# INTERNATIONAL PACKAGE INSERT

## PRODUCT NAME

INCIVO® film-coated tablets

## DOSAGE FORMS AND STRENGTHS

Each film-coated tablet contains 375 mg of telaprevir.

Yellow caplet-shaped tablets of approximately 20 mm in length, marked with "T375" on one side.

For excipients, see List of Excipients.

## CLINICAL INFORMATION

### Indications

INCIVO®, 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;
- who have previously been treated with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin, including relapsers, partial responders and null responders (see Pharmacodynamic Properties, Efficacy in previously treated adults).

In previously treated patients, when available, the use of peginterferon alfa-2a in combination with INCIVO® and ribavirin should be considered due to the limited data with peginterferon alfa-2b.

### Dosage and Administration

INCIVO®, 750 mg (two 375 mg film-coated tablets) should be taken orally every 8 hours with food (the total daily dose is 6 tablets (2250 mg)). Patients should be instructed to swallow the tablets whole (e.g., patients should not chew, break or dissolve the tablet).

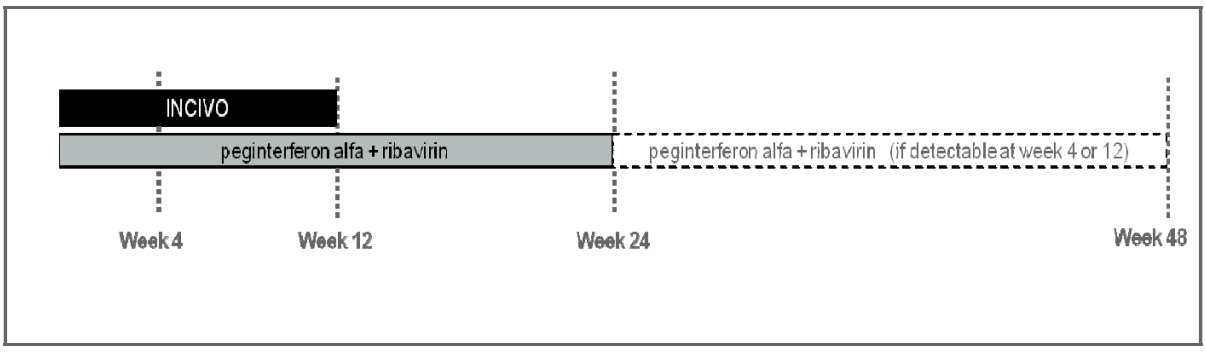
For specific dosage instructions for peginterferon alfa and ribavirin, consult the prescribing information for these medicinal products.

***Duration of treatment – Treatment-naïve adults and prior treatment relapsers***

Treatment with INCIVO® must be initiated in combination with peginterferon alfa and ribavirin and administered for 12 weeks (see Figure 1).

- Patients with undetectable HCV RNA at weeks 4 and 12 receive an additional 12 weeks of peginterferon alfa and ribavirin alone for a total treatment duration of 24 weeks.
- Patients with detectable HCV RNA at either weeks 4 or 12 receive an additional 36 weeks of peginterferon alfa and ribavirin alone for a total treatment duration of 48 weeks.
- For all patients with cirrhosis irrespective of undetectable HCV RNA at weeks 4 or 12, an additional 36 weeks of peginterferon alfa and ribavirin alone for a total treatment duration of 48 weeks is recommended (see Pharmacodynamic Properties).

**Figure 1: Duration of treatment for treatment-naïve patients and prior treatment relapsers**



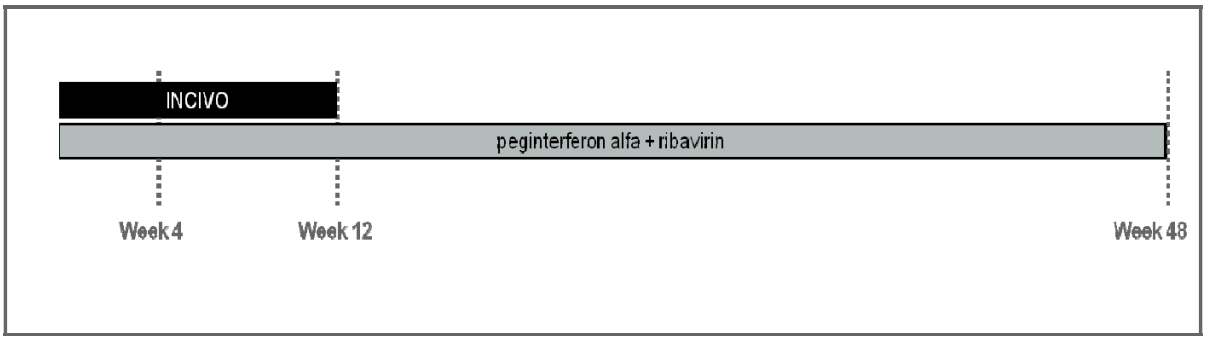
HCV RNA levels should be monitored at weeks 4 and 12 to determine treatment duration. In Phase 3 studies, the COBAS® TaqMan® test (version 2.0) was used to determine whether HCV RNA levels were undetectable (see Pharmacodynamic Properties). Detectable HCV RNA below the lower limit of assay quantification should not be used as a substitute for "undetectable", for making decisions on-treatment duration, as this may lead to an insufficient duration of therapy and higher relapse rates. See Table 1 for Guidelines for discontinuation of INCIVO®, peginterferon alfa, and ribavirin treatment.

Treatment-naïve patients with cirrhosis who have undetectable HCV-RNA at weeks 4 and 12 of INCIVO® combination-treatment may benefit from an additional 36 weeks of peginterferon alfa and ribavirin (48 weeks total) (see Pharmacodynamic Properties).

***Duration of treatment – Previously treated adults with prior partial or prior null response***

Treatment with INCIVO must be initiated in combination with peginterferon alfa and ribavirin and administered for 12 weeks, followed by peginterferon alfa and ribavirin therapy alone (without INCIVO®) for a total treatment duration of 48 weeks (see Figure 2).

**Figure 2: Duration of treatment for previously treated patients with prior partial or prior null response**




HCV RNA levels should be monitored at weeks 4 and 12. See Table 1for recommendations for Guidelines for discontinuation of INCIVO®, peginterferon alfa, and ribavirin treatment.

**All Patients**

Since it is highly unlikely that patients with inadequate viral response will achieve a sustained virologic response (SVR), it is recommended that patients with HCV RNA >1000 IU/ml at week 4 or week 12 discontinue therapy (refer to Table 1).

**Table 1: Guidelines for discontinuation of INCIVO®, peginterferon alfa, and ribavirin treatment**

| **Medicinal products** | **HCV RNA >1000 IU/ml at week 4 of treatment** | **HCV RNA >1000 IU/ml at week 12 of treatment** |
|---|---|---|
| **INCIVO®** | Permanently discontinue | INCIVO® treatment completed |
| | | |
| **Peginterferon alfa and Ribavirin** | Permanently discontinue | |

[a] treatment with INCIVO®, peginterferon alfa, and ribavirin. These guidelines may not perform similarly when a lead-in treatment with peginterferon alfa and ribavirin has been used prior to starting INCIVO® therapy (see Pharmacodynamic Properties).

In the Phase 3 studies, none of the patients with HCV RNA > 1,000 IU/ml at either week 4 or week 12 achieved SVR with continued peginterferon alfa and ribavirin treatment. In treatment-naïve patients in the Phase 3 studies, 4/16 (25%) patients with HCV RNA levels between 100 IU/ml and 1,000 IU/ml at week 4 achieved SVR. In treatment-naive patients with HCV RNA between 100 IU/ml and 1,000 IU/ml at week 12, 2/8 (25%) achieved SVR.

In prior null responders, consideration should be given to conduct an additional HCV RNA test between weeks 4 and 12. If the HCV RNA concentration is > 1,000 IU/ml, INCIVO®, peginterferon alfa, and ribavirin should be discontinued.
For patients receiving a total of 48 weeks of treatment, peginterferon alfa and ribavirin should be discontinued if HCV RNA is detectable at week 24 or week 36.
INCIVO® must be dosed with peginterferon alfa and ribavirin to prevent treatment failure.
The dose of INCIVO® must not be reduced to prevent treatment failure.
If INCIVO treatment is discontinued due to adverse drug reactions or because of insufficient virologic response, INCIVO® treatment should not be reinitiated.
There are no data on re-treating patients who have failed a course of HCV NS3-4A protease inhibitor-based therapy (see Pharmacodynamic Properties) with INCIVO®.
Refer to the respective prescribing information of peginterferon alfa and ribavirin for guidelines on dose modifications, interruptions, discontinuations or resumption of those medicinal products (see Warnings and Precautions for Use).
In case a dose of INCIVO® is missed within 4 hours of the time it is usually taken, patients should be instructed to take the prescribed dose of INCIVO® with food as soon as possible. If the missed dose is noticed more than 4 hours after the time INCIVO® should be taken, the missed dose should be skipped and the patient should resume the normal dosing schedule.

**Special Populations**

***Renal impairment***

There are no clinical data on the use of INCIVO® in HCV patients with moderate or severe renal impairment (CrCl ≤ 50 ml/min). No dose adjustment is recommended for INCIVO® in HCV patients with mild, moderate or severe renal impairment (see also Warnings and Precautions for Use and Pharmacokinetic Properties). Ribavirin is contraindicated, or used with extreme caution, in patients with CrCl < 50 ml/min (see the prescribing information for ribavirin).

***Hepatic impairment***

INCIVO is not recommended in patients with moderate to severe hepatic impairment (Child-Pugh B or C, score ≥ 7) or decompensated liver disease (see Special Warnings and Precautions for Use). Dose modification of INCIVO® is not required when administered to hepatitis C patients with mild hepatic impairment (Child-Pugh A, score 5-6).
Refer also to the prescribing information for peginterferon alfa and ribavirin which are contraindicated in Child-Pugh score ≥ 6.

***Elderly***

There are limited clinical data on the use of INCIVO® in HCV patients aged ≥ 65 years.

***Pediatric Population***

No data are available on the safety and efficacy of INCIVO® in children and adolescents.

