ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

Medicinal product no longer authorised

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

INCIVO 375 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 375 mg of telaprevir.

Excipient: 2.3 mg of sodium per film-coated tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
Yellow caplet shaped tablets of approximately 20 mm in length, marked with “T375” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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 sections 4.4 and 5.1).

4.2 Posology and method of administration

Treatment with INCIVO should be initiated and monitored by a physician experienced in the management of chronic hepatitis C.

Posology
INCIVO 1,125 mg (three 375 mg film-coated tablets) should be taken orally twice daily (b.i.d.) with food. Alternatively, 750 mg (two 375 mg tablets) can be taken orally every 8 hours (q8h) with food. The total daily dose is 6 tablets (2,250 mg). Taking INCIVO without food or without regard to the dosing interval may result in decreased plasma concentrations of telaprevir which could reduce the therapeutic effect of INCIVO.

INCIVO should be administered in conjunction with ribavirin and either peginterferon alfa-2a or -2b. Please consult sections 4.4 and 5.1 regarding the selection of peginterferon alfa-2a or -2b. For specific dosage instructions for peginterferon alfa and ribavirin, the Summary of Product Characteristics for these medicinal products should be consulted.

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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).

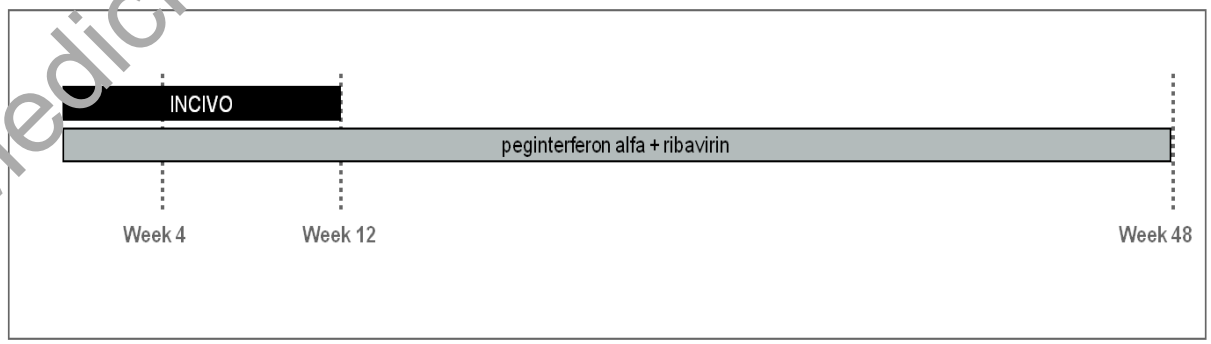
- Patients with undetectable hepatitis C virus ribonucleic acid (HCV RNA) (target not detected) at weeks 4 and 12 receive an additional 12 weeks of peginterferon alfa and ribavirin alone for a total treatment duration of 24 weeks.
- Patients with detectable HCV RNA at either weeks 4 or 12 receive an 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 (target not detected) 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 section 5.1).

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, a sensitive real-time PCR assay with a limit of quantification of 25 IU/ml and a limit of detection of 10-15 IU/ml was used to determine whether HCV RNA levels were undetectable (target not detected) (see section 5.1). Detectable HCV RNA below the lower limit of assay quantification should not be used as a substitute for "undetectable" (target not detected), 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.

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 1 for Guidelines for Discontinuation of INCIVO, Peginterferon Alfa, and Ribavirin Treatment.

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All patients

Since it is highly unlikely that patients with inadequate viral responses will achieve a sustained virologic response (SVR), it is recommended that patients with HCV RNA > 1,000 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 > 1,000 IU/ml at week 4 of treatment[a]**	**HCV RNA > 1,000 IU/ml at week 12 of treatment[a]**
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 section 5.1).

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-naive 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 patients with HCV RNA between 100 IU/ml and 1,000 IU/ml at week 12, 2/8 (25%) achieved an 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 taken with peginterferon alfa and ribavirin to prevent treatment failure.

To prevent treatment failure, the dose of INCIVO must not be reduced or interrupted.

If INCIVO treatment is discontinued due to adverse drug reactions or because of insufficient virologic response, INCIVO treatment should not be reinitiated.

Refer to the respective Summary of Product Characteristics of peginterferon alfa and ribavirin for guidelines on dose modifications, interruptions, discontinuations or resumption of those medicinal products (see section 4.4).

When administered twice daily (b.i.d.), in case a dose of INCIVO is missed within 6 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 6 hours after the time INCIVO should be taken, the missed dose should be skipped and the patient should resume the normal dosing schedule.

When administered every 8 hours (q8h), 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) (see section 4.4). In HCV-negative patients with severe renal impairment, no clinically relevant change in telaprevir exposure was observed (see section 5.2). Therefore, no dose adjustment is recommended for INCIVO in HCV patients with renal impairment.

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There are no clinical data on the use of INCIVO in patients on haemodialysis.

Refer also to the Summary of Product Characteristics for ribavirin for patients with CrCl < 50 ml/min.

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 (ascites, portal hypertensive bleeding, encephalopathy, and/or jaundice other than Gilbert's Syndrome, see section 4.4). 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 Summary of Product Characteristics for peginterferon alfa and ribavirin which are contraindicated in Child-Pugh score ≥ 6.

HCV/Human immunodeficiency virus type (HIV)-1 co-infection
HCV/HIV-1 co-infected patients should be treated in the same way as HCV mono-infected patients. Drug interactions need to be carefully taken into account, see sections 4.4 and 4.5. Patients on an efavirenz-based regimen must receive INCIVO 1,125 mg every 8 hours. For outcomes obtained in HIV co-infected patients, see section 5.1.

Liver transplant patients without cirrhosis
Treatment with INCIVO must be initiated in combination with peginterferon alfa and ribavirin and administered for 12 weeks with an additional 36 weeks of peginterferon alfa and ribavirin alone for a total treatment duration of 48 weeks. No dose adjustment of INCIVO is required in stable liver transplant patients (see sections 4.8 and 5.1). A lower ribavirin dose (600 mg/day) at initiation of INCIVO treatment is recommended (see section 5.1). At the initiation and discontinuation of INCIVO treatment, doses of co-administered tacrolimus or cyclosporine A need to be markedly adjusted (see sections 4.4 and 4.5, Immunosuppressants).

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

Paediatric population
The safety and efficacy of INCIVO in children aged < 18 years have not yet been established. No data are available.

Method of administration
Patients should be instructed to swallow the tablets whole (e.g. patients should not chew, break or dissolve the tablet).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Concomitant administration 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. These active substances include alfuzosin, amiodarone, bepridil, quinidine, astemizole, terfenadine, cisapride, pimozide, ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine), lovastatin, simvastatin, atorvastatin, sildenafil or tadalafil (only when used for treatment of pulmonary arterial hypertension), quetiapine and orally administered midazolam or triazolam (see section 4.5).

Concomitant administration with Class Ia or III antiarrhythmics, except for intravenous lidocaine (see section 4.5).

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Concomitant administration of INCIVO with active substances that strongly induce CYP3A e.g. rifampicin, St John's wort *(Hypericum perforatum*), carbamazepine, phenytoin and phenobarbital and thus may lead to lower exposure and loss of efficacy of INCIVO.

Refer to the Summary of Product Characteristics for peginterferon alfa and ribavirin for a list of their contraindications since INCIVO must be used in combination with peginterferon alfa and ribavirin.

4.4 Special warnings and precautions for use

Severe rash

Severe, potentially life-threatening and fatal skin reactions have been reported with INCIVO combination treatment. Toxic epidermal necrolysis (TEN) including fatal outcome has been observed in post-marketing experience (see section 4.8). Fatal cases have been reported in patients with progressive rash and systemic symptoms who continued to receive INCIVO combination treatment after a serious skin reaction was identified.

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. Available data suggest that peginterferon alfa, and perhaps also ribavirin, may contribute to the frequency and severity of rash associated with INCIVO combination treatment.

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 of those receiving peginterferon alfa and ribavirin.

In placebo-controlled Phase 2 and 3 trials, 0.4% of patients had suspected Drug Rash with Eosinophilia and Systemic Symptoms (**DRESS**). In INCIVO clinical experience, less than 0.1% of patients had **Stevens-Johnson Syndrome (SJS)**. All of these reactions resolved with treatment discontinuation.

DRESS presents as a rash with eosinophilia associated with one or more of the following features: fever, lymphadenopathy, facial oedema, and internal organ involvement (hepatic, renal, pulmonary). It may appear at any time after start of treatment, although the majority of cases appeared between six and ten weeks after the start of treatment with INCIVO.

Prescribers should ensure that patients are fully informed about the risk of severe rashes, and to consult with their prescriber immediately if they develop a new rash or worsening of an existing rash. All rashes should be monitored for progression and until the rash is resolved. The rash may take several weeks to resolve. Other medicinal products associated with severe cutaneous reactions should be used with caution during administration of INCIVO combination treatment to avoid potential confusion as to which medicinal product could be contributing to a severe cutaneous reaction. In the case of a serious skin reaction, discontinuation of other medicinal products known to be associated with serious skin reactions should be considered.

For additional information on mild to moderate rash, see section 4.8.

The recommendations for monitoring of cutaneous reactions, and for discontinuation of INCIVO, ribavirin and peginterferon alfa are summarised in the table below:

Extent and features of Cutaneous Reactions	**Recommendations for Monitoring of Cutaneous Reactions and Discontinuation of INCIVO, Ribavirin and Peginterferon alfa for Severe Rash**
Mild rash: localised skin eruption and/or a skin eruption with a limited distribution (up to several isolated sites on the body)	Monitor for progression or systemic symptoms until the rash is resolved.

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Moderate rash: Diffuse rash ≤ 50% of body surface area	Monitor for progression or systemic symptoms until the rash is resolved. Consider consultation with a specialist in dermatology. For moderate rash that progresses, permanent discontinuation of INCIVO should be considered. If the rash does not improve within 7 days following INCIVO discontinuation, ribavirin should be interrupted. Interruption of ribavirin may be required sooner if the rash worsens despite discontinuation of telaprevir. Peginterferon alfa may be continued unless interruption is medically indicated. For moderate rash that progresses to severe (≥ 50% body surface area), permanently discontinue INCIVO (see below).
Severe rash: Extent of rash > 50% of body surface area or associated with vesicles, bullae, ulcerations other than SJS	Permanently discontinue INCIVO immediately. Consultation with a specialist in dermatology is recommended. Monitor for progression of systemic symptoms until the rash is resolved. 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.
Serious skin reactions including rash with systemic symptoms, progressive severe rash, suspicion or diagnosis of generalised bullous eruption, DRESS, SJS/TEN, acute generalized exanthematous pustulosis, erythema multiforme	Permanent and immediate discontinuation of INCIVO, peginterferon alfa, and ribavirin. Consult with a specialist in dermatology.

If discontinued due to a skin reaction, INCIVO must not be restarted. Refer also to the Summary of Product Characteristics for peginterferon alfa and ribavirin for severe skin reactions associated with these products.

Anaemia

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. Haemoglobin 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. Haemoglobin 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 haemoglobin levels occurs during the first 4 weeks of treatment, with lowest values reached at the end of INCIVO dosing. Haemoglobin values gradually improve after completion of INCIVO dosing.

Haemoglobin should be monitored at regular intervals prior to and during INCIVO combination treatment (see section 4.4, Laboratory tests).

Ribavirin dose reduction is the preferred strategy for managing treatment-emergent anaemia. Refer to the Summary of Product Characteristics for ribavirin for information regarding dose reduction and/or

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discontinuation of ribavirin. If ribavirin is permanently discontinued for the management of anaemia, INCIVO must also be permanently discontinued. If INCIVO is discontinued for anaemia, 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.

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 INCIVO treatment and afterwards as recommended in the Summary of Product Characteristics for ribavirin, and as described below.

Hormonal contraceptives may be continued but may not be reliable during INCIVO dosing and for up to two months following cessation of INCIVO (see section 4.5). During this time, female patients of childbearing potential should use two effective non-hormonal methods of contraception. Two months after completion of INCIVO treatment, hormonal contraceptives are again appropriate as one of the two required effective methods of birth control.

For additional information, see sections 4.5 and 4.6.

Cardiovascular
Results of a study conducted in healthy volunteers demonstrated a modest effect of telaprevir 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 section 5.1). Exposure at this dose was comparable to the exposure in HCV-infected patients receiving a dose of 750 mg INCIVO every 8 hours plus peginterferon alfa and ribavirin. The potential clinical significance of these findings is uncertain.

INCIVO should be used with caution with Class Ic antiarrhythmics propafenone and flecainide, including appropriate clinical and ECG monitoring.

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 (see section 4.5). INCIVO co-administration with domperidone should be avoided (see section 4.5). INCIVO may increase concentrations of the co-administered medicinal product and this may result in an increased risk of their associated cardiac adverse reactions. In the event that co-administration of such medicinal products with INCIVO is judged strictly necessary, clinical monitoring including ECG assessments is recommended. See also section 4.3 for medicinal products 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 the metabolism of which is not mainly CYP3A4 dependent (e.g. methadone, see section 4.5).

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Such patients should be closely monitored, including ECG assessments.

