the autonomic nervous system up to a maximum dose of 1000 mg/kg in rats.

Pharmacokinetics

Absorption

Telaprevir is orally available, most likely absorbed in the small intestine, with no evidence for absorption in the colon. In clinical studies in healthy subjects in which a single 750-mg dose of telaprevir was administered after a regular breakfast, the mean telaprevir C_{max} ranged from 1692 to 2217 ng/mL, the median time of maximum concentration (t_{max}) ranged from 4.0 to 5.0 hours, the mean AUC_{∞} ranged from 10414 to14360 hr.ng/mL, and the mean half-life ($t_{1/2}$) ranged from 4.0 to 4.7 hours. In single-dose studies in healthy subjects given telaprevir in the fed state,

telaprevir exposure was greater than dose proportional between 375-mg and 1875-mg doses. Within the truncated 750-mg to 1500-mg dose range, C_{max} increased proportional to dose, and AUC increased greater than proportional to dose.

Studies with HCV-infected subjects also showed that plasma telaprevir AUC increased with increasing telaprevir dose. In multiple dose studies in HCV-infected subjects, steady-state was reached around Days 3 to 7, and telaprevir accumulated to steady-state with a mean accumulation index of 1.7.

Comparison of telaprevir exposure and the elimination half-life in healthy subjects and subjects with chronic HCV infection revealed similar results after single dose administration. In subjects with chronic HCV infection, exposure (steady-state AUC) to telaprevir was about 20 to 30% higher during co-administration with Peg-IFN. Co-administration of RBV with the combination of telaprevir and Peg-IFN did not seem to affect telaprevir exposure. Similar differences in telaprevir exposure after administration of telaprevir monotherapy or in combination with Peg-IFN/RBV were observed. Telaprevir exposure was comparable when coadministered with either Peg-IFN-alfa-2b/RBV or Peg-IFN-alfa-2a/RBV.

Distribution
In vitro, telaprevir binding to human plasma proteins ranged between 59% to 76% at telaprevir concentrations ranging from 0.1 to 20 μM, with decreased binding at higher concentrations. Telaprevir binds to both albumin and alpha-1-acid glycoprotein *in vitro,* and the binding was found to decrease with decreasing concentrations of these proteins.

Metabolism
In vitro studies using recombinant human CYP isoforms indicated that CYP3A4 was the major CYP isoform responsible for telaprevir metabolism. *In vitro* studies using recombinant aldo-ketoreductases indicated that these and potentially other reductases are also responsible for the reduction of telaprevir. Other proteolytic enzymes are also involved in the hydrolysis of telaprevir.

The metabolism of telaprevir was investigated in an open-label, non-randomized, mass balance study in which 6 healthy male subjects each received a single, oral dose of 750-mg ^{14}C-labeled telaprevir. In plasma, telaprevir and VRT-127394 were the major analytes. Metabolites were detected in feces, indicating hydrolysis, oxidation, and reduction to produce numerous metabolites and isomers. Qualitatively, the metabolites detected in humans were similar to those seen in the rat.

Excretion
Elimination in the feces was the predominant route of excretion for telaprevir and its metabolites, with minimal renal excretion. The mean percentage of the administered dose recovered in feces was 81.3% while approximately 8% of the administered dose was recovered in expired air and 1% in urine.

Food Effect

The systemic exposure (AUC) to telaprevir was decreased by about 73% when telaprevir was administered under fasting conditions compared to administration with a standard fat meal (533 kcal, 21 g fat). In addition, the fat content of the meal significantly affects exposure to telaprevir. The telaprevir exposure was decreased by about 39% with a low-fat meal (249 kcal, 3.6 g fat) and about 26% with a low-calorie, high protein meal (260 kcal, 9 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. In the Phase 3 trials INCIVEK was administered within 30 minutes of completing a meal or snack containing approximately 20 grams of fat. Therefore, INCIVEK should always be taken with food (not low-fat).

Subjects with Hepatic Impairment

Hepatic impairment decreased telaprevir exposure. Steady-state telaprevir (AUC_{8h}) in HCV-negative subjects with mild hepatic impairment (CPA) was approximately 15% lower than in healthy subjects, but this result was not considered to be clinically significant. In HCV-negative subjects with moderate hepatic impairment (CPB), steady-state telaprevir exposure (AUC_{8h}) was approximately 46% lower than that in healthy subjects. The pharmacokinetics of telaprevir were not studied in subjects with severe hepatic impairment.

Drug-Drug Interactions

Telaprevir is a substrate and a strong inhibitor of CYP3A and a substrate and inhibitor of P-gp. *In vitro* studies indicated that telaprevir is also an inhibitor of OATP1B1 and OATP2B1. No inhibition by telaprevir of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP2E1 isozymes was observed *in vitro*. *In vitro* studies also suggest that telaprevir has a low potential to induce CYP1A2, CYP2B6, CYP3A, or CYP2C. Furthermore, *in vitro* studies suggest that telaprevir is neither a substrate for BCRP, OATP1B1, OATP2B1, OCT2, MRP2, and MRP4, nor an inhibitor of BCRP, MRP2, MRP4, OCT2 and OAT1 transporters. Clinical studies were conducted to evaluate the effect of drugs that can affect or be affected by telaprevir during co-administration (see Table 17 and Table 18).