**Contraindications**

INCIVO® is contraindicated when combined with active substances 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). INCIVO® is contraindicated when combined with active substances that strongly induce CYP3A and thus may lead to lower exposure and loss of efficacy of INCIVO®. Contraindicated medicinal products are listed below in Table 2. For further details, refer to Interactions with Other Medicinal Products and Other Forms of Interaction, drug interactions, Table 3.

| **Table 2: Medicinal products that are contraindicated with INCIVO®** | |
|---|---|
| **Medicinal product class** | **Medicinal products within class that are contraindicated with INCIVO®** |

| | |
|---|---|
| Alpha 1-adrenoreceptor antagonist | Alfuzosin |
| Antiarrhythmics | |
| Class I | Quinidine, flecainide, propafenone |
| Class III | Amiodarone |
| Other | Bepridil (non-US only) |
| Antihistamines | Astemizole, terfenadine (non-US only) |
| Antimycobacterials | Rifampicin |
| Ergot derivatives | Dihydroergotamine, ergonovine, ergotamine, methylergonovine |
| GI motility agent | Cisapride (non-US only) |
| Herbal products | St. John's wort (*Hypericum perforatum*) |
| HMG CoA reductase inhibitors | Atorvastatin, lovastatin, simvastatin |
| Neuroleptic | Pimozide |
| PDE-5 inhibitor | Sildenafil, tadalafil<br>(only when used for treatment of pulmonary arterial hypertension) |
| Sedatives/hypnotics | Orally administered midazolam, triazolam |

Refer to the package inserts for peginterferon alfa and ribavirin for a list of their contraindications since INCIVO® must be used in combination with peginterferon alfa and ribavirin.

**Warnings and Precautions**

***Severe rash***

Severe, potentially life-threatening, and fatal skin reactions, including toxic epidermal necrolysis (TEN), have been reported with INCIVO® combination treatment (see Adverse Reactions).

In placebo-controlled Phase 2 and 3 trials, severe rash (primarily eczematous, pruritic and involving more than 50% body surface area) was reported in 4.8% of patients who received INCIVO® combination treatment compared to 0.4% receiving peginterferon alfa and ribavirin.

5.8% of patients discontinued INCIVO® alone due to rash events and 2.6% of patients discontinued INCIVO® combination treatment for rash events compared to none receiving peginterferon alfa and ribavirin. In placebo-controlled Phase 2 and 3 trials, 0.4% of patients had Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome). In clinical experience, less than 0.1% of patients had Stevens-Johnson Syndrome. All of these reactions resolved with treatment discontinuation.

Mild to moderate rashes should be monitored for progression. For additional information on mild to moderate rash, see Adverse Reactions.

If a severe rash (defined as involving more than 50% of body surface area) occurs, INCIVO must be discontinued immediately; peginterferon alfa and ribavirin may be continued. If improvement is not observed within 7 days of INCIVO® discontinuation, sequential or simultaneous interruption or discontinuation of ribavirin and/or peginterferon alfa should be considered; if medically indicated, earlier interruption or discontinuation of peginterferon alfa and ribavirin may be needed. Patients should be monitored until the rash is resolved.

Any rash that is associated with significant systemic symptoms, mucous membrane ulceration, target lesions, epidermal detachment, vesicles, or bullae constitutes a severe skin reaction and requires immediate and permanent discontinuation of INCIVO®, peginterferon alfa, and ribavirin.
INCIVO® must not be restarted if discontinued. Refer also to the prescribing information for peginterferon alfa and ribavirin for severe skin reactions associated with these products.

***Anemia***

In placebo-controlled Phase 2 and 3 clinical trials, the overall incidence and severity of anaemia increased with INCIVO® combination treatment compared to peginterferon alfa and ribavirin alone. Hemoglobin values of <10 g/dl were observed in 34% of patients who received INCIVO® combination treatment and in 14% of patients who received peginterferon alfa and ribavirin. Hemoglobin values of <8.5 g/dl were observed in 8% of INCIVO® combination treatment compared to 2% of patients receiving peginterferon alfa and ribavirin. A decrease in hemoglobin levels occurs during the first 4 weeks of treatment, with lowest values reached at the end of INCIVO dosing. Hemoglobin values gradually improve after INCIVO® dosing completion.
Hemoglobin should be monitored at regular intervals prior to and during INCIVO® combination treatment (see Warnings and Precautions ).
For the management of anaemia, refer to the prescribing information for ribavirin for its dose reduction guidelines. If ribavirin is permanently discontinued for the management of anaemia, INCIVO® must also be permanently discontinued. If INCIVO® is discontinued for anemia, patients may continue treatment with peginterferon alfa and ribavirin. Ribavirin may be restarted per the dosing modification guidelines for ribavirin. The dose of INCIVO® must not be reduced and INCIVO® must not be restarted if discontinued.

***Pregnancy and contraception requirements***

Because INCIVO® must be used in combination with peginterferon alfa and ribavirin, the contraindications and warnings applicable to those medicinal products are applicable to combination therapy.
Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin; therefore, extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Refer also to the prescribing information for ribavirin.
Female patients of childbearing potential and their male partners as well as male patients and their female partners must use 2 effective contraceptive methods during treatment and for 6 months after all treatment has ended. For specific recommendations, see Pregnancy, Breast-feeding and Fertility.

***Female patients***

Hormonal contraceptives may not be reliable during INCIVO® dosing (see Interactions). Therefore, female patients of childbearing potential should use 2 additional methods of effective birth control during INCIVO® dosing and for 2 months after the last intake of INCIVO®.

***Breast-feeding mothers***

It is not known whether INCIVO® is excreted in human breast milk. When administered to lactating rats, levels of INCIVO® and its major metabolite were higher in milk compared to those observed in plasma. Rat offspring exposed to INCIVO® in utero showed normal body weight at birth. However, when fed via milk from INCIVO®-treated dams, body weight gain of rat pups was lower than normal (likely due to taste aversion). After weaning, rat pup body weight gain returned to normal. Because of the potential for adverse reactions in breastfed infants, breast-feeding must be discontinued prior to initiation of therapy. See also the prescribing information for ribavirin.

***Drug interactions***

Refer to Contraindications for a listing of medicinal products that are contraindicated for use with INCIVO® due to potentially life threatening adverse events or potential loss of therapeutic effect to INCIVO®. Refer to Interaction with Other Medicinal Products and Other Forms of Interaction for established and other potentially significant drug-drug interactions.

***Cardiovascular***

Results of a study conducted in healthy volunteers demonstrated a modest effect of INCIVO at a dose of 1,875 mg every 8 hours on the QTcF interval with a placebo-adjusted maximum mean increase of 8.0 msec (90% CI: 5.1-10.9) (see Pharmacodynamic Properties). Exposure at this dose was comparable to the exposure in HCV-infected patients dosed at 750 mg INCIVO® every 8 hours plus peginterferon alfa and ribavirin. The potential clinical significance of these findings is uncertain.

Caution is recommended when prescribing INCIVO® concurrently with medicinal products known to induce QT prolongation and which are CYP3A substrates such as erythromycin, clarithromycin, telithromycin, posaconazole, voriconazole, ketoconazole, tacrolimus, salmeterol, vardenafil (see Interactions). INCIVO® co-administration with domperidone should be avoided (see Interactions). INCIVO® may increase concentrations of the co-administered medicinal product and this may result in an increased risk of their associated cardiac adverse events. In the event that co-administration of such medicinal products with INCIVO® is judged strictly necessary, clinical monitoring including ECG assessments is recommended. See Contraindications for medicinal products with a narrow therapeutic index which are contraindicated with INCIVO®.

Use of INCIVO® 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 INCIVO® in such patients is judged strictly necessary, patients should be closely monitored, including ECG assessments.

Use INCIVO® with caution in patients with:

- a history of acquired QT prolongation;
- clinically relevant bradycardia (persistent heart rate <50 bpm);
- a history of heart failure with reduced left-ventricular ejection fraction;
- a requirement for medicinal products known to prolong the QT interval but without a potential for significantly increased plasma concentrations due to CYP3A4 inhibition by INCIVO® (e.g., methadone, see Interactions with Other Medicinal Products and Other Forms of Interactions).

Electrolyte disturbances (e.g., hypokalemia, hypomagnesemia and hypocalcemia) should be monitored and corrected, if necessary, prior to initiation and during INCIVO® therapy.

***Laboratory tests***

HCV RNA levels should be monitored at weeks 4 and 12 and as clinically indicated.

The following laboratory evaluations (complete blood count with white blood cell differential counts, electrolytes, serum creatinine, liver function tests, TSH, uric acid) must be conducted in all patients prior to initiating INCIVO® combination treatment.

These are recommended baseline values for initiation of INCIVO® combination treatment:

- Hemoglobin: ≥ 12 g/dl (females); ≥ 13 g/dl (males)
- Platelet count ≥ 90000/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 thereafter.

Chemistry evaluations (electrolytes, serum creatinine, uric acid, hepatic enzymes, bilirubin, and TSH) are recommended as frequently as the hematology evaluations or as clinically indicated (see Adverse Reactions).
Refer to the prescribing information for peginterferon alfa and ribavirin, including pregnancy testing requirements (see Pregnancy and Lactation).

***General***

INCIVO® must not be administered as monotherapy and must only be prescribed in combination with both peginterferon alfa and ribavirin. The prescribing information for peginterferon alfa and ribavirin must therefore be consulted before starting therapy with INCIVO.
There are no clinical data on re-treating patients who have failed an HCV NS3-4A protease inhibitor-based therapy (see Pharmacodynamic Properties) or on use of repeated courses of INCIVO®.

***Insufficient virologic response***

In patients who have an inadequate viral response, treatment should be discontinued (see Dosage and Administration and Warnings and Precautions for Use, Laboratory tests).

***Use of INCIVO® in treatment of other HCV genotypes***

There are not sufficient clinical data to support the treatment of patients with HCV genotypes other than genotype 1. Therefore, the use of INCIVO® in patients with non-genotype-1 HCV is not recommended.

***Hepatic impairment***

INCIVO® has not been studied in patients with severe hepatic impairment (Child-Pugh C, score ≥ 10) or decompensated liver disease and is not recommended in these populations.
INCIVO® has not been studied in patients with moderate hepatic impairment (Child-Pugh B, score 7-9). The appropriate dose of INCIVO® in hepatitis C infected patients with moderate hepatic impairment has not been determined. Therefore, INCIVO® is not recommended in these patients (see Dosage and Administration and Pharmacokinetic Properties).
Refer to prescribing information for peginterferon alfa and ribavirin which must be co-administered with INCIVO®.

***Organ transplant patients***

No clinical data are available regarding the treatment of pre-, peri-, or post-transplant patients with INCIVO® in combination with peginterferon alfa and ribavirin. Therefore, the use of INCIVO® in transplant candidates or patients is not recommended (see also Interactions, Immunosuppresants).

***HCV/HIV (human immunodeficiency virus) co-infection***

INCIVO® in combination with peginterferon alfa and ribavirin was evaluated in 60 HIV-infected, HCV treatment-naïve subjects who were either not on antiretroviral therapy or were being treated with efavirenz or atazanavir/ritonavir (ATV/rtv) in combination with tenofovir disoproxil fumarate and emtricitabine or lamivudine (see Interactions, Adverse Reactions and Pharmacodynamic Properties).

***HCV/HBV (hepatitis B virus) co-infection***

There are no data on the use of INCIVO® in patients with HCV/HBV co-infection. Therefore, the use of INCIVO® in HCV/HBV co-infected patients is not recommended.