Electrolyte disturbances (e.g., hypokalaemia, hypomagnesaemia and hypocalcaemia) should be monitored and corrected, if necessary, prior to initiation and during INCIVO therapy.

Use in patients with advanced liver disease
Hypoalbuminaemia and low platelet counts have been identified as predictors of severe complications of liver disease as well as of interferon-based therapies (e.g., hepatic decompensation, serious bacterial infections). Furthermore, high rates of anaemia have been seen when using INCIVO with peginterferon and ribavirin in patients with these characteristics. INCIVO in combination with peginterferon and ribavirin is not recommended in patients with platelets < 90,000/mm^3 and/or albumin < 3.3 g/dl. When INCIVO is used in patients with advanced liver disease very close monitoring and early management of adverse events is recommended.

Laboratory tests
HCV RNA levels should be monitored at weeks 4 and 12 and as clinically indicated (see also guidelines for discontinuation of INCIVO, section 4.2).

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:
- Haemoglobin: ≥ 12 g/dl (females); ≥ 13 g/dl (males)
- Platelet count ≥ 90,000/mm^3
- Absolute neutrophil counts ≥ 1,500/mm^3
- Adequately controlled thyroid function (TSH)
- Calculated creatinine clearance ≥ 50 ml/min
- Potassium ≥ 3.5 mmol/l
- Albumin > 3.3 g/dl

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

Chemistry evaluations (electrolytes, serum creatinine, uric acid, hepatic enzymes, bilirubin, TSH) are recommended as frequently as the haematology evaluations or as clinically indicated (see section 4.8).

Refer to the Summary of Product Characteristics for peginterferon alfa and ribavirin, including pregnancy testing requirements (see section 4.6).

The use of INCIVO in combination with peginterferon alfa-2b
The Phase 3 studies were all conducted with peginterferon alfa-2a in combination with INCIVO and ribavirin. There is no data using INCIVO in combination with peginterferon alfa-2b in treatment-experienced patients and limited data in treatment-naïve patients. Naïve patients treated with either peginterferon alfa-2a/ribavirin (n = 80) or peginterferon alfa-2b/ribavirin (n = 81) in combination with INCIVO, in an open label study, had comparable SVR rates. However, patients treated with peginterferon alfa-2b experienced more frequent viral breakthrough, and were less likely to meet the criteria for shortened total treatment duration (see section 5.1).

General
INCIVO must not be administered as monotherapy and must only be prescribed in combination with both peginterferon alfa and ribavirin. The Summary of Product Characteristics 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 section 5.1).

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Insufficient virologic response
In patients who have an inadequate viral response, treatment should be discontinued (see sections 4.2 and 4.4, 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.

Renal impairment
The safety and efficacy have not been established in patients with moderate or severe renal impairment (CrCl < 50 ml/min) or in patients on haemodialysis. Refer to section 4.4, Laboratory tests. Refer also to the Summary of Product Characteristics for ribavirin for patients with CrCL < 50 ml/min (see also section 4.2 and 5.2).

Hepatic impairment
INCIVO has not been studied in patients with severe hepatic impairment (Child-Pugh C, score ≥ 10) or decompensated liver disease (ascites, portal hypertensive bleeding, encephalopathy, and/or jaundice other than Gilbert's Syndrome) and is not recommended in these populations.

INCIVO has not been studied in HCV-infected patients with moderate hepatic impairment (Child-Pugh B, score 7-9). In HCV negative patients with moderate hepatic impairment, reduced exposure to telaprevir was observed. 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 sections 4.2 and 5.2).

Refer to the Summary of Product Characteristics for peginterferon alfa and ribavirin which must be co-administered with INCIVO.

Organ transplant patients
INCIVO in combination with peginterferon alfa and ribavirin was evaluated in 74 HCV-1 infected, post-liver transplant patients without cirrhosis receiving either tacrolimus or cyclosporine A. At the initiation of INCIVO treatment, doses of co-administered tacrolimus or cyclosporine A need to be markedly reduced, including a prolongation in the dosing interval for tacrolimus, in order to maintain therapeutic plasma concentrations of the immunosuppressant. Upon completion of INCIVO, doses of tacrolimus or cyclosporine A need to be increased, and the dosing interval for tacrolimus will need to be reduced. Some patients may require higher doses of tacrolimus or cyclosporine A than at the initiation of treatment. These changes should be based on frequent monitoring of tacrolimus or cyclosporine A plasma concentrations during INCIVO treatment. For information on the use of INCIVO in combination with peginterferon alfa and ribavirin in treatment-naïve and treatment-experienced HCV-1 infected patients who were liver transplant recipients and were on a stable regimen of the immunosuppressants tacrolimus or cyclosporine A, see sections 4.2, 4.5, Immunosuppressants, 4.8, and 5.1.

No clinical data are available regarding the treatment of pre- or peri-liver or other transplant patients with INCIVO in combination with peginterferon alfa and ribavirin.

HCV/HIV co-infection
Interactions between telaprevir and HIV antiretroviral agents are frequent, and the recommendations in table 2, section 4.5, should be carefully followed.

Among HIV regimens that can be used (not limited to those below) the following should be taken into account:

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Atazanavir/ritonavir: this combination is associated with a high frequency of hyperbilirubinaemia/icterus. In Study HPC3008 (see sections 4.8 and 5.1), transient grade 3 (2.5 to ≤5 X ULN) and grade 4 (>5 X ULN) bilirubin increases during INCIVO treatment were seen in 39% and in 22% of the 59 patients on atazanavir/ritonavir, respectively.

Efavirenz: with this combination the telaprevir dose must be increased to 1,125 mg three times per day (q8h).

HCV/HBV (hepatitis B virus) co-infection
There are no data on the use of INCIVO in patients with HCV/HBV co-infection.

Paediatric 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.

Thyroid disease
Increase in thyroid stimulating hormone (TSH) may occur during INCIVO combination treatment, which may indicate worsening or recurrence of pre-existing or previous hypothyroidism, or new-onset hypothyroidism (see section 4.8). TSH levels should be determined before and during the course of INCIVO combination treatment and treated as clinically appropriate, including potential adjustment of thyroid replacement therapy in patients with pre-existing hypothyroidism (see section 4.4, Laboratory tests).

Interactions with medicinal products
Telaprevir is a strong inhibitor of the important drug metabolising enzyme CYP3A4. Increased systemic exposures are expected if telaprevir is combined with drugs highly metabolised by this enzyme. Refer to section 4.3 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 section 4.5 for established and other potentially significant drug-drug interactions.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Telaprevir is partly metabolised in the liver by CYP3A and is a P-glycoprotein (P-gp) substrate. Other enzymes are also involved in the metabolism (see section 5.2). Co-administration of INCIVO and medicinal products that induce CYP3A and/or P-gp may markedly decrease telaprevir plasma concentrations. Co-administration of INCIVO and medicinal products that inhibit CYP3A and/or P-gp may increase telaprevir plasma concentrations.

INCIVO is a strong, time-dependent inhibitor of CYP3A4 and also markedly inhibits P-gp. The time dependency indicates that inhibition of CYP3A4 may be intensified during the first 2 weeks of treatment. After ending treatment, approximately one week may be needed for the inhibition to completely disappear. 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. Based on the results of drug-drug interaction clinical studies (e.g., escitalopram, zolpidem, ethinylestradiol), induction of metabolic enzymes by telaprevir cannot be excluded.

Telaprevir inhibits organic anion transporter polypeptides (OATPs) OATP1B1 and OATP2B1. Concomitant administration of INCIVO and drugs transported by these transporters such as fluvastatin, pravastatin, rosuvastatin, pitavastatin, bosentan and repaglinide should be undertaken with caution (see table 2). Simvastatin is contraindicated due to the predicted marked increase in exposure caused by multiple mechanisms.

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Based on *in vitro* studies, telaprevir may potentially increase plasma concentrations of medicinal products in which excretion is dependent upon multidrug and toxin extrusion (MATE)-1 and MATE2-K (see table 2).

Interaction studies have only been performed in adults.

Contraindications of concomitant use (see section 4.3)
INCIVO must not be administered concurrently 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 such as cardiac arrhythmia (i.e., amiodarone, astemizole, bepridil, cisapride, pimozide, quinidine, terfenadine), or peripheral vasospasm or ischemia (i.e., dihydroergotamine, ergonovine, ergotamine, methylergonovine), or myopathy, including rhabdomyolysis (i.e., lovastatin, simvastatin, atorvastatin), or prolonged or increased sedation or respiratory depression (i.e. quetiapine, orally administered midazolam or triazolam), or hypotension or cardiac arrhythmia (i.e., alfuzosin and sildenafil for pulmonary arterial hypertension).

INCIVO must not be administered concurrently with Class Ia or III antiarrhythmics, except for intravenous lidocaine.

INCIVO should be used with caution with Class Ic antiarrhythmics propafenone and flecainide, including appropriate clinical and ECG monitoring (see section 4.4).

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

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

Carbamazepine, phenytoin and phenobarbital
Co-administration with inducers may lead to lower exposure of telaprevir with risk of lower efficacy. Potent CYP3A inducers, such as carbamazepine, phenytoin and phenobarbital, are contraindicated (see section 4.3).

Mild and moderate CYP3A inducers
Mild and moderate CYP3A inducers should be avoided, particularly in patients who are prior non-responders (partial or null responders for peginterferon alfa/ribavirin), unless specific dose recommendations are given (refer to table 2).

Other combinations
Table 2 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 reactions or loss of efficacy. Most drug-drug interaction studies have been performed with a telaprevir dose of 750 mg every 8 hours (q8h). Given that the 1,125 mg b.i.d. regimen results in the same daily dose with similar drug exposures of telaprevir, the relative drug interactions are expected to be similar.

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.

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Table 2: INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Effect on concentration of INCIVO or concomitant medicinal product and possible mechanism**	**Clinical comment**
ANALGESICS		
alfentanil fentanyl	↑ alfentanil ↑ fentanyl	Careful monitoring of therapeutic and adverse effects (including respiratory depression) is recommended when telaprevir is co-administered with alfentanil or fentanyl, including oral, buccal, nasal and extended-release transdermal or transmucosal preparations of fentanyl, especially at initiation of treatment. Dosage adjustment of fentanyl or alfentanil may be necessary. The most marked effects are expected on oral, nasal and buccal/sublingual fentanyl formulations.
ANTIARRHYTHMICS		
lidocaine (intravenous)	↑ lidocaine inhibition of CYP3A	Caution is warranted and clinical monitoring is recommended when intravenous lidocaine is administered for the treatment of acute ventricular arrhythmia.
digoxin*	↑ digoxin AUC 1.85 (1.70-2.00) C_{max} 1.50 (1.36-1.65) effect on P-gp transport in the gut	The lowest dose of digoxin should be initially prescribed. The serum digoxin concentrations should be monitored and used for titration of digoxin dose to obtain the desired clinical effect.
ANTIBACTERIALS		
clarithromycin erythromycin telithromycin troleandomycin	↑ telaprevir ↑ antibacterials inhibition of CYP3A	Caution is warranted and clinical monitoring is recommended when co-administered with INCIVO. QT interval prolongation and Torsade de Pointes have been reported with clarithromycin and erythromycin. QT interval prolongation has been reported with telithromycin (see section 4.4).
ANTICOAGULANTS		
warfarin	↑ or ↓ warfarin modulation of metabolic enzymes	It is recommended that the international normalised ratio (INR) be monitored when warfarin is co-administered with telaprevir.
dabigatran	↑ dabigatran ↔ telaprevir effect on P-gp transport in the gut	Caution is warranted, laboratory and clinical monitoring is recommended.
ANTICONVULSANTS		
carbamazepine*	↓ telaprevir AUC 0.68 (0.58-0.79) C_{max} 0.79 (0.70-0.90) C_{min} 0.53 (0.44-0.65) ↔ carbamazepine AUC 1.10 (0.99-1.23) C_{max} 1.09 (0.98-1.21) C_{min} 1.10 (0.97-1.24) induction of CYP3A by carbamazepine, and inhibition of CYP3A by telaprevir	Co-administration with carbamazepine is contraindicated.

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phenytoin*	↓ telaprevir AUC 0.53 (0.47-0.60) C_{max} 0.68 (0.60-0.77) C_{min} 0.32 (0.25-0.42) ↑ phenytoin AUC 1.31 (1.15-1.49) C_{max} 1.27 (1.09-1.47) C_{min} 1.36 (1.21-1.53) induction of CYP3A by phenytoin, and inhibition of CYP3A by telaprevir	Co-administration with phenytoin is contraindicated.
phenobarbital	↓ telaprevir ↑ or ↓ phenobarbital induction of CYP3A by phenobarbital, and inhibition of CYP3A by telaprevir	Co-administration with phenobarbital is contraindicated.
ANTIDEPRESSANTS		
escitalopram*	↔ telaprevir ↓ escitalopram AUC 0.65 (0.60-0.70) C_{max} 0.70 (0.65-0.76) C_{min} 0.58 (0.52-0.64) mechanism unknown	Clinical relevance unknown. Doses may need to be increased when combined with telaprevir.
trazodone	↑ trazodone inhibition of CYP3A	Concomitant use may lead to adverse events such as nausea, dizziness, hypotension and syncope. If trazodone is used with telaprevir, the combination should be used with caution and a lower dose of trazodone should be considered.
ANTIDIABETICS		
metformin	↑ metformin inhibition of MATE-1 and MATE2-K	Close monitoring of metformin efficacy and safety is recommended when starting or stopping INCIVO in patients receiving metformin. A dose adjustment of metformin may be necessary.
ANTIEMETICS		
domperidone	↑ domperidone inhibition of CYP3A	Co-administration of domperidone with INCIVO should be avoided (see section 4.4).