Table 17 - Drug Interactions: Summary of Pharmacokinetic Parameters for Telaprevir in the Presence of Co-administered Drugs*

	Dose and Schedule			Effect on Telaprevir PK[a]	LS Mean Ratio (90% CI) of Telaprevir PK With/Without Co-administered Drug		
Drug	Drug	Telaprevir	N		C_{max}	AUC or $C_{avg,ss}$[b]	C_{min}
Carbamazepine	200 mg q12h for 17 days	750 mg q8h for 10 days	11	↓	0.79 (0.70; 0.90)	0.68 (0.58; 0.79)	0.53 (0.44; 0.65)
Escitalopram	10 mg qd for 7 days	750 mg q8h for 14 days	13	↔	1.00 (0.95; 1.05)	0.93 (0.89; 0.97)	0.91 (0.86; 0.97)
Esomeprazole	40 mg qd for 6 days	750 mg single dose	24	↔	0.95 (0.86; 1.06)	0.98 (0.91; 1.05)	NA
Ketoconazole	Ketoconazole 400 mg single dose	750 mg single dose	17	↑	1.24 (1.10; 1.41)	1.62 (1.45; 1.81)	NA
Oral Contraceptive	Norethindrone/ ethinyl estradiol 0.5 mg/0.035 mg qd for 21 days	750 mg q8h for 21 days	23	↔	1.00 (0.93; 1.07)	0.99 (0.93; 1.05)	1.00 (0.93; 1.08)
Phenytoin	200 mg q12h for 17 days	750 mg q8h for 10 days	7	↓	0.68 (0.60; 0.77)	0.53 (0.47; 0.60)	0.32 (0.25; 0.42)
Rifampin	600 mg qd for 8 days	750 mg single dose	16	↓	0.14 (0.11; 0.18)	0.08 (0.07; 0.11)	NA
Anti-HIV Drugs							
Atazanavir (ATV)/ritonavir (rtv)	300 mg ATV/ 100 mg rtv qd for 20 days	750 mg q8h for 10 days	14	↓	0.79 (0.74; 0.84)	0.80 (0.76; 0.85)	0.85 (0.75; 0.98)
Darunavir (DRV)/ritonavir (rtv)	600 mg DRV/ 100 mg rtv bid for 20 days	750 mg q8h for 10 days	11 (N=14 for C_{max})	↓	0.64 (0.61; 0.67)	0.65 (0.61; 0.69)	0.68 (0.63; 0.74)
Efavirenz	600 mg qd for 20 days	750 mg q8h for 10 days	21	↓	0.91 (0.82; 1.02)	0.74 (0.65; 0.84)	0.53 (0.44; 0.65)
Fosamprenavir (fAPV)/ ritonavir (rtv)	700 mg fAPV/ 100 mg rtv bid for 20 days	750 mg q8h for 10 days	18	↓	0.67 (0.63; 0.71)	0.68 (0.63; 0.72)	0.70 (0.64; 0.77)
Lopinavir (LPV)/ritonavir (rtv)	400 mg LPV/ 100 mg rtv bid for 20 days	750 mg q8h for 10 days	12	↓	0.47 (0.41; 0.52)	0.46 (0.41; 0.52)	0.48 (0.40; 0.56)
Raltegravir	400 mg bid for 11 days	750 mg q8h for 7 days	20	↔	1.07 (0.98; 1.16)	1.07 (1.00; 1.15)	1.14 (1.04; 1.26)

Table 17 - Drug Interactions: Summary of Pharmacokinetic Parameters for Telaprevir in the Presence of Co-administered Drugs*

	Dose and Schedule			Effect on Telaprevir PK[a]	LS Mean Ratio (90% CI) of Telaprevir PK With/Without Co-administered Drug		
Drug	Drug	Telaprevir	N		C_{max}	AUC or $C_{avg,ss}$[b]	C_{min}
Ritonavir	100 mg single dose	750 mg single dose	14	↑	1.30 (1.15; 1.47)	2.00 (1.72; 2.33)	NA
Ritonavir	100 mg q12h for 14 days	750 mg q12h for 14 days	5	↓	0.85 (0.63; 1.13)	0.76[b,c] (0.60; 0.97)	0.68 (0.57; 0.82)
Tenofovir disoproxil fumarate (TDF)	300 mg qd TDF for 7 days	750 mg q8h for 7 days	16	↔	1.01 (0.96; 1.05)	1.00 (0.94; 1.07)	1.03 (0.93; 1.14)
Tenofovir disoproxil fumarate (TDF) and efavirenz (EFV)	600 mg EFV /300 mg TDF qd for 7 days	1125 mg q8h for 7 days	15	↓	0.86[c] (0.76; 0.97)	0.82[c] (0.73; 0.92)	0.75[c] (0.66; 0.86)
	600 mg EFV /300 mg TDF qd for 7 days	1500 mg q12h for 7 days	16	↓	0.97[c] (0.88; 1.06)	0.80[b,c] (0.73; 0.88)	0.52[c] (0.42; 0.64)

NA: not available/ not applicable; N = Number of subjects with data; qd = once daily; bid = twice daily; q8h = every 8 hours; q12h = every 12 hours

[a] The direction of the arrow (↑ = *increase*, ↓ = *decrease*, ↔ = *no change*) indicates the direction of the change in PK

[b] $C_{avg,ss}$ = Average concentrations at steady state (AUC_τ/τ).