***Pediatric population***

INCIVO® is not recommended for use in children and adolescents younger than 18 years of age because the safety and efficacy has not been established in this population.

***Important information about some of the ingredients of INCIVO®***

This medicinal product contains 2.3 mg sodium per tablet, which should be taken into consideration by patients on a controlled sodium diet.

**Interactions**

INCIVO® is metabolised in the liver by CYP3A and is a P-glycoprotein (P-gp) substrate. Other enzymes are also involved in the metabolism. Co-administration of INCIVO® and medicinal products that induce CYP3A and/or P-gp may decrease INCIVO® plasma concentrations. Co-administration of INCIVO® and medicinal products that inhibit CYP3A and/or P-gp may increase INCIVO® plasma concentrations. Administration of INCIVO® may increase systemic exposure to medicinal products that are substrates of CYP3A or P-gp, which could increase or prolong their therapeutic effect and adverse reactions.
*In vitro* studies demonstrated that INCIVO® is not a substrate for the organic anion transporter polypeptides (OATPs), OATP1B1 and OATP2B1, but is an inhibitor of these transporters. Therefore, concomitant administration of INCIVO® and OATP substrates (e.g., fluvastatin, pravastatin, rosuvastatin, and repaglinide) should be undertaken with caution.
*In vitro* studies evaluating in situ induction potential indicate that INCIVO® is not an inducer of CYP1A2, CYP2B6, CYP2C, and CYP3A. However, based on the results of drug-drug interaction clinical studies, induction of metabolic enzymes by INCIVO® cannot be excluded.
Interaction studies have only been performed in adults.

***Associations contraindicated (see Contraindications)***

*CYP3A substrates with a narrow therapeutic index*

INCIVO® must not be administered concurrently with medicinal products with a narrow therapeutic window that are substrates of cytochrome P450 3A (CYP3A). Co-administration of INCIVO may increase the plasma concentration of these medicinal products, which may lead to serious and/or life-threatening adverse reactions such as cardiac arrhythmia (i.e., amiodarone, astemizole, bepridil, cisapride, flecainide, pimozide, propafenone, quinidine, terfenadine) or peripheral vasospasm or ischemia (i.e., dihydroergotamine, ergonovine, ergotamine, methylergonovine), or myopathy, including rhabdomyolysis (i.e., atorvastatin, lovastatin, simvastatin), or prolonged or increased sedation or respiratory depression (i.e., orally administered midazolam, triazolam), or hypotension or cardiac arrhythmia (i.e., alfuzosin, sildenafil, tadalafil for pulmonary arterial hypertension).
INCIVO® must not be administered concurrently with any Class I or III antiarrhythmics.

*Rifampicin*

Rifampicin reduces the INCIVO® plasma AUC by approximately 92%. Therefore, INCIVO® must not be co-administered with rifampicin.

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

Plasma concentrations of INCIVO® can be reduced by concomitant use of the herbal preparation St. John's wort (Hypericum perforatum). Therefore, herbal preparations containing St. John's wort should not be combined with INCIVO®.

*Other combinations*

Table 3 provides dosing recommendations as a result of drug interactions with INCIVO®. 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.

**Table 3: INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS**

| **Medicinal products by therapeutic areas** | **Effect on concentration of INCIVO or concomitant medicinal product** | **Clinical comment** |
|---|---|---|
| **ANALGESICS** | | |

| | | |
|---|---|---|
| alfentanil<br>fentanyl | ↑ alfentanil<br>↑ 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<br>(systemic) | ↑ lidocaine | INCIVO®. may increase the concentrations of systemically administered lidocaine. Caution is warranted and clinical monitoring is recommended when co-administered with INCIVO®.. |
| digoxin* | ↑ digoxin<br>AUC 1.85 (1.70-2.00)<br>$C_{max}$ 1.50 (1.36-1.65) | Concentrations of digoxin were increased when co-administered with INCIVO®. 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<br>erythromycin<br>telithromycin<br>troleandomycin (non-US only) | ↑ INCIVO<br>↑ antibacterials | Concentrations of both INCIVO® and the antibacterial may be increased during co-administration. Caution is warranted and clinical monitoring is recommended when co-administered with INCIVO®.<br>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 INCIVO®. It is recommended that the international normalized ratio (INR) be monitored when warfarin is co-administered with INCIVO®. |
| **ANTICONVULSANTS** | | |

| | | |
|---|---|---|
| carbamazepine<br>phenobarbital<br>phenytoin | ↓ INCIVO<br>↑ carbamazepine<br>↑ or ↓ phenytoin<br>↑ or ↓ phenobarbital | Concentrations of the anticonvulsant may be altered and concentrations of INCIVO® may be decreased. Caution should be used when prescribing carbamazepine, phenobarbital, and phenytoin.<br>INCIVO® may be less effective in patients taking these agents concomitantly.<br>Clinical or laboratory monitoring of carbamazepine, phenobarbital, and phenytoin concentrations and dose titration are recommended to achieve the desired clinical response. |
| **ANTIDEPRESSANTS** | | |
| escitalopram*<br><br><br><br><br>trazodone | ↔ INCIVO<br>↓ escitalopram<br>AUC 0.65 (0.60–0.70)<br>$C_{max}$ 0.70 (0.65–0.76)<br>$C_{min}$ 0.58 (0.52–0.64)<br><br>↑ trazodone | Concentrations of escitalopram were decreased when co-administered with INCIVO®. Selective serotonin reuptake inhibitors such as escitalopram have a wide therapeutic index, but doses may need to be adjusted when combined with INCIVO®.<br><br>Concomitant use of trazodone and INCIVO® may increase plasma concentrations of trazodone which may lead to adverse events such as nausea, dizziness, hypotension and syncope. If trazodone is used with INCIVO®, the combination should be used with caution and a lower dose of trazodone should be considered. |
| **ANTI-EMETICS** | | |
| domperidone (non-US only) | ↑ domperidone | Concentrations of domperidone may be increased when co-administered with INCIVO®. Co-administration of domperidone with INCIVO® should be avoided. |
| **ANTIFUNGALS** | | |

| | | |
|---|---|---|
| ketoconazole*<br>itraconazole<br>posaconazole<br>voriconazole | ↑ ketoconazole<br>↑ INCIVO<br>AUC 1.62 (1.45-1.81)<br>$C_{max}$ 1.24 (1.10-1.41)<br><br>↑ itraconazole<br>↑ posaconazole<br>↑ or ↓ voriconazole | Ketoconazole increases the plasma concentrations of INCIVO®. Concomitant systemic use of itraconazole or posaconazole with INCIVO® may increase plasma concentration of INCIVO®.<br>Plasma concentrations of itraconazole, ketoconazole, or posaconazole may be increased in the presence of INCIVO®. When co-administration is required, high doses of itraconazole (> 200 mg/day) or ketoconazole (> 200 mg/day) are not recommended.<br>Caution is warranted and clinical monitoring is recommended for itraconazole, posaconazole, and voriconazole.<br>QT interval prolongation and Torsade de Pointes have been reported with voriconazole and posaconazole. QT interval prolongation has been reported with ketoconazole.<br>Due to multiple enzymes involved with voriconazole metabolism, it is difficult to predict the interaction with INCIVO®. Voriconazole should not be administered to patients receiving INCIVO® unless an assessment of the benefit/risk ratio justifies its use. |
| **ANTI GOUT** | | |

| | | |
|---|---|---|
| colchicine | ↑ colchicine | Patients with renal or hepatic impairment should not be given colchicine with INCIVO®, 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.<br>Treatment of gout flares: co-administration of colchicine in patients on INCIVO®: 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.<br>If used for prophylaxis of gout flares: co-administration of colchicine in patients on INCIVO®:<br>If the original regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg once a day.<br>If the original regimen was 0.6 mg once a day, the regimen should be adjusted to 0.3 mg once every other day.<br>Treatment of familial Mediterranean fever (FMF): co-administration of colchicine in patients on INCIVO®:<br>Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day). |
| **ANTIMYCOBACTERIAL** | | |
| rifabutin | ↓ INCIVO®<br>↑ rifabutin | Concentrations of INCIVO® may be decreased, while rifabutin concentrations may be increased during co-administration. INCIVO® may be less effective due to decreased concentrations. The concomitant use of rifabutin and INCIVO® is not recommended. |
| **BENZODIAZEPINES** | | |
| alprazolam* | ↑ alprazolam<br>AUC 1.35 (1.23-1.49)<br>$C_{max}$ 0.97 (0.92-1.03) | Concomitant use of alprazolam and INCIVO® increased exposure to alprazolam by 35%. Clinical monitoring is warranted. |

| | | |
|---|---|---|
| parenterally administered midazolam* | ↑ midazolam<br>AUC 3.40 (3.04-3.79)<br>$C_{max}$ 1.02 (0.80-1.31) | Concomitant use of parenterally administered midazolam with INCIVO® increased exposure to midazolam 3.4-fold. 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.<br>Dose reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered.<br><br>Co-administration of oral midazolam with INCIVO® is contraindicated. |
| zolpidem (non-benzodiazepine sedative)* | ↓ zolpidem<br>AUC 0.53 (0.45-0.64)<br>$C_{max}$ 0.58 (0.52-0.66) | Exposure to zolpidem was decreased by 47% when co-administered with INCIVO®. Clinical monitoring and dose titration of zolpidem is recommended to achieve the desired clinical response. |
| **CALCIUM CHANNEL BLOCKERS** | | |
| amlodipine* | ↑ amlodipine<br>AUC 2.79 (2.58-3.01)<br>$C_{max}$ 1.27 (1.21-1.33) | Exposure to amlodipine was increased 2.8-fold when co-administered with INCIVO®. Caution should be used and dose reduction for amlodipine should be considered. Clinical monitoring is recommended. |
| diltiazem<br>felodipine<br>nicardipine<br>nifedipine<br>nisoldipine<br>verapamil | ↑ calcium channel blockers | Concentrations of other calcium channel blockers may be increased when INCIVO® is co-administered. Caution is warranted and clinical monitoring of patients is recommended. |
| **CORTICOSTEROIDS** | | |
| Systemic dexamethasone | ↓ INCIVO® | Systemic dexamethasone induces CYP3A and can thereby decrease INCIVO® plasma concentrations. This may result in loss of therapeutic effect of INCIVO®. Therefore this combination should be used with caution or alternatives should be considered. |