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ANTIFUNGALS		
ketoconazole* itraconazole posaconazole voriconazole	↑ ketoconazole (200 mg) AUC 2.25 (1.93-2.61) C_{max} 1.75 (1.51-2.03) ↑ ketoconazole (400 mg) AUC 1.46 (1.35-1.58) C_{max} 1.23 (1.14-1.33) ↑ telaprevir (with ketoconazole 400 mg) AUC 1.62 (1.45-1.81) C_{max} 1.24 (1.10-1.41) ↑ itraconazole ↑ posaconazole ↑ or ↓ voriconazole Inhibition of CYP3A. Due to multiple enzymes involved with voriconazole metabolism, it is difficult to predict the interaction with telaprevir.	When co-administration is required, high doses of itraconazole (> 200 mg/day) or ketoconazole (> 200 mg/day) are not recommended. Caution is warranted and clinical monitoring is recommended for itraconazole, posaconazole, and voriconazole. QT interval prolongation and Torsade de Pointes have been reported with voriconazole and posaconazole. QT interval prolongation has been reported with ketoconazole (see section 4.4). Voriconazole should not be administered to patients receiving telaprevir unless an assessment of the benefit/risk ratio justifies its use.
ANTI-GOUT		
colchicine	↑ colchicine inhibition of CYP3A	Patients with renal or hepatic impairment should not be given colchicine with INCIVO, due to the risk of colchicine toxicity. In patients with normal renal and hepatic function, an interruption of colchicine treatment is recommended, or only a limited colchicine treatment course at a reduced colchicine dose should be used.
ANTIMYCOBACTERIALS		
rifabutin	↓ telaprevir ↑ rifabutin induction of CYP3A by rifabutin, inhibition of CYP3A by telaprevir	Telaprevir may be less effective due to decreased concentrations. The concomitant use of rifabutin and telaprevir is not recommended.
rifampicin*	↓ telaprevir AUC 0.08 (0.07-0.11) C_{max} 0.14 (0.11-0.18) ↑ rifampicin induction of CYP3A by rifampicin, inhibition of CYP3A by telaprevir	Co-administration of rifampicin with telaprevir is contraindicated.
ANTIPSYCHOTICS		
quetiapine	Due to CYP3A inhibition by telaprevir, concentrations of quetiapine are expected to increase.	Concomitant administration of INCIVO and quetiapine is contraindicated as it may increase quetiapine-related toxicity. Increased plasma concentrations of quetiapine may lead to coma.
BENZODIAZEPINES		
alprazolam*	↑ alprazolam AUC 1.35 (1.23-1.49) C_{max} 0.97 (0.92-1.03)	Clinical relevance unknown.

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parenterally administered midazolam* oral midazolam* oral triazolam	↑ midazolam (intravenous) AUC 3.40 (3.04-3.79) C_{max} 1.02 (0.80-1.31) ↑ midazolam (p.o.) AUC 8.96 (7.75-10.35) C_{max} 2.86 (2.52-3.25) ↑ triazolam inhibition of CYP3A	Co-administration should be done in a setting which ensures clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dose reduction for parenterally administered midazolam should be considered, especially if more than a single dose of midazolam is administered. Co-administration of oral midazolam or triazolam with telaprevir is contraindicated.
zolpidem (non-benzodiazepine sedative)*	↓ zolpidem AUC 0.53 (0.45-0.64) C_{max} 0.58 (0.52-0.66) mechanism unknown	Clinical relevance unknown. Increased dose of zolpidem may be required to maintain efficacy.
CALCIUM CHANNEL BLOCKERS		
amlodipine*	↑ amlodipine AUC 2.79 (2.58-3.01) C_{max} 1.27 (1.21-1.33) inhibition of CYP3A	Caution should be used and dose reduction for amlodipine should be considered. Clinical monitoring is recommended.
diltiazem felodipine nicardipine nifedipine nisoldipine verapamil	↑ calcium channel blockers inhibition of CYP3A and/or effect on P-gp transport in the gut	Caution is warranted and clinical monitoring of patients is recommended.
CCR5 ANTAGONISTS		
maraviroc*	↑ maraviroc AUC_{12} 9.49 (7.94-11.34) C_{max} 7.81 (5.92-10.32) C_{12} 10.17 (8.73-11.85) Telaprevir concentrations are not likely to be affected by maraviroc co-administration (based on historical data and the elimination pathway of telaprevir).	Maraviroc 150 mg twice daily when co-administered with telaprevir.
CORTICOSTEROIDS		
Systemic dexamethasone	↓ telaprevir induction of CYP3A	Concomitant use may result in loss of therapeutic effect of telaprevir. Therefore this combination should be used with caution or alternatives should be considered.
inhaled/nasal fluticasone budesonide	↑ fluticasone ↑ budesonide inhibition of CYP3A	Co-administration of fluticasone or budesonide and telaprevir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.
ENDOTHELIN RECEPTOR ANTAGONIST		
bosentan	↑ bosentan ↓ telaprevir induction of CYP3A by bosentan, inhibition of CYP3A and organic anion transporter polypeptides (OATPs) by telaprevir	Caution is warranted and clinical monitoring is recommended.

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HIV-ANTIVIRAL AGENTS: HIV-PROTEASE INHIBITORS (PIs)		
atazanavir/ritonavir*	↓ telaprevir AUC 0.80 (0.76-0.85) C_{max} 0.79 (0.74-0.84) C_{min} 0.85 (0.75-0.98) ↑ atazanavir AUC 1.17 (0.97-1.43) C_{max} 0.85 (0.73-0.98) C_{min} 1.85 (1.40-2.44) inhibition of CYP3A by telaprevir	Hyperbilirubinaemia is frequent with this combination. Clinical and laboratory monitoring for hyperbilirubinaemia is recommended (see section 4.4 and 4.8).
darunavir/ritonavir*	↓ telaprevir AUC 0.65 (0.61-0.69) C_{max} 0.64 (0.61-0.67) C_{min} 0.68 (0.63-0.74) ↓ darunavir AUC 0.60 (0.57-0.63) C_{max} 0.60 (0.56-0.64) C_{min} 0.58 (0.52-0.63) mechanism unknown	It is not recommended to co-administer darunavir/ritonavir and telaprevir (see section 4.4).
fosamprenavir/ritonavir*	↓ telaprevir AUC 0.68 (0.63-0.72) C_{max} 0.67 (0.63-0.71) C_{min} 0.70 (0.64-0.77) ↓ amprenavir AUC 0.53 (0.49-0.58) C_{max} 0.65 (0.59-0.70) C_{min} 0.44 (0.40-0.50) mechanism unknown	It is not recommended to co-administer fosamprenavir/ritonavir and telaprevir (see section 4.4).
lopinavir/ritonavir*	↓ telaprevir AUC 0.46 (0.41-0.52) C_{max} 0.47 (0.41-0.54) C_{min} 0.48 (0.41-0.56) ↔ lopinavir AUC 1.06 (0.96-1.17) C_{max} 0.96 (0.87-1.05) C_{min} 1.14 (0.96-1.36) mechanism unknown	It is not recommended to co-administer lopinavir/ritonavir and telaprevir (see section 4.4).
HIV-ANTIVIRAL AGENTS: REVERSE TRANSCRIPTASE INHIBITORS		
efavirenz*	↓ telaprevir 1,125 mg every 8 hours (relative to 750 mg every 8 hours) AUC 0.82 (0.73-0.92) C_{max} 0.86 (0.76-0.97) C_{min} 0.75 (0.66-0.86) ↓ efavirenz (+ TVR 1,125 mg every 8 hours) AUC 0.82 (0.74-0.90) C_{max} 0.76 (0.68-0.85) C_{min} 0.90 (0.81-1.01) induction of CYP3A by efavirenz.	If co-administered, telaprevir 1,125 mg q8h should be used (see section 4.4).

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tenofovir disoproxil fumarate*	↔ telaprevir AUC 1.00 (0.94-1.07) C_{max} 1.01 (0.96-1.05) C_{min} 1.03 (0.93-1.14) ↑ tenofovir AUC 1.30 (1.22-1.39) C_{max} 1.30 (1.16-1.45) C_{min} 1.41 (1.29-1.54) effect on P-gp transport in the gut	Increased clinical and laboratory monitoring are warranted (see section 4.4).
abacavir zidovudine	Not studied.	An effect of telaprevir on UDP-glucuronyltransferases cannot be ruled out and may affect the plasma concentrations of abacavir or zidovudine.
etravirine*	↓ telaprevir 750 mg q8h AUC 0.84 (0.71-0.98) C_{max} 0.90 (0.79-1.02) C_{min} 0.75 (0.61-0.92) ↔ etravirine (+ TVR 750 mg q8h) AUC 0.94 (0.85-1.04) C_{max} 0.93 (0.84-1.03) C_{min} 0.97 (0.86-1.10)	If co-administered, no dose adjustment is required.
rilpivirine*	↓ telaprevir 750 mg q8h AUC 0.95 (0.76-1.18) C_{max} 0.97 (0.79-1.21) C_{min} 0.89 (0.67-1.18) ↑ rilpivirine (+ TVR 750 mg q8h) AUC 1.78 (1.44-2.20) C_{max} 1.49 (1.20-1.84) C_{min} 1.93 (1.55-2.40)	If co-administered, no dose adjustment is required.
INTEGRASE INHIBITORS		
raltegravir*	↔ telaprevir AUC 1.07 (1.00-1.15) C_{max} 1.07 (0.98-1.16) C_{min} 1.14 (1.04-1.26) ↑ raltegravir AUC 1.31 (1.03-1.67) C_{max} 1.26 (0.97-1.62) C_{min} 1.78 (1.26-2.53)	If co-administered, no dose adjustment is required.
HMG-CoA REDUCTASE INHIBITORS		
atorvastatin*	↑ atorvastatin AUC 7.88 (6.82-9.07) C_{max} 10.6 (8.74-12.85) inhibition of CYP3A and OATPs by telaprevir	Co-administration of atorvastatin and telaprevir is contraindicated (see section 4.3).
fluvastatin pitavastatin pravastatin rosuvastatin	↑ statin inhibition of CYP3A and OATPs by telaprevir	Caution is warranted and clinical monitoring is recommended. Refer to section 4.3 for HMG-CoA reductase inhibitors that are contraindicated with INCIVO.

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HORMONAL CONTRACEPTIVES/OESTROGEN		
ethinylestradiol* norethindrone*	↓ ethinylestradiol AUC 0.72 (0.69-0.75) C_{max} 0.74 (0.68-0.80) C_{min} 0.67 (0.63-0.71) ↔ norethindrone AUC 0.89 (0.86-0.93) C_{max} 0.85 (0.81-0.89) C_{min} 0.94 (0.87-1.00) mechanism unknown	Additional methods of non-hormonal contraception should be used when hormonal contraceptives are co-administered with telaprevir. Patients using oestrogens as hormone replacement therapy should be clinically monitored for signs of oestrogen deficiency. Refer to sections 4.4 and 4.6.
IMMUNOSUPPRESSANTS		
cyclosporine* tacrolimus* sirolimus	↑ cyclosporine AUC 4.64 (3.90-5.51) C_{max} 1.32 (1.08-1.60) ↑ tacrolimus AUC 70.3 (52.9-93.4)** C_{max} 9.35 (6.73-13.0)** ↑ sirolimus ↑ telaprevir **calculated based on data obtained with a reduced dose inhibition of CYP3A, inhibition of transport proteins	Marked immunosuppressant dose reductions with or without prolongation of the dosing intervals will be required. Close monitoring of immunosuppressant blood levels, renal function and immunosuppressant related side effects are recommended when co-administered with telaprevir. Tacrolimus may prolong the QT interval (see section 4.4).
INHALED BETA AGONIST		
salmeterol	↑ salmeterol inhibition of CYP3A	Concurrent administration of salmeterol and telaprevir is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia (see section 4.4).
INSULIN SECRETAGOGUES		
repaglinide	↑ repaglinide inhibition of OATPs by telaprevir	Caution is warranted and clinical monitoring is recommended.
NARCOTIC ANALGESIC		
methadone*	↓ R-methadone AUC 0.71 (0.66-0.76) C_{max} 0.71 (0.66-0.76) C_{min} 0.69 (0.64-0.75) No effect on unbound R-methadone concentrations. Displacement of methadone from plasma proteins.	No adjustment of methadone dose is required when initiating co-administration of telaprevir. However, clinical monitoring is recommended as the dose of methadone during maintenance therapy may need to be adjusted in some patients. QT interval prolongation and Torsade de Pointes have been reported with methadone (see section 4.4). ECG should be monitored at baseline and regularly during telaprevir treatment.
buprenorphine*	↔ buprenorphine AUC 0.96 (0.84-1.10) C_{max} 0.80 (0.69-0.93) C_{min} 1.06 (0.87-1.30)	No adjustment of the buprenorphine dose is required when co-administered with telaprevir.