[c] Value with co-administered drug and telaprevir / value with telaprevir 750 mg q8h alone

*Data provided are under fed conditions unless otherwise noted.

Table 18 - Drug Interactions: Summary of Pharmacokinetic Parameters for Co-administered Drugs in the Presence of Telaprevir

	Dose and Schedule			Effect on Drug PK[a]	LS Mean Ratio (90% CI) of Drug PK With/Without Telaprevir		
Drug	Drug	Telaprevir	N		C_{max}	AUC	C_{min}
Alprazolam	0.5 mg single dose	750 mg q8h for 11 days	17	↑	0.97 (0.92; 1.03)	1.35 (1.23; 1.49)	NA
Amlodipine	5 mg single dose	750 mg q8h for 7 days	19	↑	1.27 (1.21; 1.33)	2.79 (2.58; 3.01)	NA
Atorvastatin	20 mg single dose	750 mg q8h for 7 days	19	↑	10.60 (8.74;12.85)	7.88 (6.84; 9.07)	NA
Buprenorphine	Buprenorphine maintenance therapy (4 to 24 mg/daily in	750 mg q8h for 7 days	14	↔	0.80 (0.69; 0.93)	0.96 (0.84; 1.10)	1.06 (0.87; 1.30)

Table 18 - Drug Interactions: Summary of Pharmacokinetic Parameters for Co-administered Drugs in the Presence of Telaprevir

	combination with naloxone)						
Carbamazepine	200 mg q12h for 17 days	750 mg q8h for 10 days	11	↔	1.09 (0.98; 1.21)	1.10 (0.99; 1.23)	1.10 (0.97; 1.24)
Cyclosporine A (CsA)	100 mg single dose when administered alone; 10 mg single dose when co-administered with telaprevir (D8)	750 mg q8h for 11 days	9	↑	0.13 (0.11; 0.16) **Dose norm.:** 1.32 (1.08; 1.60)	0.46 (0.39; 0.55) **Dose norm.:** 4.64 (3.90; 5.51)	NA
Digoxin	0.5 mg single dose	750 mg q8h for 11 days	20	↑	1.50 (1.36; 1.65)	1.85 (1.70; 2.00)	NA
Escitalopram	10 mg qd, for 7 days	750 mg q8h for 14 days	13	↓	0.70 (0.65; 0.76)	0.65 (0.60; 0.70)	0.58 (0.52; 0.64)
Ethinyl estradiol (EE), co-administered with norethindrone (NE)	0.035 mg qd EE/ 0.5 mg qd NE for 21 days	750 mg q8h for 21 days	24	↓	0.74 (0.68; 0.80)	0.72 (0.69; 0.75)	0.67 (0.63; 0.71)
Ketoconazole	400 mg single dose	1250 mg q8h for 4 doses	81	↑	1.23 (1.14; 1.33)	1.46 (1.35; 1.58)	NA
	200 mg single dose	1250 mg q8h for 4 doses	28	↑	1.75 (1.51; 2.03)	2.25 (1.93; 2.61)	NA
R-Methadone	Methadone maintenance therapy (40 to 120 mg/daily)	750 mg q8h for 7 days	15	↓	0.71 (0.66; 0.76)	0.71 (0.66; 0.76)	0.69 (0.64; 0.75)
S-Methadone	Methadone maintenance therapy (40 to 120 mg/daily)	750 mg q8h for 7 days	15	↓	0.65 (0.60; 0.71)	0.64 (0.58; 0.70)	0.60 (0.54; 0.67)
Midazolam (iv)	0.5 mg iv single dose	750 mg q8h for 9 days	22	↑	1.02 (0.8; 1.31)	3.40 (3.04; 3.79)	NA
Midazolam (oral)	2 mg oral single dose	750 mg q8h for 11 days	21	↑	2.86 (2.52; 3.25)	8.96 (7.75; 10.35)	NA
Norethindrone (NE), co-administered with	0.035 mg qd EE/ 0.5 mg qd NE for 21	750 mg q8h for 21 days	24	↔	0.85 (0.81; 0.89)	0.89 (0.86; 0.93)	0.94 (0.87; 1.0)

Table 18 - Drug Interactions: Summary of Pharmacokinetic Parameters for Co-administered Drugs in the Presence of Telaprevir