| | | |
|---|---|---|
| Inhaled/Nasal<br>fluticasone<br>budesonide | ↑ fluticasone<br>↑ budesonide | Concomitant use of inhaled fluticasone or budesonide and INCIVO® may increase plasma concentrations of fluticasone or budesonide resulting in significantly reduced serum cortisol concentrations. Co-administration of fluticasone or budesonide and INCIVO® is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects. |
| **ENDOTHELIN RECEPTOR ANTAGONIST** | | |
| bosentan | ↑ bosentan | Concentrations of bosentan may be increased when co-administered with INCIVO®. Caution is warranted and clinical monitoring is recommended. |
| **HIV-ANTIVIRAL AGENTS: HIV-PROTEASE-INHIBITORS (PIs)** | | |
| atazanavir/ritonavir* | ↓ INCIVO®<br>AUC 0.80 (0.76-0.85)<br>$C_{max}$ 0.79 (0.74-0.84)<br>$C_{min}$ 0.85 (0.75-0.98)<br>↑ atazanavir<br>AUC 1.17 (0.97-1.43)<br>$C_{max}$ 0.85 (0.73-0.98)<br>$C_{min}$ 1.85 (1.40-2.44) | In a drug interaction study in healthy volunteers where INCIVO® was co-administered with atazanavir/ritonavir, the steady-state INCIVO® exposure was reduced by 20%, while the steady-state atazanavir exposure was increased by 17%. Clinical and laboratory monitoring for hyperbilirubinaemia is recommended (see Warnings and Precautions). |
| darunavir/ritonavir* | ↓ INCIVO<br>AUC 0.65 (0.61-0.69)<br>$C_{max}$ 0.64 (0.61-0.67)<br>$C_{min}$ 0.68 (0.63-0.74)<br>↓ darunavir<br>AUC 0.60 (0.57-0.63)<br>$C_{max}$ 0.60 (0.56-0.64)<br>$C_{min}$ 0.58 (0.52-0.63) | In a drug interaction study in healthy volunteers where INCIVO® was co-administered with darunavir/ritonavir, the steady-state INCIVO® exposure was reduced by 35%, while the steady-state darunavir exposure was reduced by 40%. It is not recommended to co-administer darunavir/ritonavir and INCIVO (see Warnings and Precautions on HIV/HCV patients). |

| | | |
|---|---|---|
| fosamprenavir/ritonavir* | ↓ INCIVO®<br>AUC 0.68 (0.63-0.72<br>$C_{max}$ 0.67 (0.63-0.71)<br>$C_{min}$ 0.70 (0.64-0.77)<br>↓ amprenavir<br>AUC 0.53 (0.49-0.58)<br>$C_{max}$ 0.65 (0.59-0.70)<br>$C_{min}$ 0.44 (0.40-0.50) | In a drug interaction study in healthy volunteers where INCIVO® was co-administered with fosamprenavir/ritonavir, the steady-state INCIVO® exposure was reduced by 32%, while the steady-state amprenavir exposure was reduced by 47%. It is not recommended to co-administer fosamprenavir/ritonavir and INCIVO® (see Warnings and Precautions on HIV/HCV patients). |
| lopinavir/ritonavir* | ↓ INCIVO®<br>AUC 0.46 (0.41-0.52)<br>$C_{max}$ 0.47 (0.41-0.52)<br>$C_{min}$ 0.48 (0.40-0.56)<br>↔ lopinavir<br>AUC 1.06 (0.96-1.17)<br>$C_{max}$ 0.96 (0.87-1.05)<br>$C_{min}$ 1.14 (0.96-1.36) | In a drug interaction study in healthy volunteers where INCIVO® was co-administered with lopinavir/ritonavir, the steady-state INCIVO® exposure was reduced by 54%, while the steady-state exposure to lopinavir was not affected. It is not recommended to co-administer lopinavir/ritonavir and INCIVO® (see Warnings and Precautions on HIV/HCV patients). |
| **HIV-ANTIVIRAL AGENTS: INTEGRASE INHIBITORS** | | |
| raltegravir* | ↔ telaprevir<br>AUC 1.07 (1.00-1.15)<br>$C_{max}$ 1.07 (0.98-1.16)<br>$C_{min}$ 1.14 (1.04-1.26)<br>↑ raltegravir<br>AUC 1.31 (1.03-1.67)<br>$C_{max}$ 1.26 (0.97-1.62)<br>$C_{min}$ 1.78 (1.26-2.53) | In a drug interaction study in healthy volunteers where telaprevir was co-administered with raltegravir, the steady-state raltegravir exposure was increased by 31%, while the steady-state exposure to telaprevir was not affected. If co-administered, no dose adjustment is required for either drug. |
| **HIV-ANTIVIRAL AGENTS: REVERSE TRANSCRIPTASE INHIBITORS** | | |
| efavirenz* | ↓ INCIVO® 1,125 mg q8h<br>AUC 0.82 (0.73-0.92)<br>$C_{max}$ 0.86 (0.76-0.97)<br>$C_{min}$ 0.75 (0.66-0.86)<br>↓ efavirenz (+ TVR 1,125 mg q8h)<br>AUC 0.82 (0.74-0.90)<br>$C_{max}$ 0.76 (0.68-0.85)<br>$C_{min}$ 0.90 (0.81-1.01) | In a drug interaction study in healthy volunteers where INCIVO® (at a dose of 1125 mg every 8 hours) was co-administered with efavirenz, the steady-state efavirenz exposure was reduced by 18%. The steady-state INCIVO® exposure was reduced by 18% relative to INCIVO® administered 750 mg every 8 hours. |

| | | |
|---|---|---|
| etravirine* | ↓ telaprevir 750 mg q8h<br>AUC 0.84 (0.71-0.98)<br>$C_{max}$ 0.90 (0.79-1.02)<br>$C_{min}$ 0.75 (0.61-0.92)<br>↔ etravirine (+ TVR 750 mg q8h)<br>AUC 0.94 (0.85-1.04)<br>$C_{max}$ 0.93 (0.84-1.03)<br>$C_{min}$ 0.97 (0.86-1.10) | In a drug interaction study in healthy volunteers where telaprevir was co-administered with etravirine, the steady-state telaprevir exposure decreased by 16%; this difference is not considered to be clinically relevant. No clinically relevant effect on etravirine exposure was observed. If co-administered, no dose adjustment is required for either drug. |
| rilpivirine* | ↓ telaprevir 750 mg q8h<br>AUC 0.95 (0.76-1.18)<br>$C_{max}$ 0.97 (0.79-1.21)<br>$C_{min}$ 0.89 (0.67-1.18)<br>↑ rilpivirine (+ TVR 750 mg q8h)<br>AUC 1.78 (1.44-2.20)<br>$C_{max}$ 1.49 (1.20-1.84)<br>$C_{min}$ 1.93 (1.55-2.41) | In a drug interaction study in healthy volunteers where telaprevir was co-administered with rilpivirine, the steady-state telaprevir exposure decreased by 5%, and the steady-state rilpivirine exposure increased by 1.78-fold. These differences are not considered to be clinically relevant. If co-administered, no dose adjustment is required for either drug. |
| tenofovir disoproxil fumarate* | ↔ INCIVO®<br>AUC 1.00 (0.94-1.07)<br>$C_{max}$ 1.01 (0.96-1.05)<br>$C_{min}$ 1.03 (0.93-1.14)<br>↑ tenofovir<br>AUC 1.30 (1.22-1.39)<br>$C_{max}$ 1.30 (1.16-1.45)<br>$C_{min}$ 1.41 (1.29-1.54) | In a drug interaction study in healthy volunteers co-administration of INCIVO® and tenofovir led to an increase in tenofovir exposure by about 30%. Increased clinical and laboratory monitoring are warranted. |
| **HMG-CoA REDUCTASE INHIBITORS** | | |
| fluvastatin<br>pravastatin<br>rosuvastatin | ↑ statin | Caution is warranted and clinical monitoring is recommended.<br><br>Refer to Contraindications for HMG CoA reductase inhibitors that are contraindicated with INCIVO®. |
| **HORMONAL CONTRACEPTIVES/ESTROGEN** | | |

| | | |
|---|---|---|
| ethinyl estradiol*<br>norethindrone* | ↓ ethinyl estradiol<br>AUC 0.72 (0.69-0.75)<br>$C_{max}$ 0.74 (0.68-0.80)<br>$C_{min}$ 0.67 (0.63-0.71)<br>↔ norethindrone<br>AUC 0.89 (0.86-0.93)<br>$C_{max}$ 0.85 (0.81-0.89)<br>$C_{min}$ 0.94 (0.87-1.00) | Exposure to ethinyl estradiol was decreased by 28% when co-administered with INCIVO®. Alternative methods of non-hormonal contraception should be used when hormonal contraceptives are co-administered with INCIVO®.<br>Patients using estrogens as hormone replacement therapy should be clinically monitored for signs of estrogen deficiency.<br>Refer to Warnings and Precautions and Pregnancy, Breast-feeding and Fertility. |
| **IMMUNOSUPPRESSANTS** | | |
| cyclosporine*<br>sirolimus<br>tacrolimus* | ↑ cyclosporine<br>AUC 4.64 (3.90-5.51)<br>$C_{max}$ 1.32 (1.08-1.60)<br>↑ sirolimus<br>↑ tacrolimus<br>AUC 70.3 (52.9-93.4)<br>$C_{max}$ 9.35 (6.73-13.0) | Plasma concentrations of cyclosporine and tacrolimus are markedly increased when co-administered with INCIVO®. Plasma concentration of sirolimus may be increased when co-administered with INCIVO®, though this has not been studied. Significant dose reductions and prolongation of the dosing interval of the immunosuppressant to achieve the desired blood levels should be anticipated. Close monitoring of the immunosuppressant blood levels, and frequent assessments of renal function and immunosuppressant related side effects are recommended when co-administered with INCIVO®. Tacrolimus may prolong the QT interval. The use of INCIVO® in organ transplant candidates or patients is not recommended (see Warnings and Precautions). |
| **INHALED BETA AGONIST** | | |
| salmeterol | ↑ salmeterol | Concentrations of salmeterol may be increased when co-administered with INCIVO®.. Concurrent administration of salmeterol and INCIVO®. is not recommended. 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** | | |
| buprenorphine* | ↔ buprenorphine<br>AUC 0.96 (0.84-1.10)<br>$C_{max}$ 0.80 (0.69-0.93)<br>$C_{min}$ 1.06 (0.87-1.30) | Total exposure of buprenorphine was unchanged when co-administered with telaprevir. No adjustment of buprenorphine dose is required when initiating co-administration of telaprevir. |
| methadone* | ↓ R-methadone<br>AUC 0.71 (0.66-0.76)<br>$C_{max}$ 0.71 (0.66-0.76)<br>$C_{min}$ 0.69 (0.64-0.75) | Concentrations of methadone were reduced by 29% when co-administered with INCIVO®. No adjustment of methadone dose is required when initiating co-administration of INCIVO®.. However, clinical monitoring is recommended as the dose of methadone during maintenance therapy may need to be adjusted in some patients.<br>QT interval prolongation and Torsade de Pointes have been reported with methadone. |
| **PDE-5 INHIBITORS** | | |
| sildenafil<br>tadalafil<br>vardenafil | ↑ PDE-5 inhibitors | Concentrations of PDE-5 inhibitors may be increased when co-administered with INCIVO®.. For the treatment of erectile dysfunction, sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg dose in 72 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.<br>QT interval prolongation has been reported with vardenafil. Caution is warranted and clinical monitoring is recommended.<br>Co-administration of sildenafil or tadalafil and INCIVO®. in the treatment of pulmonary arterial hypertension is contraindicated (see Contraindications). |
| **PROTON PUMP INHIBITORS** | | |

| | | |
|---|---|---|
| esomeprazole* | ↔ INCIVO®<br>AUC 0.98 (0.91-1.05)<br>$C_{max}$ 0.95 (0.86-1.06) | Since there was no effect of esomeprazole on the plasma concentrations of INCIVO®, proton pump inhibitors can be used without dose modification. |

The direction of the arrow (↑ = *increase,* ↓ = *decrease,* ↔ = *no change*) for each pharmacokinetic parameter is based on the 90% confidence interval of the geometric mean ratio being within (↔), below (↓) or above (↑) the 80-125% range.

