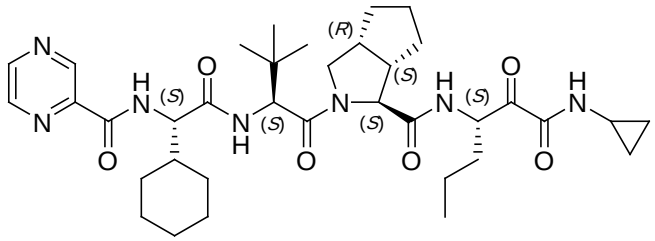
# INCIVO®

# PRODUCT INFORMATION

## NAME OF THE MEDICINE

Telaprevir

The chemical name is (1S, 3aR, 6aS)-2-((S)-2-{(S)-2-Cyclohexyl-2- [(pyrazine-2-carbonyl)-amino] -acetylamino}-3,3-dimethyl-butyryl)-octahydro-cyclopenta[c]pyrrole-1-carboxylic acid ((S)-1-cyclopropylaminooxalyl-butyl)-amide.



Molecular Formula: $C_{36}H_{53}N_7O_6$ CAS: 402957-28-2 MW: 679.9

## DESCRIPTION

The active ingredient telaprevir is an inhibitor of the Hepatitis C Virus (HCV) NS3 4A protease, an enzyme that is essential for HCV replication. Telaprevir drug substance is a white to off-white powder with a solubility in water of 0.0047 mg/mL. The apparent log ($P_{1\text{-octanol/aqueous solution}}$) values of telaprevir at room temperature (24 ± 3°C) are 3.96 (pH 1), 3.87 (pH 5), and 4.00 (pH 7). The high apparent partition coefficient is consistent with the low aqueous solubility of the drug substance, and, hence, the hydrophobic nature of telaprevir.

INCIVO is available as yellow, caplet-shaped, film-coated tablets of approximately 20 mm in length, marked with “T375” on one side. The inactive ingredients are hypromellose acetate succinate, sodium lauryl sulfate, calcium hydrogen phosphate anhydrous, croscarmellose sodium, cellulose - microcrystalline, silicon dioxide, sodium stearyl fumarate, polyvinyl alcohol, macrogol 3350, talc - purified, titanium dioxide and iron oxide yellow.

## PHARMACOLOGY

Pharmacotherapeutic group: Direct-acting antiviral.

## PHARMACODYNAMICS

Mechanism of Action

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

Antiviral activity in cell culture

In an HCV subtype 1b replicon assay, the telaprevir $IC_{50}$ value against wild-type HCV was 354 nM, similar to a subtype 1a infectious virus assay $IC_{50}$ value of280 nM. In biochemical enzymatic assays, telaprevir showed similar inhibition against HCV genotypes 1a/b (21 nM) and 2a/b (16 nM), and reduced activity against genotype 3a (57 nM) and 4a (130 nM) NS3 4A proteases. The presence of 40% human serum reduced the anti-HCV activity of telaprevir by approximately 10-fold. Evaluation of telaprevir in combination with interferon alfa or ribavirin showed additive or moderate synergy in reducing HCV-RNA levels in HCV replicon cells.

In vitro Resistance

HCV variants associated with on-treatment virologic failure or relapse were evaluated by site-directed mutagenesis in the replicon assay (see PHARMACOLOGY - Pharmacodynamics: Clinical Experience). 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.

In vitro 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 (e.g. boceprevir) 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 currently no clinical data on re-treating subjects 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 subjects with predominant telaprevir-resistant variants at baseline (pre-treatment) were rare (V36M, T54A and R155K < 1% and T54S 2.7%). Predominant baseline resistance to telaprevir does not preclude successful treatment with telaprevir, peginterferon alfa, and ribavirin.