EE	days						
Phenytoin	200 mg q12h for 17 days	750 mg q8h for 10 days	7	↑	1.27 (1.09; 1.47)	1.31 (1.15; 1.49)	1.36 (1.21; 1.53)
Tacrolimus	2 mg single dose when administered alone; 0.5 mg single dose when co-administered with telaprevir (D8)	750 mg q8h for 13 days	9	↑	2.34 (1.68; 3.25) **Dose norm.:** 9.35 (6.73; 13.0)	17.6 (13.2; 23.3) **Dose norm.:** 70.3 (52.9; 93.4)	NA
Zolpidem	5 mg single dose	750 mg q8h for 11 days	19	↓	0.58 (0.52; 0.66)	0.53 (0.45; 0.64)	NA
Anti-HIV Drugs							
Atazanavir (ATV), boosted with ritonavir (rtv)	300 mg ATV/ 100 mg rtv qd for 20 days	750 mg q8h for 10 days	7	↑	0.85 (0.73; 0.98)	1.17 (0.97; 1.43)	1.85 (1.40; 2.44)
Darunavir (DRV), boosted with ritonavir (rtv)	600 mg DRV/ 100 mg rtv bid for 20 days	750 mg q8h for 10 days	11 (N=14 for C_{max})	↓	0.60 (0.56; 0.64)	0.60 (0.57; 0.63)	0.58 (0.52; 0.64)
	600 mg DRV/ 100 mg rtv bid for 24 days	1125 mg q12h for 4 days	15	↓	0.53 (0.47; 0.59)	0.49 (0.43; 0.55)	0.42 (0.35; 0.51)
Efavirenz	600 mg qd for 20 days	750 mg q8h for 10 days	21	↔	0.84 (0.76; 0.93)	0.93 (0.87; 0.98)	0.98 (0.94; 1.02)
Efavirenz (EFV), co-administered with tenofovir disoproxil fumarate (TDF)	600 mg EFV /300 mg TDF qd for 7 days	1125 mg q8h for 7 days	15	↓	0.76 (0.68; 0.85)	0.82 (0.74; 0.90)	0.90 (0.81; 1.01)
	600 mg EFV /300 mg TDF qd for 7 days	1500 mg q12h for 7 days	16	↓	0.80 (0.74; 0.86)	0.85 (0.79; 0.91)	0.89 (0.82; 0.96)
Fosamprenavir (fAPV), boosted with ritonavir (rtv)	700 mg fAPV/ 100 mg bid rtv for 20 days	750 mg q8h for 10 days	18	↓	0.65 (0.59; 0.70)	0.53 (0.49; 0.58)	0.44 (0.40; 0.50)

Table 18 - Drug Interactions: Summary of Pharmacokinetic Parameters for Co-administered Drugs in the Presence of Telaprevir

	700 mg fAPV/ 100 mg bid rtv for 24 days	1125 mg q12h for 4 days	17 (N=18 for C_{min})	↓	0.60 (0.55; 0.67)	0.51 (0.47; 0.55)	0.42 (0.37; 0.47)
Lopinavir (LPV), boosted with ritonavir (rtv)	400 mg LPV/ 100 mg rtv bid for 20 days	750 mg q8h for 10 days	12	↔	0.96 (0.87; 1.05)	1.06 (0.96; 1.17)	1.14 (0.96; 1.36)
Raltegravir	400 mg bid for 11 days	750 mg q8h for 7 days	20	↑	1.26 (0.97; 1.62)	1.31 (1.03; 1.67)	1.78 (1.26; 2.53)
Tenofovir disoproxil fumarate	300 mg qd for 7 days	750 mg q8h for 7 days	16	↑	1.30 (1.16; 1.45)	1.30 (1.22; 1.39)	1.41 (1.29; 1.54)
Tenofovir, on co-administration of tenofovir disoproxil fumarate (TDF) and efavirenz (EFV)	600 mg EFV /300 mg TDF qd for 7 days	1125 mg q8h for 7 days	15	↑	1.22 (1.12; 1.33)	1.10 (1.03; 1.18)	1.17 (1.06; 1.28)
	600 mg EFV /300 mg TDF qd for 7 days	1500 mg q12h for 7 days	16	↑	1.24 (1.13; 1.37)	1.10 (1.03; 1.17)	1.06 (0.98; 1.15)

[a] The direction of the arrow (↑ = *increase,* ↓ = *decrease,* ↔ = *no change*) indicates the direction of the change in PK

MICROBIOLOGY:

Antiviral Activity *In Vivo*

INCIVEK 750 mg every 8 hours, co-administered with peginterferon alfa and ribavirin, produced sustained decreases in plasma HCV-RNA concentrations in the majority of subjects with genotype 1 HCV.

The initial antiviral response is due to a potent inhibition of wild-type virus by telaprevir, and subsequent clearance of preexisting telaprevir-resistant variants is achieved with continued peginterferon alfa and ribavirin treatment. Thus, telaprevir should always be dosed with peginterferon alfa and ribavirin.

Pharmacodynamics

Telaprevir is a specific inhibitor of the HCV NS3·4A protease, which is essential for viral replication. Telaprevir inhibits the active site of the NS3·4A protease with a maximal potency (Ki*) of 7-10 nM. The slow binding mechanism for the interaction of telaprevir with the HCV NS3·4A protease occurs in 2 steps, with formation of a weaker complex followed by

rearrangement to the tightly bound form. The potency of the initial complex in the first step is estimated to be in the micromolar range. In the second step, telaprevir forms a stable covalent enzyme-inhibitor (EI*) complex, which has a long enzymatic half-life of about 1 hour (Ki* = 7 nM).

In an HCV subtype 1b replicon assay, the telaprevir IC_{50} value against wild-type HCV was 0.354 µM, similar to a subtype 1a infectious virus assay IC_{50} of 0.28 µM.