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PDE-5 INHIBITORS		
sildenafil tadalafil vardenafil	↑ PDE-5 inhibitors inhibition of CYP3A	It is not recommended to co-administer sildenafil or vardenafil and telaprevir. Tadalafil for treatment of erectile dysfunction can be used with caution at a single dose not exceeding 10 mg dose in 72 hours and with increased monitoring for tadalafil associated adverse events. Co-administration of sildenafil or tadalafil and telaprevir in the treatment of pulmonary arterial hypertension is contraindicated (see section 4.3).
PROTON PUMP INHIBITORS		
esomeprazole*	↔ telaprevir AUC 0.98 (0.91-1.05) C_{max} 0.95 (0.86-1.06)	Proton pump inhibitors can be used without dose modification.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of INCIVO in pregnant women. Animal studies are insufficient with respect to human reproductive toxicity (see section 5.3). INCIVO is not recommended during pregnancy and in women of childbearing potential not using contraception.

Contraception in males and females
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.

Due to the combined treatment with peginterferon alfa and 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 INCIVO treatment. Following completion of INCIVO therapy contraceptive recommendations should be followed as in the Summary of Product Characteristics for ribavirin, and as described below.

Hormonal contraceptives may be continued but may not be reliable during INCIVO dosing and for up to two months following cessation of INCIVO (see section 4.5). During this time, female patients of childbearing potential should use two effective non-hormonal methods of contraception. Two months after completion of INCIVO treatment, hormonal contraceptives are again appropriate as one of the two required effective methods of birth control.

Refer to the Summary of Product Characteristics for ribavirin and peginterferon alpha for additional information.

Breast-feeding
Telaprevir and its major metabolite are excreted in rat milk (see section 5.3). It is not known whether telaprevir is excreted in human breast milk. Because of the potential for adverse reactions in breastfed infants, due to the combined treatment of INCIVO with peginterferon alfa and ribavirin, breast-feeding must be discontinued prior to initiation of therapy. See also the Summary of Product Characteristics for ribavirin.

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

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4.7 Effects on ability to drive and use machines

INCIVO has no or negligible influence on the ability to drive and use machines. No studies on the effects of INCIVO on the ability to drive and use machines have been performed. Syncope and retinopathy have been reported in some patients taking INCIVO and should be considered when assessing a patient's ability to drive or operate machines. Refer also to the Summary of Product Characteristics for peginterferon alfa and ribavirin for further information.

4.8 Undesirable effects

Summary of the safety profile

The overall safety profile of INCIVO is based on Phase 2 and 3 clinical trial data (both controlled and uncontrolled) containing 3,441 patients who received INCIVO combination treatment and on spontaneous postmarketing reports.

INCIVO must be administered with peginterferon alfa and ribavirin. Refer to their respective Summary of Product Characteristics for their associated adverse reactions.

The incidence of adverse drug reactions (ADRs) of at least moderate intensity (≥ Grade 2) 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 diarrhoea.
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.

Tabulated summary of adverse reactions
ADRs to INCIVO are presented in table 3.

ADRs are listed by system organ class (SOC) and frequency: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) and rare (≥ 1/10,000 to < 1/1,000). Within each frequency grouping, ADRs are presented in order of decreasing seriousness.

Table 3: Adverse drug reactions to INCIVO (taken in combination with peginterferon alfa and ribavirin) in HCV-infected patients in clinical trials[a] and post-marketing

System Organ Class (SOC)	Frequency category	Adverse Drug Reactions INCIVO, peginterferon alfa, and ribavirin combination therapy
Infections and infestations	common	oral candidiasis
Blood and lymphatic system disorders	very common	anaemia
	common	thrombocytopenia[b], lymphopenia[b]
Endocrine disorders	common	hypothyroidism
Metabolism and nutrition disorders	common	hyperuricaemia[b], hypokalaemia[b]
	uncommon	gout
Nervous system disorders	common	dysgeusia, syncope
Eye disorders	uncommon	retinopathy
Gastrointestinal disorders	very common	nausea, diarrhoea, vomiting, haemorrhoids, proctalgia
	common	anal pruritus, rectal haemorrhage, anal fissure
	uncommon	proctitis, pancreatitis
Hepatobiliary disorders	common	hyperbilirubinaemia[b]

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Skin and subcutaneous tissue disorders	very common	pruritus, rash
	common	eczema, swelling face, exfoliative rash
	uncommon	drug rash with eosinophilia and systemic symptoms (DRESS), urticaria
	rare	SJS, TEN, erythema multiforme
Renal and urinary disorders	uncommon	blood creatinine increased[b], pre-renal azotemia with or without acute renal failure
General disorders and administration site conditions	common	oedema peripheral, product taste abnormal

[a] the placebo-controlled Phase 2 and Phase 3 Studies (pooled data) included 1,346 HCV-infected patients

[b] incidence rates are based on adverse event reporting rates (additionally, see *Laboratory abnormalities* below)

In the analysis of an additional study, Study C211, the safety profile of combination therapy with INCIVO 1,125 mg twice daily was similar to the safety profile for patients receiving combination therapy with INCIVO 750 mg every 8 hours. No new safety findings were identified.

Laboratory abnormalities

Selected laboratory abnormalities of at least moderate intensity (≥ Grade 2) that represent a worsening from baseline and are considered ADRs observed in HCV-infected patients treated with INCIVO combination treatment from the pooled data from the placebo-controlled Phase 2 and Phase 3 trials are presented in the table below:

Table 4: Selected laboratory abnormalities (DAIDS[a] Grade ≥ 2) that represent a worsening from baseline and are considered adverse drug reactions in HCV-infected patients treated with INCIVO combination treatment from the pooled data from the placebo-controlled Phase 2 and Phase 3 trials

		Grade 2	Grade 3	Grade 4
Increase[b]				
	uric acid	17.9% (10.1-12.0 mg/dl)	4.6% (12.1-15.0 mg/dl)	1.1% (> 15.0 mg/dl)
	bilirubin	13.6% (1.6-2.5 x ULN)	3.6% (2.6-5.0 x ULN)	0.3% (> 5.0 x ULN)
	total cholesterol	15.4% (6.20–7.77 mmol/l 240 - 300 mg/dl)	2.0% (> 7.77 mmol/l > 300 mg/dl)	NA
	low-density lipoprotein	6.9% (4.13–4.90 mmol/l 160–190 mg/dl)	2.5% (≥ 4.91 mmol/l ≥ 191 mg/dl)	NA
	creatinine	0.9% (1.4–1.8 x ULN)	0.2% (1.9-3.4 x ULN)	0% (> 3.4 x ULN)
Decrease[b]				
	haemoglobin	27.0% (9.0-9.9 g/dl or any decrease 3.5-4.4 g/dl)	51.1% (7.0-8.9 g/dl or any decrease ≥ 4.5 g/dl)	1.1% (< 7.0 g/dl)
	platelet count	24.4% (50,000–99,999/mm^3)	2.8% (25,000–49,999/mm^3)	0.2% (< 25,000/mm^3)
	absolute lymphocyte count	13.1% (500-599/mm^3)	11.8% (350-499/mm^3)	4.8% (< 350/mm^3)
	potassium	1.6% (2.5–2.9 mEq/l)	0% (2.0-2.4 mEq/l)	0% (< 2.0 mEq/l)

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NA = not applicable

[a] The Division of AIDS Table for Grading the Severity of Adult and Paediatric Adverse Events (DAIDS, version 1.0, December 2004) was used in the pooled laboratory datasets.

[b] The incidence was calculated by the number of patients for each parameter.

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 section 4.4).

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.

Description of selected adverse reactions

Rash

Severe, potentially life-threatening and fatal skin reactions have been reported with INCIVO combination treatment, including DRESS, SJS, and TEN (see section 4.4). 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.

See section 4.4 for recommendations for monitoring of rash and discontinuation of INCIVO, ribavirin, and peginterferon alfa. 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 several weeks to resolve.

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. Erythropoisis-stimulating agents (ESAs) were generally not permitted and used in only 1% of patients 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 peginterferon alfa and ribavirin alone. Transfusion rates over the whole study period were 4.6% and 1.6%, respectively. In placebo-controlled Phase 2 and 3 trials, 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 section 4.4).

Anorectal signs and symptoms

In clinical trials, the majority of these events (e.g., haemorrhoids, anorectal discomfort, anal pruritus, and rectal burning) were mild to moderate, very few led to treatment discontinuation and resolved after completion of INCIVO dosing.

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Patients Co-infected with HIV-1
The overall safety profile of INCIVO in HCV/HIV-1 co-infected patients (either not on antiretroviral therapy or on antiretroviral therapy) was similar to the safety profile in mono-infected HCV patients, except for patients receiving atazanavir/ritonavir who frequently experienced a transient increase in indirect bilirubin levels (including grades 3 to 4) through week 2, returning to near baseline by week 12 (see section 4.4).

Liver transplant patients without cirrhosis
The overall safety profile of INCIVO in treatment- naïve and treatment-experienced HCV-1 infected patients who were liver transplant recipients on a stable regimen of the immunosuppressants tacrolimus or cyclosporine A was generally similar to the safety profile of INCIVO in patients without a history of liver transplantation, although anaemia was reported more frequently (55.4% versus 32.1% in the Phase 2-3 safety pooling) during the INCIVO treatment phase. To manage anaemia, at initiation of INCIVO treatment a lower starting dose of ribavirin (600 mg/day) was used; during the overall treatment phase the ribavirin dose was further reduced in 36.5% of patients, 41.9% received ESAs and 21.6% received blood transfusions (see sections 4.4 and 4.5, Immunosuppressants).

Paediatric population
The safety and efficacy of INCIVO in children aged < 18 years have not yet been established. No data are available.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

The highest documented INCIVO dose administered is 1,875 mg every 8 hours for 4 days in healthy volunteers. In that study, the following common adverse events were reported more frequently with the 1,875 mg every 8 hours regimen compared to the 750 mg every 8 hours regimen: nausea, headache, diarrhoea, 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. Gastric lavage should only be performed if this can be done within one hour after ingestion. Administration of activated charcoal may also be used to aid in the removal of unabsorbed active substance.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Direct-acting antiviral, ATC code: J05AE11.

Mechanism of action
Telaprevir is an inhibitor of the HCV NS3•4A serine protease, which is essential for viral replication.

In vitro studies
Activity of telaprevir against HCV

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

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

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

Cross-resistance
Telaprevir-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 telaprevir-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 patients who have failed an HCV NS3-4A protease inhibitor-based therapy, such as telaprevir, nor are there data on repeated courses of telaprevir treatment.

Clinical virology studies
In Phase 2 and 3 clinical trials of telaprevir, treatment-naïve and prior treatment-failure patients with predominant telaprevir-resistant variants at baseline (pre-treatment) were rare (V36M, T54A and R155K < 1% and T54S 2.7%). Predominant baseline resistance to telaprevir does not preclude successful treatment with telaprevir, peginterferon alfa, and ribavirin. The impact of predominant telaprevir-resistant variants at baseline is likely greatest in patients with a poor interferon response, such as prior null responders.

A total of 215 of 1,169 patients treated with a T12/PR regimen in a Phase 3 clinical trial had on-treatment virologic failure (n = 125) or relapse (n = 90). Based on population sequencing analyses of HCV in these 215 patients, the emergence of telaprevir-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%) patients. Sequence analyses of the telaprevir-resistant variants identified substitutions at 4 positions in the NS3-4A protease region, consistent with the mechanism of action for telaprevir (V36A/M, T54A/S, R155K/T, and A156S/T/V). In the C211 Phase 3 clinical trial, there was no difference in the type of emerging variants between patients receiving telaprevir 1,125 mg twice daily (b.i.d.) and patients receiving telaprevir 750 mg every 8 hours (q8h). Similar proportions of patients in both treatment groups had telaprevir-resistant variants at the time of failure. On-treatment virologic failure during telaprevir treatment was predominantly associated with higher-level resistant variants, and relapse was predominantly associated with lower-level resistant variants or wild-type virus.

Patients with HCV genotype 1a predominately had V36M and R155K single and combination variants, while patients 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 patients treated with telaprevir, on-treatment virologic failure was more frequent in patients 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 section 5.1, Clinical Experience, Efficacy in Previously Treated Adults).

The resistance profile observed in Study HPC3008 in HCV/HIV-1 co-infected patients was similar to the resistance profile in mono-infected HCV patients.

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The resistance profile observed in Study HPC3006 in treatment-naïve and treatment-experienced HCV-1 infected liver transplant recipients who were on a stable regimen of the immunosuppressants tacrolimus or cyclosporine A was similar to the resistance profile in HCV-infected patients without a liver transplant.