***Pediatric population***

Interaction studies have only been performed in adults.

**Pregnancy, Breast-feeding and Fertility**

***Pregnancy and contraception requirements***

INCIVO® has shown no teratogenic potential in rats and mice and is not considered a developmental toxicant in these species.

Because INCIVO® must be used in combination with ribavirin and peginterferon alfa, the contraindications and warnings applicable to those medicinal products are applicable to combination therapy.

Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. As any birth control method can fail, at least 2 reliable forms of effective contraception must be used.

***Female patients***

Female patients of childbearing potential and their male partners must use 2 effective contraceptive methods during treatment and for 6 months after all treatment has ended.

INCIVO® combination therapy should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Pregnancy testing should occur monthly during INCIVO® combination therapy and for 6 months after all therapy has stopped.

Hormonal contraceptives may not be reliable during INCIVO® dosing (see Interactions). Therefore, female patients of childbearing potential should use 2 additional methods of effective birth control during INCIVO® dosing and for 2 months after the last intake of INCIVO®. Examples of non-hormonal methods of contraception include a male condom OR female condom (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. As of 2 months after completion of INCIVO® treatment, hormonal contraceptives can again be used as one of the 2 required effective methods of birth control; however, specific prescribing information recommendations should be respected.

Refer also to the prescribing information for ribavirin.

***Male patients and their female partners***

Male patients and their female partners of childbearing potential must use 2 effective contraceptive methods during treatment and for 6 months after all treatment has ended. Men whose partners are pregnant must be instructed to use a condom to minimize exposure of ribavirin to the partner. Pregnancy testing in non-pregnant female partners is recommended before INCIVO combination therapy, every month during INCIVO® combination therapy, and for 6 months after ribavirin therapy has ended.

Refer also to the prescribing information for ribavirin.

***Breastfeeding***

It is not known whether INCIVO® is excreted in human breast milk. When administered to lactating rats, levels of INCIVO® and its major metabolite were higher in milk compared to those observed in plasma. Rat offspring exposed to INCIVO® in utero showed normal body weight at

birth. However, when fed via milk from INCIVO® treated dams, body weight gain of rat pups was lower than normal (likely due to taste aversion). After weaning, rat pup body weight gain returned to normal. Because of the potential for adverse reactions in breastfed infants, breast-feeding must be discontinued prior to initiation of therapy. See also the prescribing information for ribavirin.

***Fertility***

INCIVO® had no effects on fertility or fecundity when evaluated in rats.

**Effects on Ability to Drive and Use Machines**

INCIVO® has no or negligible influence on the ability to drive and use machines. However, peginterferon alfa, which must be used in combination with INCIVO®, may have an effect. Refer to the prescribing information for peginterferon alfa for further information.

**Adverse Reactions**

The overall safety profile of INCIVO® is based on all available pooled Phase 2 and 3 clinical trial data (both controlled and uncontrolled) containing 2641 subjects who received INCIVO® combination treatment.

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

***Adverse Drug Reactions Identified in the Safety Assessment of the Phase 2 and Phase 3 Studies***

The incidence of adverse drug reactions (ADRs) of at least Grade 2 in severity was higher in the INCIVO® group than in the placebo group.

During the INCIVO®/placebo treatment phase, the most frequently reported ADRs of at least Grade 2 in severity in the INCIVO® group (incidence ≥ 5.0%) were anaemia, rash, pruritus, nausea, and diarrhea.

During the INCIVO®/placebo treatment phase, the most frequently reported ADRs of at least Grade 3 in the INCIVO® group (incidence ≥ 1.0%) were anaemia, rash, thrombocytopenia, lymphopenia, pruritus, and nausea.

ADRs to INCIVO® of at least moderate intensity (≥ Grade 2) are presented in Table 4.

ADRs are listed by system organ class and frequency: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), and rare ( ≥ 1/10000 to < 1/1000). Within each frequency grouping, ADRs are presented in order of decreasing frequency.

**Table 4: Adverse drug reactions to INCIVO® (taken in combination with peginterferon alfa and ribavirin) of at least Grade 2 intensity versus placebo/peginterferon alfa and ribavirin in HCV-infected subjects**

**Pooled placebo-controlled studies 108, C216, 104, 104EU, and 106**

| **System Organ Class**<br><br>Frequency category | **Adverse Drug Reaction** | **INCIVO®, peginterferon alfa, and ribavirin combination therapy**<br>N = 1346 (%) | **Placebo/peginterferon alfa and ribavirin**<br>N = 764 (%) |
|---|---|---|---|
| ***Infections and infestations*** | | | |
| uncommon | Oral candidiasis | 9 (0.7) | 1 (0.1) |
| ***Blood and lymphatic system disorders*** | | | |
| very common | Anaemia | 282 (21.0) | 65 (8.5) |
| ***Endocrine disorders*** | | | |
| uncommon | Hypothyroidism | 5 (0.4) | 0 |
| ***Metabolism and nutrition disorders*** | | | |

| | | | |
|---|---|---|---|
| uncommon | Gout | 3 (0.2) | 0 |
| ***Nervous system disorders*** | | | |
| common | Dysgeusia<br>Syncope | 16 (1.2)<br>13 (1.0) | 3 (0.4)<br>3 (0.4) |
| ***Eye disorders*** | | | |
| uncommon | Retinopathy | 3 (0.2) | 0 |
| ***Gastrointestinal disorders*** | | | |
| common | Nausea<br>Diarrhea<br>Hemorrhoids<br>Vomiting<br>Proctalgia<br>Anal pruritus | 128 (9.5)<br>84 (6.2)<br>56 (4.2)<br>54 (4.0)<br>47 (3.5)<br>17 (1.3) | 43 (5.6)<br>26 (3.4)<br>3 (0.4)<br>18 (2.4)<br>5 (0.7)<br>0 |
| uncommon | Rectal haemorrhage<br>Anal fissure<br>Proctitis | 10 (0.7)<br>9 (0.7)<br>3 (0.2) | 3 (0.4)<br>0<br>0 |
| ***Skin and subcutaneous tissue disorders*** | | | |
| very common | Pruritus<br>Rash | 219 (16.3)<br>216 (16.0) | 32 (4.2)<br>37 (4.8) |
| common | Eczema | 25 (1.9) | 5 (0.7) |
| uncommon | Swelling face<br>Drug rash with eosinophilia and systemic symptoms<br>Urticaria<br>Exfoliative rash | 7 (0.5)<br>6 (0.4)<br><br>3 (0.2)<br>2 (0.1) | 0<br>0<br><br>1 (0.1)<br>0 |
| ***General disorders and administration site conditions*** | | | |
| uncommon | Edema peripheral | 5 (0.4) | 0 |

ADRs related to laboratory findings were thrombocytopenia, lymphopenia, hyperuricaemia, hypokalemia, hyperbilirubinemia, and blood creatinine increased (see Table 5).

***Description of Selected Adverse Drug Reactions***

*Rash*

For severe rash, see Special Warnings and Precautions for Use. In placebo-controlled Phase 2 and 3 trials, the overall incidence and severity of rash increased when INCIVO® was co-administered with peginterferon alfa and ribavirin. During INCIVO® treatment, rash events (all grades) were reported in 55% of patients who received INCIVO® combination treatment and in 33% of patients who received peginterferon alfa and ribavirin.

More than 90% of rashes were of mild or moderate severity. The rash reported during INCIVO® combination treatment was assessed as a typically pruritic, eczematous rash, and involved less than 30% of body surface area. Half the rashes started during the first 4 weeks, but rash can occur at any time during INCIVO® combination treatment. Discontinuation of INCIVO® combination treatment is not required for mild and moderate rash.

Patients experiencing mild to moderate rash should be monitored for signs of progression; however, progression was infrequent (less than 10%). In clinical trials, the majority of patients were administered antihistamines and topical corticosteroids. Improvement of rash occurs after INCIVO® dosing completion or discontinuation; however, rashes may take weeks for complete resolution.

*Anaemia*

In placebo-controlled Phase 2 and 3 trials, anaemia (all grades) was reported in 32.1% of patients who received INCIVO® combination treatment and in 14.8% of patients who received

peginterferon alfa and ribavirin. Ribavirin dose reductions were used for management of anaemia. 21.6% of patients receiving INCIVO® combination treatment required ribavirin dose reduction for anaemia compared to 9.4% of patients receiving peginterferon alfa and ribavirin alone. Erythropoiesis-stimulating agents (ESAs) were generally not permitted and used in only 1% of subjects in the Phase 2 and 3 clinical trials.. In the placebo-controlled Phase 2 and 3 trials, transfusions were reported during the INCIVO®/placebo treatment phase in 2.5% of patients receiving INCIVO® combination treatment and 0.7% in patients receiving peginterferfon alfa and ribavirin alone. Transfusion rates over the whole study period were 4.6% and 1.6%, respectively.In placebo-controlled Phase 2 and 3trials, 1.9% of patients discontinued INCIVO® alone due to anaemia, and 0.9% of patients discontinued INCIVO® combination treatment due to anaemia compared to 0.5% receiving peginterferon alfa and ribavirin (see Warnings and Precautions).

*Anorectal signs and symptoms*

In clinical trials, 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 resolved after completion of INCIVO® dosing.

***Laboratory Abnormalities***

Selected DAIDS Grade 2 and above laboratory abnormalities that represent a worsening from baseline and are considered ADRs observed in HCV-infected subjects treated with INCIVO® combination treatment are presented in Table 5.