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. In an HCV protease mouse model, telaprevir inhibited HCV protease–dependent secreted alkaline phosphatase secretion from the liver with an ED_{50} of <0.3 mg/kg.

The current standard treatment of HCV infection is a combination of Peg-IFN and RBV. When studied in combination in the HCV replicon assay, the activity of telaprevir was additive to moderately synergistic with interferon-alfa (IFN-α) and additive with RBV.

Resistance

In Vitro Studies

HCV variants associated with on-treatment virologic failure or relapse were evaluated by site-directed mutagenesis in the replicon assay. 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 IC_{50}), and the A156V/T and V36M+R155K variants conferred higher levels of *in vitro* resistance to telaprevir (>25-fold increase in telaprevir IC_{50}). Replicon variants generated from patient-derived sequences showed similar results.

The *in vitro* replication capacity of telaprevir-resistant variants was lower than that of wild-type virus. All telaprevir-resistant variants studied remained fully sensitive to interferon-alfa and ribavirin.

Clinical Virology Studies

In Phase 2 and 3 clinical trials of telaprevir, treatment-naïve and prior treatment-failure subjects with 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). In the C211 Phase 3 clinical trial, there was no difference in the type of emerging variants between subjects receiving telaprevir 1125 mg twice daily and subjects receiving telaprevir 750 mg q8h. Similar proportions of subjects in both treatment groups had telaprevir-resistant variants at the time of failure. 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) (see **CLINICAL TRIALS**).

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.

Of a combined 255 treatment-naïve and previously treated subjects from Phase 3 studies 108, 111, and C216 in whom telaprevir-resistant variants had emerged during treatment, 152 (60%) no longer had resistant variants detected by population sequencing (median follow-up of 10 months). Of the 393 resistant variants present in the 255 subjects, 68% of NS3-36, 84% of NS3-54, 59% of NS3-155, 86% of NS3-156, and 52% of NS3-36M+NS3-155K variants were no longer detected.

In a follow-up study of 56 treatment-naïve and prior treatment-failure subjects who were treated with a telaprevir regimen in a Phase 2 study and did not achieve SVR, telaprevir-resistant variants were no longer detected in 89% (50/56) of subjects (median follow-up of 25 months). Clonal sequencing analysis of a subset of subjects who had wild-type HCV by population sequencing (n=20), comparing the frequency of resistant variants before the start of telaprevir treatment and at follow-up, showed that the HCV variant population in all subjects had returned to pre-treatment levels.

An analysis was conducted to explore the association between the detection (population-based assay) of baseline NS3/4A amino acid substitutions/polymorphisms and treatment outcome in Trials 108, 111, and C216. Baseline polymorphisms at NS3 position Q80 (Q80K, Q80L, Q80R), which are frequently observed in HCV genotype 1a-infected subjects and have been reported to reduce the activity of some HCV NS3/4A protease inhibitors, were not associated with reduced INCIVEK efficacy.

Pharmacogenomics
Information about IL28B substudies in study 108, C216, and C211 includes a table of SVR rates by genotype (Table 19).

Table 19 - SVR Rates by rs12979860 Genotype

Trial	rs12979860 Genotype	SVR, n/N (%)

		T12/PR	Pbo/PR48
108 (treatment-naïve)	C/C	45/50 (90%)	35/55 (64%)
	C/T	48/68 (71%)	20/80 (25%)
	T/T	16/22 (73%)	6/26 (23%)
		T12 /PR48[a]	**Pbo/PR48**
C216 (previously treated)	C/C	60/76 (79%)	5/17 (29%)
	C/T	160/266 (60%)	9/58 (16%)
	T/T	49/80 (61%)	4/30 (13%)
C211 (treatment-naïve)		**T12(twice daily)/PR**	**T12(q8h)/PR**
	C/C	97/105 (92%)	92/106 (87%)
	C/T	139/206 (67%)	141/208 (68%)
	T/T	38/58 (66%)	37/57 (65%)

[a] Lead-in and immediate start T12/PR regimens pooled.

TOXICOLOGY

Single-Dose Toxicity

No apparent noteworthy effects were observed in single-dose oral toxicity studies evaluating a telaprevir spray dried dispersion (SDD) formulation in mice and rats at doses up to 1000 mg/kg bodyweight.

Repeat-Dose Toxicity

Telaprevir SDD formulations were evaluated in repeat-dose oral toxicity studies up to 6 and 9 months in duration in rats and dogs, respectively at doses ranging from 1 to 1000 mg/kg/day in rats and 15 to 500 mg/kg/day in dogs. These evaluations identified toxicities (described below) which precluded determination of no observed adverse effect levels (NOAELs) and derivation of comparative systemic exposure margins. In rats, the hematopoetic system (e.g., decreased red blood cell parameters, increased reticulocytes) with accompanied bone marrow and splenic changes (e.g., changes in bone marrow cytology, increased spleen weight, histopathological lesions in spleen), the liver (e.g., increased liver weight, increased in hepatic transaminases, hepatocellular hypertrophy and single-cell necrosis), and the male reproductive system such as the testis and epididymis (e.g., decreased testes and epididymis weights, small soft testes, degeneration of germinal epithelium, degeneration/necrosis of individual germ cells, hypospermia/aspermia) were identified as target organs of toxicity. In dogs, the hematopoetic system (e.g., anemia, increased reticulocytes, accompanied bone marrow and splenic changes), the liver (e.g., increased liver weight, histologic changes, increased Kupffer cell pigmentation), and the vascular system (e.g., vasculitis affecting multiple organs including heart, stomach, ovary,

and epididymis) were identified as target organs of toxicity. The findings appear to be reversible within 3 months post cessation of treatment with exception of the liver effects in rats, organ weight changes in the spleen and testes in rats, and increased cholesterol and myelofibrosis in bone marrow of the sternum in dogs.