Follow-up analysis of INCIVO-treated patients who did not achieve an SVR showed that the population of wild-type virus increased and the population of telaprevir-resistant variants became undetectable over time after the end of telaprevir treatment. Of a combined 255 treatment-naïve and previously treated patients from Phase 3 studies 108, 111, and C216 in whom telaprevir-resistant variants had emerged during treatment, 152 (60%) patients no longer had resistant variants detected by population sequencing (median follow-up of 10 months). Of the 393 resistant variants detected in the 255 patients, 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 98 treatment-naïve and prior treatment-failure patients who were treated with a INCIVO regimen in a Phase 2 or Phase 3study and did not achieve SVR, telaprevir-resistant variants were no longer detected in 85% (83/98) of patients (median follow-up of 27.5 months). Clonal sequencing analysis of a subset of patients who had wild-type HCV by population sequencing (n=20), comparing the frequency of resistant variants before the start of telaprevir treatment and at follow-up, showed that the HCV variant population in all patients had returned to pre-treatment levels. The median time for telaprevir-resistant variants to become undetectable by population sequencing was longer for variants NS3-36 (6 months), NS3-155 (9 months) and NS3-36M+NS3-155K (12 months) predominantly observed in patients with genotype 1a than for variants NS3-54 (2 months) and NS3-156 (3 months) predominantly observed in patients with genotype 1b.

Clinical efficacy and safety

The efficacy and safety of INCIVO in patients with genotype 1 chronic hepatitis C were evaluated in four Phase 3 studies: 3 in treatment-naïve patients and 1 in previously treated patients (relapsers, partial responders, and null responders). Patients in these studies, 108, 111 and C216, 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 (q8h); the peginterferon alfa-2a dose was 180 µg/week, and the ribavirin dose was 1,000 mg/day (patients weighing < 75 kg) or 1,200 mg/day (patients 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 for Studies 108, 111, and C216, 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.

In the description of the Phase 3 study outcomes for Study C211, HPC3008 and HPC3006, SVR12, considered virologic cure, was defined based on HCV RNA below the limit of quantification (25 IU/ml) using the last measurement in the visit window 12 weeks after the planned end of treatment.

Efficacy in treatment-naïve adults

Study C211

Study C211 was a randomised, open-label, Phase 3 study conducted in treatment-naïve patients who were randomised to one of two treatment groups: INCIVO 750 mg every 8 hours [T12(q8h)/PR] or INCIVO 1,125 mg twice daily [T12(b.i.d.)/PR] in combination with peginterferon alfa-2a and ribavirin. The primary objective was to demonstrate the noninferiority of T12(b.i.d.)/PR over T12(q8h)/PR. All patients received 12 weeks of treatment with INCIVO in combination with peginterferon alfa-2a and ribavirin. At week 12, INCIVO dosing ended and patients continued on peginterferon alfa-2a and ribavirin treatment. The total treatment duration was determined based on

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the patients' individual on-treatment viral response. If a patient achieved undetectable HCV RNA (target not detected) at week 4, the total treatment duration was 24 weeks. Otherwise, the total treatment duration was 48 weeks.

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

The SVR12 rate for the T12(b.i.d.)/PR group was 74% (274/369) compared to 73% (270/371) in the T12(q8h)/PR group with 95% confidence interval of the difference: -4.9%, 12.0%. The lower limit of the 95% CI (-4.9%) was greater than the pre-determined noninferiority margin of -11% and therefore the non inferiority of T12(b.i.d.)/PR over T12(q8h)/PR was demonstrated. Table 5 shows the response rates for the T12(b.i.d.)/PR group and the T12(q8h)/PR group.

Table 5: Response rates: Study C211

Treatment outcome	T12(b.i.d.)/PR N = 369 % (n/N)	T12(q8h)/PR N = 371 % (n/N)
SVR12	74% (274/369)	73% (270/371)
Undetectable HCV RNA (target not detected) at week 4[a]	69% (256/369)	67% (250/371)
Undetectable HCV RNA (target not detected) at weeks 4 and 12	66% (244/369)	63% (234/371)
SVR in patients with undetectable HCV RNA (target not detected) at weeks 4 and 12	89% (218/244)	89% (209/234)
SVR in patients who did not have undetectable HCV RNA (target not detected) at weeks 4 and 12	45% (56/125)	45% (61/137)
Patients without SVR	26% (95/369)	27% (101/371)
On-treatment virologic failure[b]	10% (38/369)	10% (36/371)
Relapse[c]	8% (23/300)	6% (19/293)
Other[d]	9% (34/369)	12% (46/371)

T12(b.i.d.)/PR: INCIVO 1,125 mg twice daily for 12 weeks with peginterferon alfa-2a and ribavirin for 24 or 48 weeks; T12(q8h)/PR: INCIVO 750 mg every 8 hours for 12 weeks with peginterferon alfa-2a and ribavirin for 24 or 48 weeks

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

[b] On-treatment-virologic failure includes patients who met a protocol-defined virologic stopping rule and/or 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. The denominator when calculating the relapse rate represents the number of patients with end-of-treatment response (HCV RNA < 25 IU/ml).

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

Table 6 shows SVR rates by IL28B genotype and the stage of liver fibrosis at baseline.

Table 6: SVR rates for patient subgroups: Study C211

Subgroup	T12(b.i.d.)/PR N = 369 % (n/N)	T12(q8h)/PR N = 371 % (n/N)
IL28B genotype		
CC	92% (97/105)	87% (92/106)
CT	67% (139/206)	68% (141/208)
TT	66% (38/58)	65% (37/57)
Baseline liver fibrosis		
No fibrosis or minimal fibrosis	80% (138/172)	79% (140/177)

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Portal fibrosis	79% (75/95)	80% (68/85)
Bridging fibrosis	67% (32/48)	64% (38/59)
Cirrhosis	54% (29/54)	49% (24/49)

T12(b.i.d.)/PR: INCIVO 1,125 mg twice daily for 12 weeks with peginterferon alfa-2a and ribavirin for 24 or 48 weeks;
T12(q8h)/PR: INCIVO 750 mg every 8 hours for 12 weeks with peginterferon alfa-2a and ribavirin for 24 or 48 weeks

Study 108 (ADVANCE)
Study 108 was a randomised, double-blind, parallel-group, placebo-controlled, Phase 3 study conducted in treatment-naïve patients. 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. Patients who had undetectable HCV RNA (target not detected) at weeks 4 and 12 received 24 weeks of peginterferon alfa-2a and ribavirin treatment, and patients who did not have undetectable HCV RNA (target not detected) 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 telaprevir-matching placebo for the first 12 weeks and peginterferon alfa-2a and ribavirin for 48 weeks.

The 1,088 enrolled patients had a median age of 49 years (range: 18 to 69); 58% of the patients 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 ≥ 800,000 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 7 shows the response rates for the recommended T12/PR and the Pbo/PR48 groups.

Table 7: Response rates: Study 108

Treatment outcome	**T12/PR N = 363 n/N (%)**	**Pbo/PR48 N = 361 n/N (%)**
SVR[a]	79% (285/363) (74%, 83%)[b]	46% (166/361) (41%, 51%)[b]
Undetectable HCV RNA (target not detected) at weeks 4 and 12 (eRVR)	58% (212/363)	8% (29/361)
SVR in eRVR patients	92% (195/212)	93% (27/29)
No eRVR	42% (151/363)	92% (332/361)
SVR in no eRVR patients	60% (90/151)	42% (139/332)
HCV RNA < 25 IU/ml at End of Treatment	82% (299/363)	62% (225/361)
Relapse	4% (13/299)	26% (58/225)

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. The difference in SVR rates (95% confidence interval) between the T12/PR and Pbo/PR groups was 33 (26, 39).

[b] 95% confidence interval

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, HCV genotype subtype, baseline HCV RNA (< 800,000, ≥ 800,000 IU/ml), and extent of liver fibrosis. Table 8 shows SVR rates for patient subgroups.

Table 8: 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)

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BMI ≥ 30 kg/m^2	73% (56/77)	44% (38/87)
Baseline HCV RNA ≥ 800,000 IU/ml	77% (215/281)	39% (109/279)
HCV genotype 1a	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, randomised, open label study conducted in treatment-naïve patients. The study was designed to compare SVR rates in patients with undetectable HCV RNA (target not detected) 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). Patients with undetectable HCV RNA (target not detected) at weeks 4 and 12 were randomised 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 patients with undetectable HCV RNA (target not detected) at weeks 4 and 12.

The 540 enrolled patients had a median age of 51 years (range 19 to 70); 60% of the patients 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 > 800,000 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%) patients had undetectable HCV RNA (target not detected) at weeks 4 and 12. Table 9 shows response rates. In patients who had undetectable HCV RNA (target not detected) 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 9: Response rates: Study 111

	Patients with undetectable HCV RNA (target not detected) at weeks 4 and 12		**T12/PR All Patients[a] N=540**
Treatment outcome	**T12/PR24 N = 162**	**T12/PR48 N = 160**	
SVR	92% (149/162) (87%, 96%)[b]	90% (144/160) (84%, 94%)[b]	74% (398/540) (70%, 77%)[b]
HCV RNA < 25 IU/ml at End of Treatment	98% (159/162)	93% (149/160)	79% (424/540)
Relapse	6% (10/159)	1% (2/149)	4% (19/424)

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 patients includes the 322 patients with undetectable HCV RNA (target not detected) at weeks 4 and 12 and the 218 other patients treated in the study (118 who did not have undetectable HCV RNA (target not detected) at week 4 and 12 and 100 who discontinued the study before week 20, when randomisation occurred).

[b] 95% confidence interval

The SVR rate for Black patients was 62% (45/73). Table 10 shows SVR rates by extent of liver fibrosis at baseline.

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Table 10: SVR rates by extent of liver fibrosis at baseline: Study 111			
	Patients with undetectable HCV RNA (target not detected) at weeks 4 and 12		T12/PR All Patients[a]
Subgroup	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 patients includes the 322 patients with undetectable HCV RNA (target not detected) at weeks 4 and 12 and the 218 other patients treated in the study (118 who did not have undetectable HCV RNA (target not detected) at weeks 4 and 12 and 100 who discontinued the study before week 20, when randomisation occurred)

Efficacy in previously treated adults

Study C216 (REALIZE)

Study C216 was a randomised, double-blind, placebo-controlled, Phase 3 study conducted in patients 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 (patients 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 (patients 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 non-responder-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).

Patients were randomised 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 patients had a median age of 51 years (range: 21 to 70); 70% of the patients were male; 26% had a body mass index ≥ 30 kg/m^2; 5% were Black; 11% were Hispanic or Latino; 89% had baseline HCV RNA levels $\geq 800{,}000$ 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 % (n/N)	Pbo/PR48 % (n/N)
SVR		
Prior relapsers[a]	84% (122/145) (77%, 90%)[b]	22% (15/68) (13%, 34%)[b]
Prior partial responders[a]	61% (30/49) (46%, 75%)[b]	15% (4/27) (4%, 34%)[b]
Prior null responders[a]	31% (22/72) (20%, 43%)[b]	5% (2/37) (1%, 18%)[b]
HCV RNA < 25 IU/ml at End of Treatment		
Prior relapsers	87% (126/145)	63% (43/68)

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Prior partial responders	73% (36/49)	15% (4/27)
Prior null responders	39% (28/72)	11% (4/37)
Relapse		
Prior relapsers	3% (4/126)	63% (27/43)
Prior partial responders	17% (6/36)	0% (0/4)
Prior null responders	21% (6/28)	50% (2/4)

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 interval) 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] 95% confidence interval

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

Table 13 shows the SVR rates by week 4 response (< 1 $\log_{10}$ or ≥ 1 $\log_{10}$ reduction in HCV RNA) for prior partial responders and for prior null responders in the T12(DS)/PR group.

Table 13: SVR rates by week 4 response (< 1 $\log_{10}$ or ≥ 1 $\log_{10}$ reduction) in the T12(DS)/PR48 group: Study C216

Prior Treatment Response	**T12(DS)/PR % (n/N)[a]**	
	< 1 $\log_{10}$ reduction in HCV RNA at week 4	**≥ 1 $\log_{10}$ reduction in HCV RNA at week 4**
Prior partial responders	56% (10/18)	63% (17/27)
Prior null responders	15% (6/41)	54% (15/28)

[a] only includes data on patients who had week 4 HCV RNA available

Study 106 and Study 107

Study 106 was a randomised, double-blind, placebo-controlled, Phase 2 study that enrolled patients 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

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(target not detected) 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 patients who were treated in the control group (placebo, peginterferon alfa-2a, and ribavirin) of a Phase 2 study of telaprevir 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 (target not detected) at week 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, randomised study C208 in treatment-naïve patients.
All patients received 12 weeks of INCIVO in combination with the peginterferon alfa/ribavirin standard therapy. Patients were randomised to 1 of 4 treatment groups:

- INCIVO 750 mg every 8 hours with peginterferon alfa-2a 180 µg/week and ribavirin 1,000 or 1,200 mg/day
- INCIVO 750 mg every 8 hours with peginterferon alfa-2b 1.5 µg/kg/week and ribavirin 800 or 1,200 mg/day
- INCIVO 1,125 mg every 12 hours with peginterferon alfa-2a 180 µg/week and ribavirin 1,000 or 1,200 mg/day
- INCIVO 1,125 mg every 12 hours with peginterferon alfa-2b 1.5 µg/kg/week and ribavirin 800 or 1,200 mg/day

Peginterferon alfa-2a/peginterferon alfa-2b and ribavirin were used according to their relevant Summary of Product Characteristics. At week 12, INCIVO dosing ended and patients continued on standard therapy only. 73.8% (59/80) of patients in the pooled peginterferon alfa-2a group met the criteria (undetectable HCV RNA (target not detected) at week 4 through week 20) for the shortened 24 week peginterferon/ribavirin treatment duration versus 61.7% (50/81) of patients in the pooled peginterferon alfa-2b group.