**Table 5: Laboratory abnormalities, DAIDS Grade ≥ 2, considered adverse drug reactions, in HCV-infected subjects**

**Pooled placebo-controlled studies 108, C216, 104, 104EU, and 106**

**Based on 1346 subjects who received T12/PR from the Phase 2 and 3 trials**

| **Laboratory parameter** | **DAIDS toxicity range*** | **INCIVO®, peginterferon alfa, and ribavirin combination therapy (%)** | **peginterferon alfa and ribavirin(%)** |
|---|---|---|---|
| Absolute lymphocyte count, decrease | | | |
| Grade 2 | 500-599/$mm^3$ | 13.1% | 5.6% |
| Grade 3 | 350-499/$mm^3$ | 11.8% | 4.4% |
| Grade 4 | <350/$mm^3$ | 4.8% | <1% |
| Creatinine, increase | | | |
| Grade 2 | 1.4-1.8 x ULN | <1% | <1% |
| Grade 3 | 1.9-3.4 x ULN | <1% | 0% |
| Haemoglobin, 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% |
| Hyperbilirubinemia | | | |
| Grade 2 | 1.6-2.5 x ULN | 13.6% | 6.8% |
| Grade 3 | 2.6-5.0 x ULN | 3.6% | 1.1% |

| | | | |
|---|---|---|---|
| Grade 4 | >5.0 x ULN | <1% | <1% |
| Hyperuricaemia | | | |
| 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% |
| Hypokalaemia | | | |
| Grade 2 | 2.5-2.9 mEq/l | 1.6% | 0.3% |
| Grade 3 | 2.0-2.4 mEq/l | 0% | 0% |
| Low-density lipoprotein, increase | | | |
| Grade 2 | 4.13-4.90 mmol/l<br>160-190 mg/dl | 6.9% | 2.1% |
| Grade 3 | ≥4.91 mmol/l<br>≥191 mg/dl | 2.5% | 0.4% |
| 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% | <1% |
| Grade 4 | <25000/$mm^3$ | <1% | <1% |
| Total cholesterol, increase | | | |
| Grade 2 | 6.20-7.77 mmol/l<br>240-300 mg/dl | 15.4% | 1.6% |
| Grade 3 | >7.77 mmol/l<br>>300 mg/dl | 2.0% | <1% |

ULN = Upper Limit of Normal

Note: incidence was calculated by number of subjects for each parameter

* The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 1.0 (December 2004)

Most laboratory values return to levels observed with peginterferon alfa and ribavirin by week 24, except platelet counts, which remain at levels lower than observed with peginterferon alfa and ribavirin until week 48 (see Warnings and Precautions).

Increases in serum uric acid occur very commonly during treatment with INCIVO® in combination with peginterferon alfa and ribavirin. After the end of INCIVO® treatment, uric acid values typically decrease over the following 8 weeks and are comparable to those observed in patients receiving peginterferon alfa and ribavirin alone.

***Additional Adverse Drug Reactions to INCIVO®, Peginterferon Alfa, and Ribavirin Combination Therapy Identified in Other Clinical Trials***

Stevens-Johnson syndrome (rare < 0.1%) that resolved after treatment discontinuation (see Warnings and Precautions)

***Patients Co-infected with HIV-1***

The safety profile of INCIVO® in HCV/HIV-1 co-infected subjects (n = 60) either not on antiretroviral therapy or being treated with efavirenz in combination with tenofovir disoproxil fumarate and emtricitabine was similar to the safety profile in mono-infected HCV subjects. Subjects receiving atazanavir/ritonavir in the INCIVO® 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.

***Additional Adverse Drug Reactions to INCIVO®, Peginterferon Alfa, and Ribavirin Combination Therapy Identified in Post-marketing experience***

Skin and subcutaneous tissue disorders

Toxic epidermal necrolysis (TEN) (see Warnings and Precautions).

**Overdose**

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

No specific antidote is available for overdose with INCIVO®. Treatment of overdose with INCIVO® consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. If indicated, elimination of unabsorbed active substance may be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in the removal of unabsorbed active substance.

It is not known whether INCIVO® is dialyzable by peritoneal or hemodialysis.

## PHARMACOLOGICAL PROPERTIES

### Pharmacodynamic Properties

Pharmacotherapeutic group: Direct-acting antiviral, ATC code: <not yet assigned>.

***Mechanism of action***

INCIVO® is a specific inhibitor of the HCV NS3•4A serine protease, which is essential for viral replication.

***In vitro studies***

Activity of INCIVO® against HCV

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

*Resistance*

HCV variants associated with on-treatment virologic failure or relapse were evaluated by site-directed mutagenesis in the replicon assay (see Pharmacodynamic Properties, Clinical experience). Variants V36A/M, T54A/S, R155K/T, and A156S conferred lower levels of in vitro resistance to INCIVO® (3- to 25-fold increase in INCIVO® $IC_{50}$), and the A156V/T and V36M+R155K variants conferred higher levels of in vitro resistance to INCIVO® (> 25-fold increase in INCIVO® $IC_{50}$). Replicon variants generated from patient-derived sequences showed similar results.

The in vitro replication capacity of INCIVO®-resistant variants was lower than that of wild-type virus.

***Cross-resistance***

INCIVO®-resistant variants were tested for cross-resistance against representative protease-inhibitors in the HCV replicon system. Replicons with single substitutions at position 155 or 156 and double variants with substitutions at residues 36 and 155 showed cross-resistance to all protease-inhibitors tested with a wide range of sensitivities. All INCIVO®-resistant variants studied remained fully sensitive to interferon-alfa, ribavirin, and representative HCV nucleoside and non-nucleoside polymerase inhibitors in the replicon system. There are no clinical data on re-treating subjects who have failed an HCV NS34A protease inhibitor-based therapy, such as INCIVO®, nor are there data on repeated courses of INCIVO® treatment.

***Clinical virology studies***

In Phase 2 and 3 clinical trials of INCIVO®, treatment naïve and prior treatment-failure subjects with predominant INCIVO®-resistant variants at baseline (pre-treatment) were rare (V36M, T54A and R155K < 1% and T54S 2.7%). Predominant baseline resistance to INCIVO® does not preclude successful treatment with INCIVO®, peginterferon alfa, and ribavirin.

A total of 215 of 1169 subjects treated with a T12/PR regimen in a Phase 3 clinical trial had on-treatment virologic failure (n = 125) or relapse (n = 90) (see Pharmacodynamic Properties,

Clinical experience). Based on population sequencing analyses of HCV in these 215 subjects, the emergence of INCIVO®-resistant HCV variants was detected in 105 (84%) virologic failures and in 55 (61%) relapsers, and wild-type virus was detected in 15 (12%) virologic failures and in 24 (27%) relapsers. HCV sequencing data were not available for 16 (7%) subjects. Sequence analyses of the INCIVO®-resistant variants identified substitutions at 4 positions in the NS3-4A protease region, consistent with the mechanism of action for INCIVO® (V36A/M, T54A/S, R155K/T, and A156S/T/V). On-treatment virologic failure during INCIVO® 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 INCIVO®, 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 Pharmacodynamic Properties, Clinical experience, Efficacy in previously treated adults).

Follow-up analysis of INCIVO® treated subjects who did not achieve an SVR showed that the population of wild-type virus increased and the population of INCIVO®-resistant variants became undetectable over time after the end of INCIVO® treatment. Of a combined 255 treatment naïve and previously treated subjects from Phase3 studies 108, 111, and C216 in whom INCIVO®-resistant variants had emerged during treatment, 152 (60%) subjects no longer had resistant variants detected by population sequencing (median follow-up of 10 months). Of the 393 resistant variants detected in these 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 INCIVO® regimen in a Phase 2 study and did not achieve SVR, INCIVO®-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 INCIVO® treatment and at follow-up, showed that the HCV variant population in all subjects had returned to pre-treatment levels.

***Pharmacodynamic effects***

*Clinical studies examining QT interval*

In two double-blind, randomized, placebo- and active-controlled studies conducted to evaluate the effect on the QT interval, INCIVO® monotherapy at a dose of 750 mg every 8 hours was not associated with a clinically relevant effect on $QT_cF$ interval. In one of those studies, a INCIVO® 1,875 mg every 8 hours regimen was evaluated and the placebo-adjusted maximum mean increase in $QT_cF$ was 8.0 msec (90% CI: 5.1-10.9). Plasma concentrations with the INCIVO® 1,875 mg every 8 hours dose used in this trial were comparable to those observed in studies in HCV-infected patients who received INCIVO® 750 mg every 8 hours in combination with peginterferon alfa-2a and ribavirin.

***Clinical experience***

The efficacy and safety of INCIVO® in subjects with genotype 1 chronic hepatitis C were evaluated in three Phase 3 studies: 2 in treatment naïve subjects and 1 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. Unless otherwise indicated, INCIVO® was administered at a dosage of

750 mg every 8 hours; the peginterferon alfa-2a dose was 180 µg/week, and the ribavirin dose was 1000 mg/day (subjects weighing < 75 kg) or 1200 mg/day (subjects weighing ≥ 75 kg). Plasma HCV RNA values were measured using the COBAS® TaqMan® HCV test (version 2.0), for use with the High Pure System. The assay had a lower limit of quantification of 25 IU/ml. In the description of Phase 3 study outcomes below, SVR, considered virologic cure, was defined based on the HCV RNA assessment in the study week 72 visit window, using the last measurement in the window. In the case of missing data within the week 72 window, the last HCV RNA data point from week 12 of follow-up onwards was used. In addition, the limit of quantification of 25 IU/ml was used to determine SVR.

***Efficacy in treatmentnaïve adults***

*Study 108 (ADVANCE)*

Study 108 was a randomised, double-blind, parallel-group, placebo-controlled, Phase 3 study conducted in treatment naïve subjects. INCIVO® 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 peginterferon alfa-2a and ribavirin for either 24 or 48 weeks. Subjects who had undetectable HCV RNA at weeks 4 and 12 received 24 weeks of peginterferon alfa-2a and ribavirin treatment, and subjects who did not have undetectable HCV RNA at week 4 and week 12 received 48 weeks of peginterferon alfa-2a and ribavirin treatment. The control regimen (Pbo/PR) had a fixed treatment duration of 48 weeks, with INCIVO® matching placebo for the first 12 weeks and peginterferon alfa-2a and ribavirin for 48 weeks.

The 1088 enrolled subjects had a median age of 49 years (range: 18 to 69); 58% of the subjects were male; 23% had a body mass index ≥ 30 kg/m$^2$; 9% were Black; 11% were Hispanic or Latino; 77% had baseline HCV RNA levels ≥ 800000 IU/ml; 15% had bridging fibrosis; 6% had cirrhosis; 59% had HCV genotype 1a; and 40% had HCV genotype 1b.

The SVR rate for the T8/PR group was 72% (261/364) (P < 0.0001 compared to Pbo/PR48 group). Table 6 shows the response rates for the recommended T12/PR and the Pbo/PR48 groups.