Genotoxicity and Carcinogenicity
Ribavirin was shown to be genotoxic in several *in vitro* and *in vivo* assays. Ribavirin was not oncogenic in a 6-month p53+/- transgenic mouse study or a 2-year carcinogenicity study in rat. See the prescribing information for ribavirin.

Evidence of genotoxicity was not observed with telaprevir in a bacterial mutagenicity assay, *in vitro* mammalian chromosomal aberration assay, or *in vivo* micronucleus study in mouse. Telaprevir has not been tested for its carcinogenic potential.

Reproductive and Development Toxicity
Animal studies have shown that ribavirin induced reversible toxicity in males while peginterferon alfa may impair female fertility. See the prescribing information for ribavirin and peginterferon alfa.

Telaprevir SDD formulation was evaluated in a fertility and early embryonic development study in rats, with males receiving doses up to 300 mg/kg/day prior to and through completion of the second of a total of 3 cohabitations and females receiving doses up to 500 mg/kg/day prior to the first cohabitation through Gestation Day (GD) 7. Untreated females were mated with treated male rats in the second cohabitation and with recovering males approximately 3 months post cessation of treatment in the third cohabitation. While no effects on mating and fertility index were noted in this study, telaprevir-related effects on fertility parameters were noted in rats. In repeat-dose studies, the no observed adverse effect level (NOAEL) for degenerative testicular toxicity was established at exposures 0.17-fold the human exposures at the recommended clinical dose. Potential effects on sperm (e.g., decreased % motile sperm and increased non-motile sperm count) were observed in the rat fertility study at exposures 0.30-fold the human exposures at the recommended clinical dose. Additional effects on fertility included minor increases in percent preimplantation loss, the percent of dams with nonviable embryos and percent of nonviable conceptuses per litter. These effects are likely associated with testicular toxicity in male rats but contributions of the female cannot be ruled out.

Telaprevir SDD formulation was evaluated in embryo-fetal development studies in pregnant mice at doses up to 1000 mg/kg/day from GD 6 through 15 and in pregnant rats at doses up to 500 mg/kg/day from GD 7 through 17. No gross external, soft tissue or skeletal fetal alterations (malformations or variations) were considered related to telaprevir. Under the conditions tested, telaprevir did not appear to have teratogenic potential in these species.

Telaprevir SDD formulation was administered to female rats (F0 generation) in a prenatal and postnatal development study at doses up to 500 mg/kg/day from GD 7 through Lactation Day (LD) 20. Telaprevir had no apparent effects on natural delivery parameters. Decreases in pup bodyweights were noted during lactation. Pup bodyweight gains were comparable to control

post-weaning. No developmental effects were noted in F1 generation rats, no effects on Caesarian-sectioning or litter parameters were noted in F1 generation females sacrificed on gestation day 21, and no fetal alterations related to F0 maternal exposures to telaprevir were noted.

Telaprevir has not been tested in juvenile animals.

Local Tolerance
Under the conditions tested, telaprevir was a non-irritant from both the dermal and ocular perspectives and was concluded to be negative for skin sensitizing potential. The M11 metabolite of telaprevir, VRT-841125, was concluded positive for skin sensitizing potential and showed that a telaprevir metabolite can act as an antigen in a delayed type hypersensitivity reaction. Due to low circulating levels of M11 metabolite, the potential clinical significance of this finding is uncertain.

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PART III: CONSUMER INFORMATION

Pr INCIVEK®
Telaprevir Tablets

This leaflet is part III of a three-part "Product Monograph" published when INCIVEK was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about INCIVEK. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

- Adult patients with chronic hepatitis C who have either not received previous treatment or who failed prior treatment with peginterferon alfa or peginterferon alfa and ribavirin.

INCIVEK **must not be taken by itself** to treat chronic hepatitis C. INCIVEK **must be used in combination** with two other medications (peginterferon alfa and ribavirin) to treat chronic hepatitis C. **It is important that you also read and follow the CONSUMER INFORMATION for the other medications** because they have additional important information about your treatment that is not covered in this CONSUMER INFORMATION leaflet. You should receive and read the CONSUMER INFORMATION each time you fill or refill prescriptions for those medications.

INCIVEK is sometimes called **INCIVEK combination treatment** because it is always used in combination with two other medications.

INCIVEK is taken for 12 weeks as part of the combination treatment; the other two medications are taken for a longer period of time. Your doctor will tell you how long to take the other 2 medications.

What it does:
INCIVEK is a prescription medicine. It treats a disease in adults called **chronic hepatitis C** (chronic means lasting a long time). The hepatitis C virus infects the liver and is also present in the blood. INCIVEK does not work by itself. It is always used in combination with peginterferon alfa and ribavirin.