A total of 215 of 1,169 subjects treated with a T12/PR regimen in Phase 3 clinical trials had on-treatment virologic failure (n = 125) or relapse (n = 90). Based on population sequencing analyses of HCV in these 215 subjects, 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%) subjects. Sequence analyses of the telaprevir-resistant variants identified substitutions predominantly at 4 positions in the NS3-4A protease region, consistent with the mechanism of action for telaprevir (V36, T54, R155, and A156). 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.

In an additional pooled analysis of subjects who did not achieve SVR (on-treatment virologic failure or relapse) from the controlled Phase 3 clinical trials, NS3 amino acid substitutions V36M/A/L, T54A/S, R155K/T, and A156S/T were determined to emerge frequently on INCIVO treatment (Table 1). Nearly all of these substitutions have been shown to reduce telaprevir anti-HCV activity in cell culture or biochemical assays. No clear evidence of treatment-emergent substitutions in the

NS3 helicase domain or NS4A coding regions of the HCV genome was observed among INCIVO-treated subjects who did not achieve SVR.

Subjects with HCV genotype 1a predominately had V36M and R155K single and combination variants, while subjects with HCV genotype 1b predominately had V36A, T54A/S, and A156S/T variants. This difference is likely due to the higher genetic barrier for the V36M and R155K substitutions for genotype 1b than genotype 1a. Among subjects treated with telaprevir, on-treatment virologic failure was more frequent in subjects with genotype 1a than with genotype 1b and more frequent in prior null responders than in other populations (treatment-naïve, prior relapsers, prior partial responders; see PHARMACOLOGY - Pharmacodynamics: Clinical Experience, Efficacy in Previously Treated Adults).

**Table 1: Treatment Emergent Substitutions in Pooled Phase 3 Studies:**

**Subjects who did not achieve SVR24 in INCIVO Combination Treatment Arms**

| **Emerging Substitutions[1] in NS3** | **Percent of No SVR Subjects (n)**<br><br>**N=525** | **Percent Subtype 1a**<br><br>**No SVR Subjects (n)**<br><br>**N=356** | **Percent Subtype 1b**<br><br>**No SVR Subjects (n)**<br><br>**N=169** |
|---|---|---|---|
| Any substitution at V36, T54, R155, A156 or D168 | 62% (323) | 69% (247) | 45% (76) |
| R155K/T | 38% (201) | 56% (200) | 0.6% (1) |
| V36M | 33% (178) | 49% (173) | 3% (5) |
| V36M + R155K[2] | 27% (142) | 40% (142) | 0% (0) |
| T54A/S | 13% (68) | 9% (31) | 22% (37) |
| V36A/L | 12% (65) | 10% (37) | 17% (28) |
| A156S/T | 9% (48) | 8% (28) | 12% (20) |
| V36G/I, I132V, R155G/M, A156V/F/N or D168N | Less than 2% | Less than 2% | Less than 2% |

[1]Alone or in combination with other substitutions (includes mixtures)
[2]Subjects with this combination are also encompassed in two V36M and R155K rows above.

Persistence of Resistance-Associated Variants

Follow-up analysis of INCIVO-treated subjects who did not achieve an SVR showed that the population of wild-type virus increased and the population of telaprevir-resistant variants became undetectable over time after the end of telaprevir treatment. Of a combined 255 treatment-naïve and previously treated subjects from Phase 3 studies 108, 111, and C216 in whom telaprevir-resistant variants had emerged during treatment, 152 (60%) subjects no longer had resistant variants detected by population sequencing (median follow-up of 10 months). Of the 393 resistant variants detected in the 255 subjects, 68% of NS3-36, 84% of NS3-54, 59% of NS3-155, 86% of NS3-156, and 52% of NS3-36M+NS3-155K variants were no longer detected.

In a follow-up study of 98 treatment-naïve and prior treatment-failure subjects who were treated with a INCIVO regimen in a Phase 2 or Phase 3 study and did not achieve SVR, telaprevir-resistant variants were no longer detected in 85% (83/98) of subjects (median follow-up of 27.5 months). Clonal sequencing analysis of a subset of subjects who had wild-type HCV by

population sequencing (n=20), comparing the frequency of resistant variants before the start of telaprevir treatment and at follow-up, showed that the HCV variant population in all subjects had returned to pre-treatment levels.