Table 14: Pooled response rates: Study C208

Treatment outcome	T12P(2a)R48 N = 80 (%) n/N	T12P(2b)R48 N = 81 (%) n/N
SVR[a]	83.8 (67/80)	81.5 (66/81)
Viral breakthrough	5 (4/80)	12.3 (10/81)
Relapse	8.1 (6/74[b])	4.2 (3/71[b])

T12/P(2a)R48: INCIVO for 12 weeks in combination with peginterferon alfa-2a and ribavirin for 24 or 48 weeks
T12/P(2b)R48: INCIVO for 12 weeks in combination with peginterferon alfa-2b and ribavirin for 24 or 48 weeks

[a] 95% confidence interval for the difference was (-10.8, 12.1)

[b] Denominator was the number of patients with undetectable HCV RNA (target not detected) at end of treatment

<u>*Long-term efficacy data*</u>
Study M12-720 (EXTEND)
A 3-year follow-up study of patients who achieved SVR with an INCIVO-based regimen showed that > 99% (122/123) of patients maintained their SVR status through the available follow-up period (median duration of 22 months).

<u>*Efficacy in adults with HCV/HIV-1 co-infection*</u>
Study 110
Study 110 was a phase II randomised, double-blind, placebo-controlled study conducted in patients with chronic genotype 1 HCV/HIV co-infection who were treatment-naïve for hepatitis C. Patients 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. Patients were randomised to 12 weeks of INCIVO (750 mg every 8 hours if taken in

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combination with atazanavir/ritonavir, tenofovir disoproxil fumarate, and emtricitabine or lamivudine OR 1,125 mg every 8 hours if taken in combination with efavirenz, tenofovir disoproxil fumarate, and emtricitabine) or placebo. All patients received peginterferon alfa-2a and ribavirin for 48 weeks. Fifty-five out of 60 patients received ribavirin at a fixed dose of 800 mg/day and the remaining 5 patients received a weight-based ribavirin dose. At baseline, 3 (8%) patients had bridging fibrosis and 2 (5%) patients had cirrhosis in the T12/PR48 arm. In the Pbo/PR arm, 2 (9%) patients had baseline bridging fibrosis and no patients had baseline cirrhosis. Table 15 shows the response rates for the T12/PR48 and the Pbo/PR48 arms. The response rate in the Pbo/PR arm was higher than that seen in other clinical studies of peginterferon bitherapy (historical SVR rates < 36%).

Table 15: Response Rates: Study 110

Treatment Outcome	T12/PR48 % (n/N)	Pbo/PR % (n/N)
Overall SVR12 rate[a]	74% (28/38)	45% (10/22)
Patients on an efavirenz-based regimen	69% (11/16)	50% (4/8)
Patients on an atazanavir/ritonavir-based regimen	80% (12/15)	50% (4/8)
Patients not receiving antiretroviral therapy	71% (5/7)	33% (2/6)

T12/PR48: INCIVO for 12 weeks with peginterferon alfa-2a and ribavirin for 48 weeks; Pbo/PR: placebo for 12 weeks with peginterferon alfa-2a and ribavirin for 48 weeks

[a] HCV RNA< 25 IU/ml in the week 12 follow-up window

Study HPC3008

Study HPC3008 was an open-label, Phase 3b study conducted in patients with chronic genotype 1 HCV/HIV-1 co-infection who were treatment-naïve for hepatitis C or who did not achieve SVR with prior treatment with peginterferon alfa (2a or 2b) and ribavirin (including prior relapsers, prior partial responders and prior null responders). Patients were required to have an HIV-1 RNA < 50 copies/ml and CD4 count > 300 cells/mm^3 at screening. Patients received INCIVO at a dosage of 750 mg every 8 hours, except for patients on an efavirenz based regimen who received INCIVO at a dosage of 1,125 mg every 8 hours. Treatment-naive patients or prior relapsers who were non-cirrhotic and achieved extended rapid virologic response (eRVR) received 12 weeks of treatment with INCIVO plus peginterferon alfa-2a and ribavirin followed by 12 weeks of treatment with peginterferon alfa-2a and ribavirin (total treatment duration of 24 weeks). Treatment-naive patients and prior relapsers who did not achieve eRVR, prior partial responders, prior null responders, and all cirrhotic patients received 12 weeks of treatment with INCIVO plus peginterferon alfa-2a and ribavirin followed by 36 weeks of treatment with peginterferon alfa-2a and ribavirin (total treatment duration of 48 weeks). All patients received ribavirin at a fixed dose of 800 mg/day. Antiretroviral therapy regimens included efavirenz, atazanavir/ritonavir, raltegravir, etravirine, or darunavir/ritonavir in combination with tenofovir or abacavir and either lamivudine or emtricitabine.

The primary objective of the study was to assess the antiviral efficacy of INCIVO, peginterferon alfa-2a, and ribavirin in HCV/HIV-1 co-infected patients as measured by SVR12.

The 162 enrolled patients had a median age of 46 years (range: 20 to 67 years); 78.4% of the patients were male; 6.8% had a body mass index ≥ 30 kg/m^2; 4.3% were Black; 1.9% were Asian; 87.0% had baseline HCV RNA levels ≥ 800,000 IU/ml; 17.3% had bridging fibrosis; 13.0% had cirrhosis; 65.6% had HCV genotype 1a; 33.8% had HCV genotype 1b; 39.5% (n = 64) were HCV treatment-naïve; 17.9% (n = 29) were prior relapsers; 11.1% (n = 18) were prior partial responders; 31.5% (n = 51) were prior null responders. Median (range) CD4 cell count at baseline was 651 (277 to 1,551 cells/mm^3).

Table 16 shows the response rates in treatment-naïve patients and in treatment-experienced patients by subgroup (treatment-naïve, prior relapsers and prior non-responders).

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Table 16: Treatment outcome in adult patients with genotype 1 HCV infection and HIV-1 co-infection in Study HPC3008)			
		Treatment-Experienced Patients by Subgroup	
Treatment Outcome	**Treatment-Naïve Patients N = 64 % (n/N)**	**Prior Relapsers N = 29 % (n/N)**	**Prior Non-responders[a] N = 69 % (n/N)**
SVR12	64.1% (41/64)	62.1% (18/29)	49.3% (34/69)
Undetectable HCV RNA (target not detected) at weeks 4 and 12	57.8% (37/64)	48.3% (14/29)	42.0% (29/69)
SVR in patients with undetectable HCV RNA (target not detected) at weeks 4 and 12	83.8% (31/37)	92.9% (13/14)	89.7% (26/29)
SVR in patients who did not have undetectable HCV RNA (target not detected) at weeks 4 and 12	37.0% (10/27)	33.3% (5/15)	20.0% (8/40)
SVR rates for patients with or without cirrhosis			
Patients without cirrhosis	65.5% (38/58)	61.5% (16/26)	52.6% (30/57)
Patients with cirrhosis	50.0% (3/6)	66.7% (2/3)	33.3% (4/12)
Outcome for patients without SVR12			
On-treatment virologic failure[b]	21.9% (14/64)	3.4% (1/29)	37.7% (26/69)
Relapse[c]	8.9% (4/45)	5.3% (1/19)	8.1% (3/37)
Other[d]	7.8% (5/64)	31.0% (9/29)	8.7% (6/69)

[a] Prior non-responders includes prior partial responders and prior null responders.

[b] On-treatment virologic failure was defined as meeting a virologic stopping rule and/or having viral breakthrough.

[c] Relapse was defined as having HCV RNA ≥ 25 IU/ml during the follow-up period after previous HCV RNA < 25 IU/ml at planned end of treatment and not achieving SVR12.

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

Liver transplant recipients

Study HPC3006 was an open-label, Phase 3b study in treatment- naïve and treatment-experienced chronic genotype 1 HCV-infected patients who were first time liver transplant recipients and were on a stable regimen of the immunosuppressants tacrolimus or cyclosporine A. No patients had cirrhosis of the liver graft. Patients received INCIVO at a dosage of 750 mg every 8 hours. All patients started with a dose of 600 mg/day of ribavirin and 180 µg/week of peginterferon alfa-2a. All patients received 12 weeks of treatment with INCIVO plus peginterferon alfa-2a and ribavirin followed by 36 weeks of treatment with peginterferon alfa-2a and ribavirin (total treatment duration of 48 weeks).

The primary objective of the study was to assess the antiviral efficacy of INCIVO, peginterferon alfa-2a, and ribavirin in HCV-infected liver transplant recipients as measured by SVR12.

The 74 enrolled patients had a median age of 56 years (range: 43 to 68 years); 91.9% of the patients were male; 24.3% had a body mass index ≥ 30 kg/m^2; 1.4% were Black; 95.9% had baseline HCV RNA levels ≥ 800,000 IU/ml; 10.8% had bridging fibrosis; none had cirrhosis; 38.9% had HCV genotype 1a; 58.3% had HCV genotype 1b; 2.8% had HCV genotype 1d; 21.6% had IL28B genotype CC; 54.1% had IL28B genotype CT; 24.3% had IL28B genotype TT; 28.4% (n = 21) were HCV treatment- naïve; 71.6% (n = 53) were treatment-experienced [14.9% (n = 11) were prior relapsers; 40.5% (n = 30) were prior non-responders; 16.2% (n = 12) could not be classified]; median time since liver transplantation was 2.5 years (range: 0.6 to 9.5 years); 67.6% (n = 50) received tacrolimus; 32.4% (n = 24) received cyclosporine A.

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Table 17 shows the overall response rates in treatment- naïve and treatment-experienced chronic genotype 1 HCV- infected liver transplant recipients and by subgroup (patients receiving tacrolimus or cyclosporine A).

Table 17: Treatment outcome in genotype 1 HCV-infected liver transplant recipients (Study HPC3006)

Treatment outcome	Patients receiving tacrolimus N = 50 % (n/N)	Patients receiving cyclosporine A N = 24 % (n/N)	All patients N = 74 % (n/N)
SVR12	66% (33/50)	83% (20/24)	72% (53/74)
Outcome for patients without SVR12			
All patients			
On-treatment virologic failure[a]	12% (6/50)	8% (2/24)	11% (8/74)
Relapse[b]	11% (4/37)	0	7% (4/56)
Other[c]	14% (7/50)	8% (2/24)	12% (9/74)

[a] On-treatment virologic failure was defined as meeting a virologic stopping rule or having viral breakthrough. Note that the virologic stopping rules taken into account in this treatment outcome analysis are actual stopping rules, i.e., those derived from disposition and exposure data, as opposed to mathematical stopping rules, i.e., derived from the HCV RNA data.

[b] Relapse was defined as having detectable plasma HCV RNA from planned end of treatment onwards after previous HCV RNA < 25 IU/ml at planned end of HCV treatment, and not achieving SVR12. The denominator is the number of patients with HCV RNA < 25 IU/ml at planned end of treatment or a missing HCV RNA assessment at planned end of treatment and HCV RNA < 25 IU/ml during follow-up from planned end of treatment onwards.

[c] Other includes patients with detectable HCV RNA at their actual end of treatment but who did not meet the definition of on-treatment virologic failure, and patients with a missing HCV RNA assessment during planned follow-up.

Clinical Studies Examining QT Interval

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

Paediatric population

No clinical studies have been performed in paediatric patients.

The European Medicines Agency has deferred the obligation to submit the results of studies with INCIVO in one or more subsets of the paediatric population in chronic hepatitis C (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetic properties of telaprevir have been evaluated in healthy adult volunteers and in subjects with chronic HCV infection. Telaprevir can be administered orally with food as 375 mg tablets, 1,125 mg twice daily (b.i.d.) for 12 weeks, in combination with peginterferon alfa and ribavirin. Alternatively, telaprevir can be administered orally with food as 375 mg tablets, 750 mg every 8 hours (q8h) for 12 weeks, in combination with peginterferon alfa and ribavirin. Exposure to telaprevir is higher during co-administration of peginterferon alfa and ribavirin than after administration of telaprevir alone.

Telaprevir exposure is comparable during co-administration with either peginterferon alfa-2a and ribavirin or peginterferon alfa-2b and ribavirin.

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Absorption
Telaprevir is orally available, most likely absorbed in the small intestine, with no evidence for absorption in the colon. Maximum plasma concentrations after a single dose of telaprevir are generally achieved after 4 – 5 hours. *In vitro* studies performed with human Caco-2 cells indicated that telaprevir is a substrate of P-glycoprotein (P-gp).

Telaprevir exposure was similar regardless of whether the total daily dose of 2,250 mg was administered as 750 mg every 8 hours (q8h) or 1,125 mg twice daily (b.i.d.). Based upon population pharmacokinetic modelling of telaprevir steady-state exposures, the Geometric Mean Least Square Ratios (90% CI) of 1,125 mg twice daily (b.i.d.) versus 750 mg every 8 hours (q8h) were 1.08 (1.02; 1.13) for $AUC_{24,ss}$, 0.878 (0.827; 0.930) for $C_{trough,ss}$, and 1.18 (1.12;1.24) for $C_{max,ss}$.