When it should not be used:
Do not take INCIVEK if you:

- Are allergic to any of the ingredients in INCIVEK (see *What the non-medicinal ingredients are*).
- Are pregnant or planning to become pregnant while on INCIVEK combination treatment or during the six (6) months after treatment ends. Talk to your doctor if you are pregnant or plan to become pregnant.
- Are a man with a sexual partner who is pregnant or may become pregnant at any time while you are being treated with INCIVEK combination treatment, or during the six (6) months after your combination treatment ends.
- Are taking any of the medicines listed under **"Do not take INCIVEK with any of the medicines below"** in the **INTERACTIONS WITH THIS MEDICATION** section.

What the medicinal ingredient is:
telaprevir

What the non-medicinal ingredients are:
Colloidal silicon dioxide, croscarmellose sodium, D&C Red No. 40, dibasic calcium phosphate (anhydrous), FD&C Blue No. 2, hypromellose acetate succinate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, sodium lauryl sulfate, sodium stearyl fumarate, talc, and titanium dioxide

What dosage forms it comes in:
Each INCIVEK **tablet** contains 375 mg of telaprevir.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Fatal and non-fatal serious skin reactions including Toxic Epidermal Necrolysis (TEN), Stevens-Johnson Syndrome (SJS) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). These serious skin reactions may require urgent treatment in a hospital and may result in death.
- Contact your doctor immediately if you develop serious skin symptoms (see Warnings below) and your doctor will decide if you need treatment for your rash or if you need to stop taking INCIVEK, or any of your other medicines.
- Never stop taking INCIVEK combination treatment without talking with your doctor first.

Contact your doctor immediately if you develop symptoms of a serious skin reaction (see Serious Warnings and Precautions box) such as:

• blisters or skin lesions
• swelling of your face
• mouth sores or ulcers
• rash, with or without itching
• red or inflamed eyes like "pink eye" (conjunctivitis)
• fever

INCIVEK must be taken in combination with both peginterferon alfa and ribavirin. The co-administered drug, ribavirin, may cause birth defects and death of the fetus. Extreme care must be taken to avoid pregnancy.

Tell your doctor immediately if you or your partner become pregnant while on INCIVEK combination treatment or during the six (6) months after treatment ends.

Birth control pills, birth control patches or other forms of birth control that contain hormones may not work to prevent pregnancy while you are taking INCIVEK.

You must use at least two (2) forms of birth control when you take INCIVEK combination treatment and for the six (6) months after treatment. If you use birth control that contains hormones, you must use two (2) other forms of birth control and continue to do so for at least two (2) months after you finish taking INCIVEK.

Talk to your doctor about what type of birth control is best for you while taking INCIVEK combination treatment.

Do not breastfeed your baby while taking INCIVEK. It is not known whether INCIVEK passes into human breast milk.

BEFORE you use INCIVEK talk to your doctor about your medical history. Tell your doctor if you have any of the following:

- Received a treatment for hepatitis C that did not work
- Liver problems (other than hepatitis C infection)
- Hepatitis B infection
- Blood problems
- HIV (Human Immunodeficiency Virus)/AIDS or any problems with your immune system
- Kidney problems
- History of gout or high uric acid levels in the blood
- Taking medicine because of an organ transplant; or have had a recent organ transplant
- Thyroid problems
- Heart problems such as heart failure, irregular or slow heartbeat, or a condition called long QT syndrome
- Any other medical problems

Your health care professional will check your blood regularly for anemia and other possible blood problems while you are taking INCIVEK combination treatment.

Drugs that cause an effect on the electrical conduction of the heart known as QTc prolongation should be taken with caution in patients receiving INCIVEK. Tell your doctor if you take any of the following drugs that have been associated with QTc interval prolongation and/or torsade de pointes including, but not limited to, the following: quinidine, amiodarone, sotalol, flecainide, propafenone, fluoxetine, methadone, erythromycin, moxifloxacin, quinine, ketoconazole, haloperidol, vardenafil, ritonavir, or salmeterol.

Tell your health care provider about all the medicines you take including over-the-counter medicines, vitamins and herbal medicines. Keep a list of them with you and show it to your health care provider and pharmacist each time you get a new medicine. (See *Interactions with this medication*).

INTERACTIONS WITH THIS MEDICATION

Do not take INCIVEK with any of the medicines below. They can cause serious or life-threatening reactions with INCIVEK.

Medicines that should <u>not</u> be taken with INCIVEK

Medicine Name	Example of Brand Names
Alfuzosin	Xatral®
Amiodarone	Cordarone®
Astemizole	Hismanal®†
Carbamazepine	Tegretol®
Cisapride	Prepulsid®†
Dihydroergotamine	D.H.E.
Eletriptan	Relpax®
Eplerenone	Inspra®
Ergonovine	Methergine®
Ergotamine	None
Flecainide	Tambocor™
Lovastatin	Mevacor®
Methylergonovine	None†
Midazolam (oral formulation)	Versed®†
Phenobarbital	None
Phenytoin	Dilantin®
Pimozide	Orap®
Propafenone	Rythmol®
Quinidine	None
Rifampin	Rifadin®, Rofact®, Rifater®
St. John's Wort (*Hypericum perforatum)*	None
Terfenadine	Allergy Relief†
Simvastatin	Zocor®
Sildenafil (only when used for a condition called Pulmonary Arterial Hypertension or PAH)	Revatio™
Triazolam	None
Vardenafil	Levitra®

† Not currently marketed in Canada.