**Table 6: Response rates: Study 108**

| **Treatment outcome** | **T12/PR N = 363 n/N (%)** | **Pbo/PR48 N = 361 n/N (%)** |
|---|---|---|
| **SVR**[a] | 79% (285/363) | 46% (166/361) |
| Undetectable HCV RNA at week 4 | 68% (246/363) | 9% (34/361) |
| Undetectable HCV RNA at weeks 4 and 12 | 58% (212/363) | 8% (29/361) |
| SVR in subjects with undetectable HCV RNA at weeks 4 and 12 | 92% (195/212) | 93% (27/29) |
| SVR in subjects who did not have undetectable HCV RNA at weeks 4 and 12 | 60% (90/151) | 42% (139/332) |
| **Outcome for Subjects without SVR** | 21% (78/363) | 54% (195/361) |
| On-treatment virologic failure[b] | 7% (27/363) | 29% (105/361) |
| Relapse[c] | 4% (13/299) | 26% (58/225) |
| Other[d] | 10% (38/363) | 9% (32/361) |

T12/PR: INCIVO® 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

[a] P<0.0001; T12/PR compared to Pbo/PR48.

[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 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 ≥ 25 IU/ml at the last observation within the SVR follow-up visit window..

[d] Other includes subjects with detectable HCV RNA at the time of their last study drug but who did not have viral breakthrough, and subjects with a missing SVR assessment.

SVR rates were higher (absolute difference of at least 28%) for the T12/PR group than for the Pbo/PR48 group across subgroups by sex, age, race, ethnicity, body mass index, geographic region, HCV genotype subtype, baseline HCV RNA (< 800000, ≥ 800000 IU/ml), and extent of liver fibrosis. Table 7 shows SVR rates for subject subgroups.

**Table 7: SVR rates for patient 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) |
| 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 ≥ 800000 IU/ml | 77% (215/281) | 39% (109/279) |
| HCV genotype 1a | 75% (162/217) | 43% (90/210) |
| HCV genotype 1b | 84% (119/142) | 51% (76/149) |
| 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: INCIVO® 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)*

Study 111 was a Phase 3, randomized, open-label study conducted in treatment naïve subjects. The study was designed to compare SVR rates in subjects with undetectable HCV RNA at weeks 4 and 12 who were treated with INCIVO® for 12 weeks in combination with peginterferon alfa-2a and ribavirin for either 24 weeks (T12/PR24 regimen) or 48 weeks (T12/PR48 regimen). Subjects with undetectable HCV RNA at weeks 4 and 12 were randomized at week 20 to receive either 24 weeks or 48 weeks of peginterferon alfa-2a and ribavirin treatment. 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.

The 540 enrolled subjects had a median age of 51 years (range: 19 to 70); 60% of the subjects were male; 32% had a body mass index ≥ 30 kg/m$^2$; 14% were Black; 10% were Hispanic or Latino; 82% had baseline HCV RNA levels > 800000 IU/ml; 16% had bridging fibrosis; 11% had cirrhosis; 72% had HCV genotype 1a; and 27% had HCV genotype 1b.

A total of 352 (65%) subjects had undetectable HCV RNA at weeks 4 and 12. Table 8 shows response rates. In subjects who had undetectable HCV RNA at weeks 4 and 12, there was no additional benefit to extending peginterferon alfa-2a and ribavirin treatment to 48 weeks (difference in SVR rates of 2%; 95% confidence interval: -4%, 8%).

**Table 8: Response rates: Study 111**

| Treatment outcome | Subjects with undetectable HCV RNA at weeks 4 and 12 | | T12/PR All Subjects[a] N = 540 |
|---|---|---|---|
| | T12/PR24 N = 162 | T12/PR48 N = 160 | |
| **SVR** | 92% (149/162) | 90% (144/160) | 74% (398/540) |
| **Outcome for subjects without SVR** | 8% (13/162) | 10% (16/160) | 26% (142/540) |
| On-treatment virologic failure[b] | 2% (3/162) | 3% (5/160) | 8% (44/540) |
| Relapse[c] | 6% (10/159) | 1% (2/149) | 4% (19/424) |
| Other[d] | 0% (0/162) | 6% (9/160) | 15% (79/540) |

T12/PR24: INCIVO® for 12 weeks with peginterferon alfa-2a and ribavirin for 24 weeks; T12/PR48: INCIVO® 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).

[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 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 ≥ 25 IU/ml at the last observation within the SVR follow-up visit window

[d] Other includes subjects with detectable HCV RNA at the time of their last study drug but who did not have viral breakthrough, and subjects with a missing SVR assessment.

The SVR rate for Black subjects was 62% (45/73). Table 9 shows SVR rates by extent of liver fibrosis at baseline.

**Table 9: 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: INCIVO® for 12 weeks with peginterferon alfa-2a and ribavirin for 24 weeks; T12/PR48: INCIVO® 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 randomisation occurred)

*Study 110*

Study 110 was a Phase 2 randomised, double-blind, placebo-controlled study conducted in subjects with chronic genotype 1 HCV/HIV co-infection who were treatment-naïve for hepatitis C. Subjects were either not on antiretroviral therapy (CD4 count ≥ 500 cells/mm$^3$), or had stable controlled HIV (HIV RNA < 50 copies/ml, CD4 count ≥ 300 cells/mm$^3$) being treated with efavirenz or atazanavir/ritonavir in combination with tenofovir disoproxil fumarate and emtricitabine or lamivudine. Subjects were randomised to 12 weeks of INCIVO® (750 mg every 8 hours if taken in combination with atazanavir/ritonavir, tenofovir disoproxil fumarate, and emtricitabine or lamivudine OR 1125 mg every 8 hours if taken in combination with efavirenz, tenofovir disoproxil fumarate, and emtricitabine) or placebo. All subjects received peginterferon alfa-2a and ribavirin for 48 weeks. Fifty-five out of 60 subjects received ribavirin at a fixed dose of 800 mg/day and the remaining 5 subjects received a weight-based ribavirin dose. Table 10 shows the response rates for the T12/PR48 and the Pbo/PR48 arms.

**Table 10: Response Rates: Study 110**

| Treatment Outcome | T12/PR48<br>% (n/N) | Pbo/PR<br>% (n/N) |
|---|---|---|
| Overall SVR12 rate[a] | 74% (28/38) | 45% (10/22) |
| Subjects on an efavirenz-based regimen | 69% (11/16) | 50% (4/8) |
| Subjects on an atazanavir/ritonavir-based regimen | 80% (12/15) | 50% (4/8) |
| Subjects not receiving antiretroviral therapy | 71% (5/7) | 33% (2/6) |
| [a] HCV RNA< 25 IU/ml in the week 12 follow-up window | | |

***Efficacy in previously treated adults***

*Study C216 (REALIZE)*

Study C216 was a randomized, double-blind, placebo-controlled, Phase 3 study conducted in subjects who did not achieve SVR with prior treatment with peginterferon alfa-2a and ribavirin or peginterferon alfa-2b and ribavirin. 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 was comprised of 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 a peginterferon and ribavirin) and prior null responders (less than 2 $\log_{10}$ reduction in HCV RNA at week 12 of prior treatment with peginterferon and ribavirin).

Subjects were randomized in a 2:2:1 ratio to one of three treatment groups: simultaneous start (T12/PR48): INCIVO® from day 1 through week 12; delayed start (T12(DS)/PR48): INCIVO from week 5 through week 16; Pbo/PR48: placebo through week 16. All treatment regimens had a 48-week duration of peginterferon alfa-2a and ribavirin treatment.

The 662 enrolled subjects had a median age of 51 years (range: 21 to 70); 70% of the subjects were male; 26% had a body mass index $\geq 30$ kg/m$^2$; 5% were Black; 11% were Hispanic or Latino; 89% had baseline HCV RNA levels > 800,000 IU/ml; 22% had bridging fibrosis; 26% had cirrhosis; 54% had HCV genotype 1a, and 46% had HCV genotype 1b.

SVR rates for the T12(DS)/PR group were 88% (124/141) for prior relapsers, 56% (27/48) for prior partial responders, and 33%(25/75) for prior null responders. Table 11 shows the response rates for the recommended simultaneous start (T12/PR48) and the Pbo/PR48 arms.

**Table 11: Response rates: Study C216**

| Treatment outcome | T12/PR48<br>% (n/N) | Pbo/PR48<br>% (n/N) |
|---|---|---|
| **SVR** | | |
| Prior relapsers[a] | 84% (122/145) | 22% (15/68) |
| Prior partial responders[a] | 61% (30/49) | 15% (4/27) |
| Prior null responders[a] | 31% (22/72) | 5% (2/37) |
| **Undetectable HCV RNA at weeks 4 and 12** | | |
| Prior relapsers | 66% (95/145) | 3% (2/68) |
| **Treatment outcomes for subjects without SVR** | | |

| | | |
|---|---|---|
| **Prior relapsers** | N=145 | N=68 |
| On-treatment virologic failure[b] | 1% (2/145) | 26% (18/68) |
| Relapse[c] | 3% (4/126) | 63% (27/43) |
| Other[d] | 12% (17/145) | 12% (8/68) |
| **Prior partial responders** | N=49 | N=27 |
| On-treatment virologic failure[b] | 16% (8/49) | 70% (19/27) |
| Relapse[c] | 17% (6/36) | 0%(0/4) |
| Other[d] | 10% (5/49) | 15% (4/27) |
| **Prior null responders** | N=72 | N=37 |
| On-treatment virologic failure[b] | 57% (41/72) | 84% (31/37) |
| Relapse[c] | 21% (6/28) | 50% (2/4) |
| Other[d] | 4% (3/72) | 5% (2/37) |

T12/PR48: INCIVO® 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

[a] *P*<0.001, T12/PR compared to Pbo/PR48. The difference in SVR rates (95% confidence interal) between the T12/PR and Pbo/PR groups were 63 (51, 74) for prior relapsers, 46 (27, 66) for prior partial responders, and 26 (13, 39) for prior null responders.

[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 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 ≥ 25 IU/ml at the last observation within the SVR follow-up visit window .

[d] Other includes subjects with detectable HCV RNA at the time of their last study drug but who did not have viral breakthrough, and subjects with a missing SVR assessment.

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, race, ethnicity, body mass index, HCV genotype subtype, baseline HCV RNA level, and extent of liver fibrosis. Table 12 shows SVR rates by extent of liver fibrosis.