The exposure to telaprevir 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 telaprevir 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, telaprevir should be taken with food.

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

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

Biotransformation
Telaprevir 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 telaprevir (30-fold less active), pyrazinoic acid, and a metabolite that underwent reduction at the α-ketoamide bond of telaprevir (not active) were found to be the predominant metabolites of telaprevir.

CYP3A4 is partly responsible for the metabolism of telaprevir. Other enzymes are also involved in the metabolism such as aldo-keto reductases and other proteolytic enzymes. Studies using recombinant human CYP supersomes showed that telaprevir was a CYP3A4 inhibitor, and a time- and concentration-dependent inhibition of CYP3A4 by telaprevir was observed in human liver microsomes. No relevant inhibition by telaprevir of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1 isozymes was observed *in vitro*. No relevant induction by telaprevir of CYP1A2, CYP2B6, CYP2C, and CYP3A isozymes was observed *in vitro*. Based on the results of drug-drug clinical interaction studies (e.g., escitalopram, zolpidem, ethinylestradiol), induction of metabolic enzymes by telaprevir cannot be excluded.

In vitro studies demonstrated that telaprevir is not an inhibitor of UGT1A9 or UGT2B7. *In vitro* studies with recombinant UGT1A3 suggested that telaprevir may inhibit this enzyme. The clinical relevance of this is uncertain as administration of telaprevir 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 telaprevir of alcohol dehydrogenase was observed *in vitro*. However, sufficiently high concentrations were not tested for intestinal inhibition to be excluded.

Suppression by telaprevir and VRT-127394 of CYP enzymes regulated via CAR, PXR and Ah nuclear receptors was observed *in vitro* in human hepatocytes. Clinical drug-drug interaction studies with substrates of CYP2B6, CYP2C8, CYP2D6, CYP2C19 and UGT1A1, UGT2B7 and UGT1A3 indicate no clinically relevant impact of the suppression observed *in vitro*. For other enzymes and transporters

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(e.g., CYP1A1, CYP1A2, BCRP, OATPs) regulated by the same nuclear receptors, the potential clinical impact is unknown.

Transporters
In vitro studies demonstrated that telaprevir is an inhibitor of OATP1B1 and OATP2B1.

No relevant inhibition by telaprevir of the organic cation transporter (OCT) OCT2 was observed *in vitro*.

Telaprevir is a weak *in vitro* inhibitor of the transporters multidrug and toxin extrusion (MATE) MATE1 and MATE2-K with an IC_{50} of 28.3 µM and 32.5 µM, respectively. The clinical implication of this finding are currently unknown.

Elimination
Following administration of a single oral dose of 750 mg ^{14}C-telaprevir in healthy subjects, 90 % of total radioactivity 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 – telaprevir 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 telaprevir 750 mg typically ranged from about 4.0 to 4.7 hours. At steady-state, the effective half-life is about 9-11 hours.

Linearity/non-linearity
The exposure (AUC) to telaprevir 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 telaprevir exposure.

Special populations
Paediatric population
Data in the paediatric population are currently not available.

Renal impairment
The pharmacokinetics of telaprevir 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 telaprevir C_{max} and AUC were 10% and 21% greater, respectively, compared to healthy subjects (see section 4.2).

Hepatic impairment
Telaprevir is primarily metabolised in the liver. Steady-state exposure to telaprevir was 15% lower in subjects with mild hepatic impairment (Child-Pugh Class A, score 5-6) compared to healthy subjects. Steady-state exposure to telaprevir was 46% lower in subjects with moderate hepatic impairment (Child-Pugh Class B, score 7-9) compared to healthy subjects. Effect on unbound telaprevir concentrations is unknown (see sections 4.2 and 4.4).

Gender
The effect of subject gender on telaprevir pharmacokinetics was evaluated using population pharmacokinetics of data from Phase 2 and 3 studies of INCIVO. No relevant effect of gender was identified.

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Race
Population pharmacokinetic analysis of INCIVO in HCV-infected subjects indicated that the exposure to telaprevir was similar in Blacks/African-Americans and Caucasians.

Elderly
There is limited pharmacokinetic data on the use of INCIVO in HCV patients aged ≥ 65 years and no data in subjects > 70 years of age.

5.3 Preclinical safety data

Animal toxicology and/or pharmacology
In rats and dogs, telaprevir was associated with a reversible reduction of red blood cell parameters accompanied by a regenerative response. In both rats and dogs, AST/ALT elevations were observed in most studies, of which the increase in ALT in rats was not normalised after recovery.
Histopathological findings in the liver were similar in both rat and dog studies, of which not all were fully resolved after recovery. In rats (but not in dogs), telaprevir caused degenerative changes in testes which were reversible and did not affect fertility. In general, exposure levels in relation to human values were low in animal pharmacology and toxicology studies.

Carcinogenesis and mutagenesis
Telaprevir has not been tested for its carcinogenic potential. Neither telaprevir 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
Telaprevir had no effects on fertility or fecundity when evaluated in rats.

Embryo-fœtal development
Telaprevir readily crosses the placenta in both rat and mouse giving a foetal: maternal exposure of 19 - 50%. Telaprevir did not have any teratogenic potential in rat or mouse. In a fertility and early embryonic development study in rats, an increase in non-viable conceptuses was observed. Dosing of the animals did not result in any exposure margin when compared to human exposure.

Excretion into milk
When administered to lactating rats, levels of telaprevir and its major metabolite were higher in milk compared to those observed in plasma. Rat offspring exposed to telaprevir in utero showed normal body weight at birth. However, when fed via milk from telaprevir-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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
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

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macrogol
talc
titanium dioxide (E171)
iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original bottle. Keep the bottle tightly closed in order to protect from moisture. Do not remove the desiccant.

6.5 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.

INCIVO is available in packs containing 1 bottle (total of 42 film-coated tablets) or 4 bottles (total of 168 film-coated tablets).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Janssen Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/720/001 4-bottle pack
EU/1/11/720/002 1-bottle pack

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 September 2011

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10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

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ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

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A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Janssen-Cilag S.p.A.
Via C. Janssen
IT-04100 Borgo San Michele
Latina, Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency.
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The Marketing Authorisation Holder shall agree to the format and content of the healthcare professional educational pack with the National Competent Authority prior to launch in the Member State.
The Marketing Authorisation Holder shall ensure that all physicians who are expected to prescribe or use INCIVO are provided with a healthcare professional educational pack containing the following:
- The Summary of Product Characteristics
- The Patient Information Leaflet
- The Physician Leaflet

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The Physician Leaflet should contain the following key elements:

- Rash and Severe Cutaneous Adverse Reactions safety data from Phases 2 and 3
- Incidence of rash and severe cutaneous reactions
- Grading and management of rash and severe cutaneous reactions, particularly with respect to criteria for the continuation or discontinuation of telaprevir and the other treatment components.
- Pictures of rash according to different grades

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ANNEX III

LABELLING AND PACKAGE LEAFLET

Medicinal product no longer authorised

A. LABELLING

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (1-bottle pack)

1. NAME OF THE MEDICINAL PRODUCT

INCIVO 375 mg film-coated tablets
telaprevir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 375 mg of telaprevir.

3. LIST OF EXCIPIENTS

Contains sodium.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

42 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Swallow the tablets whole.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original bottle. Keep the bottle tightly closed in order to protect from moisture.

Medicinal product no longer authorised

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/11/720/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

incivo 375 mg

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL (1-bottle pack)

1. NAME OF THE MEDICINAL PRODUCT

INCIVO 375 mg film-coated tablets
telaprevir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 375 mg of telaprevir.

3. LIST OF EXCIPIENTS

Contains sodium.

4. PHARMACEUTICAL FORM AND CONTENTS

42 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Swallow the tablets whole.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not remove the desiccant.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original bottle. Keep the bottle tightly closed in order to protect from moisture.

Medicinal product no longer authorised

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/11/720/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (4-bottle pack)

1. NAME OF THE MEDICINAL PRODUCT

INCIVO 375 mg film-coated tablets
telaprevir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 375 mg of telaprevir.

3. LIST OF EXCIPIENTS

Contains sodium.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

168 film-coated tablets (4 bottles containing 42 tablets each)
The bottles are not to be distributed individually.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Swallow the tablets whole.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original bottle. Keep the bottle tightly closed in order to protect from moisture.

Medicinal product no longer authorised

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/11/720/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

incivo 375 mg

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL (4-bottle pack)

1. NAME OF THE MEDICINAL PRODUCT

INCIVO 375 mg film-coated tablets
telaprevir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 375 mg of telaprevir.

3. LIST OF EXCIPIENTS

Contains sodium.

4. PHARMACEUTICAL FORM AND CONTENTS

42 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Swallow the tablets whole.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not remove the desiccant.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original bottle. Keep the bottle tightly closed in order to protect from moisture.

Medicinal product no longer authorised

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/11/720/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Medicinal product no longer authorised

B. PACKAGE LEAFLET

Medicinal product no longer authorised

Package leaflet: Information for the user

INCIVO 375 mg film-coated tablets
telaprevir

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What INCIVO is and what it is used for

INCIVO acts against the virus that causes hepatitis C infection and is used to treat chronic hepatitis C infection in adult patients (aged 18–65 years) in combination with peginterferon alfa and ribavirin. INCIVO contains a substance called telaprevir and belongs to a group of medicines called 'NS3-4A protease inhibitors'. The NS3-4A protease inhibitor reduces the amount of hepatitis C virus in your body. INCIVO must not be taken alone and must be taken in combination with peginterferon alfa and ribavirin to be sure your treatment works. INCIVO can be used for patients with chronic hepatitis C infection who have never been treated before or can be used in patients with chronic hepatitis C infection who have been treated previously with an interferon-based regimen.

2. What you need to know before you take INCIVO

Do not take INCIVO if you are allergic to telaprevir or any of the other ingredients of this medicine (listed in section 6).

See the package leaflets for peginterferon alfa and ribavirin for a list of their contraindications (e.g. pregnancy precautions for men and women) since INCIVO must be used in combination with peginterferon alfa and ribavirin. Ask your doctor if you are unsure about any contraindications mentioned in the package leaflets.

Do not use INCIVO in combination with any of the following medicines as they may increase the risk of severe side effects, and/or affect the way INCIVO or the other medicine works:

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Medicine (name of the active substance)	Purpose of the medicine
alfuzosin	to treat symptoms of an enlarged prostate (alpha-1-adrenoreceptor antagonists)
amiodarone, bepridil, quinidine, other Class Ia or III antiarrhythmics	to treat certain heart disorders such as irregular heart beat (antiarrhythmics)
astemizole, terfenadine	to treat allergy symptoms (antihistamines)
rifampicin	to treat some infections like tuberculosis (antimycobacterial)
dihydroergotamine, ergonovine, ergotamine, methylergonovine	to treat migraine and headaches (ergot derivatives)
cisapride	to treat some stomach conditions (gastrointestinal motility agents)
St John's wort (*Hypericum perforatum*)	an herbal product to relieve anxiety
atorvastatin, lovastatin, simvastatin	to lower cholesterol levels (HMG CoA reductase inhibitors)
pimozide	to treat psychiatric conditions (neuroleptics)
sildenafil, tadalafil	Sildenafil or tadalafil must not be used to treat a heart and lung disorder called pulmonary arterial hypertension. There are other uses for sildenafil and tadalafil. Please see section 'Other medicines and INCIVO'.
quetiapine	to treat schizophrenia, bipolar disorder and major depressive disorder
midazolam (taken by mouth), triazolam (taken by mouth)	to help you sleep and/or relieve anxiety (sedatives/hypnotics)
carbamazepine, phenobarbital, phenytoin	to treat epileptic seizures (anticonvulsants)

If you are taking any of the above, ask your doctor about switching to another medicine.

Warnings and precautions
Talk to your doctor or pharmacist before taking INCIVO.

INCIVO must be taken in combination with peginterferon alfa and ribavirin. It is therefore very important that you read the package leaflets that are provided with these medicines, too. If you have any questions about your medicines, please ask your doctor or pharmacist.

Make sure that you check the following points and tell your doctor treating your hepatitis C virus (HCV) if any of these apply to you.

- Skin rash
  Patients taking INCIVO may develop a skin rash. There may be itching with the rash. Usually the rash is mild or moderate, but the rash may be, or may become, severe and/or life-threatening. **You should contact your doctor immediately** if you develop a rash or have a

Medicinal product no longer authorised

rash that gets worse. INCIVO must not be restarted if discontinued by your doctor. **You must carefully read the information under Rash in section 4 Possible Side Effects.**

- Anaemia (decrease in your red blood cells)
  Tell your doctor if you experience tiredness, weakness, shortness of breath, light-headedness, and/or the feeling of the heart racing. These may be symptoms of anaemia.

- Heart problems
  Tell your doctor if you have heart failure, irregular heartbeat, slow heart rate, an abnormality shown in your heart tracing (ECG) called 'long QT syndrome', or a family history of a heart condition called 'congenital QT syndrome'.
  Your doctor may request additional monitoring during your INCIVO treatment.