This is **not** a complete list of medicines that you should tell your doctor about. You should check with your doctor or pharmacist before taking any other drug with INCIVEK.

Other medicines that may interact with INCIVEK.
The following medicines may interact with INCIVEK. Dosage of INCIVEK or the other drug may have to be revised or other change may be required. Talk to your doctor if you are taking any of these drugs:

- alfentanil, alprazolam, amlodipine, atorvastatin, bosentan, budesonide, buspirone, clarithromycin, colchicine, cyclosporine, darunavir, dexamethasone (systemic), diazepam, digoxin, diltiazem, efavirenz, erythromycin, escitalopram, felodipine, fentanyl, fluticasone, fluvastatin, fosamprenavir, itraconazole, ketoconazole, lidocaine (systemic), lopinavir,

methadone, midazolam (parenteral), nicardipine, nifedipine, nisoldipine, posaconazole, pravastatin, repaglinide, rifabutin, rosuvastatin, salmeterol, sildenafil (for erectile dysfunction), sirolimus, tacrolimus, tadalafil, telithromycin, trazodone, verapamil, voriconazole, warfarin, zolpidem.

PROPER USE OF THIS MEDICATION

Usual adult dose:

- Take INCIVEK exactly as your doctor tells you. Your doctor will tell you how much INCIVEK to take. Do not change the amount you take unless your doctor tells you to.
- INCIVEK is taken for twelve (12) weeks as part of the combination treatment.
- **Always take your INCIVEK dose with food (not low-fat).**
- **Three (3)** tablets of INCIVEK are taken two (2) times a day. Each dose should be taken no less than ten (10) hours apart and no more than fourteen (14) hours apart. The total dose is 6 tablets per day.
- Take INCIVEK tablets whole, with water. Do not break or crush INCIVEK tablets before you swallow them. Do not chew INCIVEK. It has a bitter taste. Tell your health care professional if you have problems swallowing whole tablets.
- Do not stop taking INCIVEK unless your doctor tells you to. If you think there is a reason to stop taking INCIVEK, talk to your doctor before doing so.
- If your doctor tells you to stop taking INCIVEK, you should not start taking it again even if the reason for stopping goes away. **If INCIVEK is stopped you can not restart treatment with INCIVEK.**

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

- If you miss a dose **within six (6) hours** of when you usually take it, take your dose with food as soon as possible.
- If you miss a dose and it is **more than six (6) hours** after the time you usually take it, **skip that dose only** and take the next dose at your normal dosing schedule. Do not double dose.
- If you miss **more than one dose** call your doctor right away.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Before you start taking INCIVEK, talk to your doctor about the possible side effects.

The common side effects of INCIVEK include:

- Rash (mild to moderate)
    - A rash can happen at any time with INCIVEK combination treatment. There may be itching with the rash. In most people who develop rash, the rash is mild or moderate and it goes away when treatment ends.
    - It is possible for any rash, even a mild rash, to get worse. **Call your doctor right away if you get a rash or if you have a rash that gets worse.** Your doctor will decide if you need medicine for the rash or if you need to stop taking INCIVEK or any of your other medications.
- Itching can happen with or without rash; it is common and usually goes away when treatment ends.
- Anal or rectal problems are common and may be uncomfortable. They usually go away either during or after you finish your treatment.
    - Hemorrhoids (swollen veins in the rectum or anus, the opening to the rectum)
    - Discomfort or burning around or near the anus
    - Itching around or near the anus
- INCIVEK combination treatment may cause anemia.
    - Anemia occurs when your blood does not have enough red blood cells. The red blood cells carry and deliver oxygen to your body.
    - Anemia may make you feel tired, weak, or low on energy. Anemia may also make you feel dizzy or short of breath.

Other common side effects of INCIVEK combination treatment:

- Nausea, diarrhea, vomiting and taste alteration.

Rare side effect of INCIVEK combination treatment:

- **Serious skin reactions have been reported (e.g., blistering and peeling skin, ulcers, rash, and fever).** If you get a serious skin reaction, **stop using all products** and call your doctor right away.

Tell your health professional about any side effect that bothers you or does not go away.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Rash with or without itching		√	
	Symptoms of anemia including feeling tired, weak, low on energy, dizzy or short of breath.		√	
	Fainting		√	
Rare **See Warnings and Precautions**	**Serious skin reactions such as:** rash, with or without itching, blisters or skin lesions, mouth sores or ulcers, red or inflamed eyes, swelling of your face, fever.		√	

This is not a complete list of side effects. For any unexpected effects while taking INCIVEK, contact your doctor or pharmacist.

HOW TO STORE IT

Store at 25°C; excursions permitted to 15-30°C.

Keep INCIVEK and all medicines out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.vrtx.ca
or by contacting the sponsor, Vertex Pharmaceuticals (Canada) Incorporated
at: 877-634-VRTX (8789)

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