**Table 12: SVR rates by extent of liver fibrosis at baseline: Study C216**

| **Extent of liver fibrosis** | **T12/PR** | **Pbo/PR48** |
|---|---|---|
| **Prior relapsers** | | |
| No or minimal fibrosis or portal fibrosis | 84% (68/81) | 32% (12/38) |
| Bridging fibrosis | 86% (31/36) | 13% (2/15) |
| Cirrhosis | 82% (23/28) | 7% (1/15) |
| **Prior partial responders** | | |
| No or minimal fibrosis or portal fibrosis | 79% (19/24) | 18% (3/17) |
| Bridging fibrosis | 71% (5/7) | 0 (0/5) |
| Cirrhosis | 33% (6/18) | 20% (1/5) |
| **Prior null responders** | | |
| No or minimal fibrosis or portal fibrosis | 31% (9/29) | 6% (1/18) |
| Bridging fibrosis | 47% (8/17) | 0 (0/9) |
| Cirrhosis | 19% (5/26) | 10% (1/10) |

T12/PR48: INCIVO® 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

*Study 106 and Study 107*

Study 106 was a randomized, double-blind, placebo-controlled, Phase 2 study that enrolled subjects who had failed prior treatment with peginterferon alfa-2a and ribavirin or peginterferon

alfa-2b and ribavirin. Among prior relapsers in the T12/PR24 treatment group who had undetectable HCV RNA at weeks 4 and 12 of treatment, the SVR rate was 89% (25/28) and the relapse rate was 7%.
Study 107 was an open-label, rollover study for subjects who were treated in the control group (placebo, peginterferon alfa-2a, and ribavirin) of a Phase 2 study of INCIVO® and who did not achieve SVR in the Phase 2 study. Among prior relapsers in the T12/PR24 treatment group who had undetectable HCV RNA at weeks 4 and 12 of treatment, the SVR rate was 100% (24/24).

***Use of peginterferon alfa-2a or 2b***

Two types of peginterferon alfa (2a and 2b) were studied in the Phase 2a open-label, randomized study C208 in treatment naïve subjects. All subjects received 12 weeks of INCIVO® in combination with the peginterferon alfa/ribavirin standard therapy. Subjects were randomised to 1 of 4 treatment groups:

- INCIVO® 750 mg every 8 hours with peginterferon alfa-2a 180 µg/week and ribavirin 1000 or 1200 mg/day
- INCIVO® 750 mg every 8 hours with peginterferon alfa-2b 1.5 µg/week and ribavirin 800 or 1200 mg/day
- INCIVO® 1125 mg every 12 hours with peginterferon alfa-2a 180 µg/week and ribavirin 1000 or 1200 mg/day
- INCIVO® 1125 mg every 12 hours with peginterferon alfa-2b 1.5 µg/week and ribavirin 800 or 1200 mg/day

Peginterferon alfa-2a/peginterferon alfa-2b and ribavirin were used according to their relevant Prescribing Information.
At week 12, INCIVO® dosing ended and subjects continued on standard therapy only. The percentage of subjects with SVR in the pooled peginterferon alfa-2a group was 83.8%, in the pooled peginterferon alfa-2b group 81.5% with a 95% confidence interval for the difference of (-10.8, 12.1).

***Long term efficacy data***

*Study 112 (EXTEND)*

A 3-year follow-up study of subjects who achieved SVR with a INCIVO®-based regimen showed that > 99% (122/123) of subjects maintained their SVR status through the available follow-up period (median duration of 22 months).

***Pediatric population***

No clinical studies have been performed in pediatric subjects.

**Pharmacokinetic Properties**

The pharmacokinetic properties of INCIVO® have been evaluated in healthy adult volunteers and in subjects with chronic HCV infection. INCIVO® is to be administered orally with food as 375 mg tablets, 750 mg every 8 hours for 12 weeks, in combination with peginterferon alfa and ribavirin. Exposure to INCIVO® is higher during co-administration of peginterferon alfa and ribavirin than after administration of INCIVO® alone.
INCIVO® exposure is comparable during co-administration with either peginterferon alfa-2a and ribavirin or peginterferon alfa-2b and ribavirin.

***Absorption***

INCIVO® 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 INCIVO® are generally achieved after 4-5 hours. In vitro studies performed with human Caco-2 cells indicated that INCIVO® is a substrate of P-glycoprotein (P-gp).
The exposure to INCIVO® was increased by 20% when taken following a high-fat caloric meal (56 g fat, 928 kcal) compared to an intake following a standard normal caloric meal (21 g fat,

533 kcal). When compared to administration following a standard normal caloric meal, exposure (AUC) decreased by 73% when INCIVO® was taken on an empty stomach, by 26% following a low-calorie high-protein meal (9 g fat, 260 kcal), and by 39% following a low-calorie low-fat meal (3.6 g fat, 249 kcal). Therefore, INCIVO® should be taken with food.

***Distribution***

INCIVO is approximately 59% to 76% bound to plasma proteins. INCIVO® binds primarily to alpha 1-acid glycoprotein and albumin.

After oral administration, the typical apparent volume of distribution (Vd) was estimated to be 252L, with an inter-individual variability of 72.2%.

***Biotransformation***

INCIVO® is extensively metabolised in the liver, involving hydrolysis, oxidation, and reduction. Multiple metabolites were detected in faeces, plasma, and urine. After repeated oral administration, R-diastereomer of INCIVO® (30-fold less active), pyrazinoic acid, and a metabolite that underwent reduction at the α-ketoamide bond of INCIVO® (not active) were found to be the predominant metabolites of INCIVO®.

In vitro studies using recombinant human cytochrome P450 (CYP) isoforms indicated that CYP3A4 was the major CYP isoform responsible for CYP-mediated INCIVO® metabolism. *In vitro* studies using recombinant aldo-ketoreductases indicated that these and potentially other reductases are also responsible for the reduction of INCIVO®. Other proteolytic enzymes are also involved in the hydrolysis of INCIVO®. Studies using recombinant human CYP supersomes showed that INCIVO® was a CYP3A4 inhibitor, and a time-and concentration-dependent inhibition of CYP3A4 by INCIVO® was observed in human liver microsomes. No relevant inhibition by INCIVO® of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP2E1 isozymes was observed in vitro. No relevant induction by INCIVO® of CYP1A2, CYP2B6, CYP2C, and CYP3A isozymes was observed *in vitro*. Based on the results of clinical drug-drug interaction studies, induction of metabolic enzymes cannot be excluded.

*In vitro* studies demonstrated that INCIVO® is not an inhibitor of UGT1A9 or UGT2B7. *In vitro* studies with recombinant UGT1A3 suggested that INCIVO® may inhibit this enzyme. The clinical relevance of this is uncertain as administration of INCIVO® with a single dose of buprenorphine, a partial UGT1A3 substrate, to healthy adult subjects did not result in increases in buprenorphine exposures. No relevant inhibition by INCIVO® of alcohol dehydrogenase was observed *in vitro*.

***Transporters***

*In vitro* studies demonstrated that INCIVO® is an inhibitor of the organic anion transporting polypeptides (OATP) OATP1B1 and OATP2B1.

No relevant inhibition by INCIVO® of the organic cation transporter (OCT) OCT2, or the organic anion transporter (OAT) OAT1 was observed *in vitro*.

***Elimination***

Following administration of a single oral dose of 750 mg $^{14}$C-INCIVO® in healthy subjects, 90% of total radioactivitiy was recovered in faeces, urine and expired air within 96 hours post-dose. The median recovery of the administered radioactive dose was approximately 82% in the faeces, 9% in exhaled air and 1% in urine. The contribution of unchanged $^{14}$C-INCIVO® and VRT-127394 towards total radioactivity recovered in faeces was 31.8% and 18.7%, 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 INCIVO® 750 mg typically ranged from about 4.0 to 4.7 hours.

***Linearity/non-linearity***

The exposure (AUC) to INCIVO® increased slightly greater than proportionally to the dose after single-dose administration of 375 up to 1,875 mg with food, possibly due to saturation of metabolic pathways or efflux transporters.
An increase in dose from 750 mg every 8 hours to 1,875 mg every 8 hours in a multiple-dose study resulted in a less than proportional increase (i.e., about 40%) in INCIVO® exposure.

***Special populations***

*Pediatric population*

Data in the pediatric population are currently not available.

*Renal impairment*

The pharmacokinetics of INCIVO® were assessed after administration of a single dose of 750 mg to HCV-negative subjects with severe renal impairment (CrCl < 30 ml/min). The mean INCIVO® $C_{max}$ and AUC were 10% and 21% greater, respectively, compared to healthy subjects (see Dosage and Administration).

*Hepatic impairment*

INCIVO® is primarily metabolised in the liver. Steady-state exposure to INCIVO® was 15% lower in subjects with mild hepatic impairment (Child Pugh Class A, score 5-6) compared to healthy subjects. Steady-state exposure to INCIVO® was 46% lower in subjects with moderate hepatic impairment (Child Pugh Class B, score 7-9) compared to healthy subjects (see Dosage and Administration and Warnings and Precautions).

*Gender*

The effect of subject gender on INCIVO® pharmacokinetics was evaluated using population pharmacokinetics of data from Phase 2 and 3 studies of INCIVO®. No dose adjustments are deemed necessary based on gender.

*Race*

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

*Elderly*

There is limited clinical data on the use of INCIVO® in HCV patients aged ≥ 65 years.

## NON-CLINICAL INFORMATION

***Carcinogenesis, mutagenesis, impairment of fertility***

*Carcinogenesis and mutagenesis*

INCIVO® has not been tested for its carcinogenic potential. Neither INCIVO® nor its major metabolite caused damage to DNA when tested in the standard battery of mutagenesis assays, in the presence and absence of metabolic activation.

*Impairment of fertility*

INCIVO® had no effects on fertility or fecundity when evaluated in rats.

***Animal toxicology and/or pharmacology***

In rats and dogs, INCIVO® was associated with a reversible reduction of red blood cell parameters accompanied by a regenerative response. In rats, telaprevir caused degenerative changes in testes which were reversible and did not affect fertility.

## PHARMACEUTICAL INFORMATION

**List of Excipients**

*Tablet core*: Each tablet contains the excipients: hypromellose acetate succinate, calcium hydrogen phosphate (anhydrous), microcrystalline cellulose, silica colloidal anhydrous, sodium lauryl sulphate, croscarmellose sodium, sodium stearyl fumarate

*Tablet film-coat:* polyvinyl alcohol, macrogol, talc, titanium dioxide (E171), and iron oxide yellow (E172).

**Incompatibilities**
Not applicable.
**Shelf Life**
See expiry date on the outer pack.
**Storage Conditions**
Do not store above 30 ºC.
Store in the original bottle. Keep the bottle tightly closed in order to protect from moisture. Do not remove the desiccant.
Keep out of (the sight and) reach of children.
**Nature and Contents of Container**
High-density polyethylene (HDPE) bottle containing 42 film-coated tablets and fitted with polypropylene (PP) child-resistant closure and induction seal liner. Desiccant (one pouch or two pouches) is added.
42 oral tablets per bottle. To be distributed in a 1-bottle pack or 4-bottle multi-pack.
**Instructions for Use and Handling**
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.
**Instructions for Disposal**
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

**MANUFACTURED BY**
See outer carton.

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