- Liver problems
  Tell your doctor if you have had other problems with your liver such as liver failure. Signs might be yellowing of the skin or eyes (jaundice), swelling of the stomach (ascites) or legs due to fluid, and bleeding from swollen veins (varices) in the gullet (oesophagus). Your doctor may evaluate how severe your liver disease is before deciding if you can take INCIVO.

- Infections
  Tell your doctor if you have an hepatitis B infection so that your doctor can decide if INCIVO is right for you.

- Organ transplant
  Tell your doctor if you have had or are going to have a liver or other organ transplant as INCIVO might not be right for you in this situation.

Blood tests
Your doctor will do blood tests before starting treatment and regularly during your treatment:
- to see how much virus is in your blood and to determine if you have the type of virus (genotype 1) that can be treated with INCIVO. Decisions related to your treatment may be made based on the results of these tests. Your doctor will monitor your early response to treatment and how much virus is in your blood. If your treatment is not working, your doctor may stop your medicines. If your doctor stops INCIVO, it should not be restarted.
- to check if you have anaemia (decrease in your red blood cells).
- to check for changes in some values of your blood cells or chemistry. These can be seen in the results from blood tests. Your doctor will explain these to you. Examples are: blood count levels, thyroid (a gland in your neck that controls your metabolism) levels, liver and kidney tests.

INCIVO has only been used in a limited number of patients of 65 years or older. If you belong to this age group, please discuss the use of INCIVO with your doctor.

Children and adolescents
INCIVO is not for use in children or adolescents, because it has not been sufficiently studied in patients under 18 years of age.

Other medicines and INCIVO
INCIVO may affect other medicines or other medicines may affect INCIVO. Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Tell your doctor if you take any of the following medicines:

Medicine (name of the active substance)	**Purpose of the medicine**
flecainide, propafenone	to treat certain heart disorders such as irregular heart beat (antiarrhythmics)

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alfentanil, fentanyl	to treat pain (analgesics) or used during surgery to induce sleep
digoxin, intravenous lidocaine	to treat certain heart disorders such as abnormal heart beat (antiarrhythmics)
clarithromycin, erythromycin, telithromycin, troleandomycin	to treat bacterial infections (antibacterials)
warfarin, dabigatran	to prevent blood clots (anticoagulants)
escitalopram, trazodone	to treat mood disorders (antidepressants)
metformin	to treat diabetes (antidiabetics)
domperidone	to treat vomiting and nausea (antiemetics)
itraconazole, ketoconazole, posaconazole, voriconazole	to treat fungal infections (antifungals)
colchicine	to treat inflammatory arthritis (anti-gout agents)
rifabutin	to treat certain infections (antimycobacterials)
alprazolam, midazolam through injection	to help you sleep and/or relieve anxiety (benzodiazepines)
zolpidem	to help you sleep and/or relieve anxiety (non-benzodiazepine sedatives)
amlodipine, diltiazem, felodipine, nicardipine, nifedipine, nisoldipine, verapamil	to decrease blood pressure (calcium channel blockers)
maraviroc	to treat HIV infections (CCR5 antagonist)
budesonide, inhaled/nasal fluticasone, dexamethasone if taken by mouth or through injection	to treat asthma or to treat inflammatory and autoimmune conditions (corticosteroids)
bosentan	to treat a heart and lung disorder called pulmonary arterial hypertension (endothelin receptor antagonist)
atazanavir/ritonavir, darunavir/ritonavir, fosamprenavir/ritonavir, lopinavir/ritonavir	to treat HIV infections (HIV-protease inhibitors)
abacavir, efavirenz, tenofovir disoproxil fumarate, zidovudine	to treat HIV infections (reverse transcriptase inhibitors)
fluvastatin, pitavastatin, pravastatin, rosuvastatin	to lower cholesterol levels (HMG CoA reductase inhibitors)
all types of hormonal contraceptives ('the pill')	hormonal contraceptives
oestrogen-based medicines	hormone replacement therapy
cyclosporine, sirolimus, tacrolimus	to lower your immune system (immunosuppressants), medicines used in some rheumatic diseases or to avoid problems with organ transplants
salmeterol	to improve breathing for asthma (inhaled beta agonists)
repaglinide	to treat type II diabetes (blood glucose lowering medicine)
methadone	for the treatment of opioid (narcotic) dependence
sildenafil, tadalafil, vardenafil	to treat erectile dysfunction or to treat a heart and lung disorder called pulmonary arterial hypertension (PDE-5 inhibitors)

INCIVO with food and drink
INCIVO must always be taken together with food. The food is important to get the right levels of medicine in your body.

Pregnancy and breast-feeding
If you are **pregnant**, you must not take INCIVO. INCIVO must be used in combination with

Medicinal product no longer authorised

peginterferon alfa and ribavirin. Ribavirin can damage your unborn baby. It is therefore absolutely essential that you take all precautions not to get pregnant during this therapy.

If you or your female partner become pregnant during INCIVO treatment or the months that follow, you must contact your doctor immediately (see section 'Pregnancy precautions for men and women' below).

If you are **breast-feeding**, you must stop breast-feeding before starting to take INCIVO. It is not known whether telaprevir, the active ingredient in INCIVO, is found in human breast milk.

Ask your doctor or pharmacist for advice before taking any medicine.

Pregnancy precautions for men and women
Since INCIVO must be used in combination with ribavirin and ribavirin can be very damaging to an unborn baby, both female and male patients must take **special precautions** in order to prevent pregnancy. Any birth control method can fail, and, therefore, you and your partner must use at least two effective birth control methods **during INCIVO therapy** and **afterwards**. Following the end of the INCIVO treatment, please see the ribavirin package leaflet regarding continued contraception requirements.

Female patients of childbearing age and their male partners
A hormonal contraceptive ('the pill') may not be reliable during the treatment with INCIVO. Therefore, you and your partner must use two other birth control methods during the time you are taking INCIVO and for 2 months after stopping this medicine.

You must read the package leaflets for peginterferon alfa and ribavirin for additional information.

Driving and using machines
Some patients may experience fainting or problems with vision during INCIVO treatment. Do not drive or operate machines if you feel faint or have problems with your vision while taking INCIVO. See also the package leaflets for peginterferon alfa and ribavirin.

INCIVO contains sodium
This medicine contains 2.3 mg sodium per tablet, which should be taken into consideration by patients on a controlled sodium diet. Tell your doctor if you have to take care of your salt intake and follow a low sodium diet.

3. How to take INCIVO

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Instructions for proper use
Your doctor will decide on the appropriate dose regimen for you.
The recommended dose regimen is:
- **3 tablets** of INCIVO **twice daily (morning and evening) with food**. The total dose is 6 tablets per day,
  or
- **2 tablets** of INCIVO **every 8 hours with food**. The total dose is 6 tablets per day.

If you have both hepatitis C virus infection and human immunodeficiency virus infection, and are taking efavirenz, the recommended dose regimen is **3 tablets** of INCIVO **every 8 hours with food**.

You must always take INCIVO with food as this is important to get the right levels of medicine in your body. You must not reduce your dose of INCIVO. Swallow the tablets whole. Do not chew,

Medicinal product no longer authorised

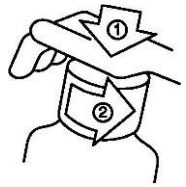
break, or dissolve the tablets before you swallow them. Tell your health care provider if you have problems swallowing whole tablets.

Since INCIVO treatment always needs to be used together with peginterferon alfa and ribavirin, please also check the package leaflets for the dosage instructions of these medicines. If you need help, ask your doctor or pharmacist.

Take INCIVO with peginterferon alfa and ribavirin for 12 weeks. The total duration of treatment of peginterferon alfa and ribavirin varies from 24 to 48 weeks depending on treatment response and whether you have been treated before. Your doctor will measure blood levels of your virus at weeks 4 and 12 to determine your treatment duration. The recommended total duration of treatment for patients who have received a liver transplant is 48 weeks. Please check with your doctor and follow the recommended duration of treatment.

If your doctor stops INCIVO because of side effects or because your treatment is not working, INCIVO should not be restarted.

Removing the child resistant cap



The plastic bottle comes with a child resistant cap and should be opened as follows:
- Push the plastic screw cap down while turning it counter clockwise.
- Remove the unscrewed cap.

If you take more INCIVO than you should
Contact your doctor or pharmacist immediately to ask for advice.
In case of overdose you may experience nausea, headache, diarrhoea, decreased appetite, abnormal taste and vomiting.

If you forget to take INCIVO
If you are taking INCIVO twice daily (morning and evening)
If you notice the missed dose **within 6 hours**, you must take three tablets immediately. Always take the tablets with food. If you notice the missed dose **after 6 hours**, then skip the intake and take the next doses as usual. Do not take a double dose to make up for a forgotten dose.

If you are taking INCIVO every 8 hours
If you notice the missed dose **within 4 hours**, you must take two tablets immediately. Always take the tablets with food. If you notice the missed dose **after 4 hours**, then skip the intake and take the next doses as usual. Do not take a double dose to make up for a forgotten dose.

If you stop using INCIVO
Unless your doctor tells you to stop, continue taking INCIVO in order to ensure that your medicine continues to work against the virus. INCIVO must not be restarted if discontinued by your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Medicinal product no longer authorised

Rash
Patients taking INCIVO frequently get an itchy skin rash. Usually the rash is mild or moderate, but the rash may be, or may become, severe and/or life-threatening. Rarely patients may have other symptoms with the rash that may be a sign of a severe skin reaction.

Contact your doctor immediately if you get a skin rash.

Also contact your doctor immediately:
- if your rash worsens, OR
- if you develop other symptoms with a rash such as:
  - fever
  - tiredness
  - swelling of the face
  - swelling of lymph glands, OR
- if you have a wide-spread rash with peeling skin which may be accompanied by fever, flu-like symptoms, painful skin blisters, and blisters in the mouth, eyes, and/or genitals.

Your doctor should check your rash to determine how to manage it. Your doctor may stop your treatment. INCIVO must not be restarted if discontinued by your doctor.

Contact your doctor immediately also if you develop any of the following symptoms:
- tiredness, weakness, shortness of breath, light-headedness, and/or feeling of heart racing. These may be symptoms of anaemia (decrease in your red blood cells);
- fainting;
- painful inflammation of the joints most commonly in the foot (gout);
- problems with your eyesight;
- bleeding from the anus;
- swelling of the face.

The frequency rate of the side effects associated with INCIVO is given below.

Very common side effects (affects more than 1 in 10 people):
- low red blood cell count (anaemia);
- nausea, diarrhoea, vomiting;
- swollen veins in the rectum or anus (haemorrhoids), pain in the anus or rectum;
- skin rash and itching of the skin.

Common side effects (affects less than 1 in 10 people):
- fungal infection in the mouth;
- low blood platelet count, decrease in lymphocytes (a type of white blood cell), decrease in thyroid gland activity, increase in uric acid in your blood, decrease in potassium in your blood, increase in bilirubin in your blood;
- change in taste;
- fainting;
- itching around or near the anus, bleeding around or near the anus or rectum, a small tear in the skin that lines the anus that may cause pain and/or bleeding during bowel movements;
- red, cracked, dry, scaly skin (eczema), rash with red, cracked, dry, scaly skin (exfoliative rash);
- swelling of the face, swelling of the arms and/or legs (oedema);
- abnormal product taste.

Uncommon side effects (affects less than 1 in 100 people):
- increase in creatinine in your blood;
- painful inflammation of the joints most commonly in the foot (gout);
- damage to back of the eye (retina);
- inflammation of the anus and rectum;
- inflamed pancreas

Medicinal product no longer authorised

- severe rash, which may be accompanied by fever, fatigue, swelling of the face or lymph glands, increase of eosinophils (type of white blood cells), effects on liver, kidney or lung (a reaction called DRESS);
- hives (urticaria)
- dehydration. Signs and symptoms of dehydration include increased thirst, dry mouth, decreased urine frequency or volume, and dark coloured urine. It is important to stay hydrated with fluids during INCIVO combination treatment.

Rare side effects (affects less than 1 in 1,000 people):
- a wide-spread severe rash with peeling skin which may be accompanied by fever, flu-like symptoms, blisters in the mouth, eyes, and/or genitals (Stevens-Johnson syndrome).

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

See also the package leaflets for peginterferon alfa and ribavirin for side effects reported for these products.

5. How to store INCIVO

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.

INCIVO tablets should be stored in the original bottle. Keep the bottle tightly closed in order to protect from moisture. Each bottle contains one pouch or two pouches of desiccant to keep the tablets dry. Do not remove this desiccant from the bottle. Do not eat the desiccant.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What INCIVO contains
The active substance is telaprevir. Each tablet of INCIVO contains 375 mg of telaprevir.
The other ingredients are:
Tablet core
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), iron oxide yellow (E172)

What INCIVO looks like and contents of the pack
Film-coated tablet. Yellow caplet-shaped tablets of approximately 20 mm in length, marked with 'T375' on one side.
INCIVO is available in packs containing one bottle or 4 bottles per carton. Each bottle contains one pouch or two pouches to keep the tablets dry (desiccant).
Not all pack-sizes may be marketed.

Medicinal product no longer authorised

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Turnhoutseweg 30
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Manufacturer
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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency (EMA) web site: http://www.ema.europa.eu/.

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