## PHARMACOKINETICS

The pharmacokinetic properties of telaprevir have been evaluated in healthy adult volunteers and in subjects with chronic HCV infection. Telaprevir is to be administered orally with food as 750 mg (two film coated 375 mg tablets) every 8 hours 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.

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).

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.

*In vitro* studies using recombinant human cytochrome P450 (CYP) isoforms indicated that CYP3A4 was the major CYP isoform responsible for telaprevir metabolism. 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 inhibition by telaprevir of CYP1A2, CYP2C9, CYP2C19, and CYP2D6 isozymes was observed *in vitro*. *In vitro* studies also suggest that telaprevir has a low potential to induce CYP2C, CYP3A, or CYP1A and is therefore considered unlikely to demonstrate induction-based drug-drug interactions when co-administered with corresponding substrates.

Elimination:

Following administration of a single oral dose of 750 mg $^{14}$C-telaprevir in healthy subjects, 90% of total radioactivitiy was recovered in faeces, urine and expired air within 96 hours post-dose. The median recovery of the administered radioactive dose was approximately 82% in the faeces, 9% in exhaled air and 1% in urine. The contribution of unchanged $^{14}$C – 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.

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 DOSAGE AND ADMINISTRATION).

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 (see DOSAGE AND ADMINISTRATION).

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 dose adjustments are deemed necessary based on gender.

Race:

Population pharmacokinetic analysis of INCIVO in HCV-infected subjects indicated that race had no apparent effect on the exposure to telaprevir. There are limited efficacy and safety data in the clinical development program in Asian patients.

Elderly:

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

Clinical trials

Clinical experience

The efficacy and safety of INCIVO in subjects with genotype 1 chronic hepatitis C were evaluated in three Phase 3 studies: 2 in treatment-naïve subjects and 1 in previously treated subjects. The study in previously treated subjects enrolled prior relapsers (subjects with HCV RNA undetectable at end of treatment with a pegylated interferon-based regimen, but HCV RNA detectable within 24 weeks of treatment follow-up) and prior non-responders (subjects who did not have undetectable HCV RNA levels during or at the end of a prior course of at least 12 weeks of treatment). The non-responder-population was comprised of two subgroups: prior partial responders (greater than or equal to 2 $\log_{10}$ reduction in HCV RNA at week 12, but not achieving HCV RNA undetectable at end of treatment with a peginterferon and ribavirin) and prior null responders (less than 2 $\log_{10}$ reduction in HCV RNA at week 12 of prior treatment with peginterferon and ribavirin). Subjects in these studies had compensated liver disease, detectable HCV RNA, and liver histopathology consistent with chronic hepatitis C. Unless otherwise indicated, INCIVO was administered at a dosage of 750 mg every 8 hours; the peginterferon alfa-2a dose was 180 µg/week, and the ribavirin dose was 1,000 mg/day (subjects weighing < 75 kg) or 1,200 mg/day (subjects weighing ≥ 75 kg). Plasma HCV RNA values were measured using the COBAS® TaqMan® HCV test (version 2.0), for use with the High Pure System. The assay had a lower limit of quantification of 25 IU/ml. In the description of Phase 3 study outcomes below, SVR, considered virologic cure, was defined based on the HCV RNA assessment in the study week 72 visit window, using the last measurement in the window. In the case of missing data within the week 72 window, the last HCV RNA data point from week 12 of follow-up onwards was used. In addition, the limit of quantification of 25 IU/ml was used to determine SVR.

***Efficacy in treatment-naïve adults***

***Study 108 (ADVANCE)***

Study 108 was a randomised, double-blind, parallel-group, placebo-controlled, Phase 3 study conducted in treatment-naïve subjects. INCIVO was given for the first 8 weeks of treatment (T8/PR regimen) or the first 12 weeks of treatment (T12/PR regimen) in combination with peginterferon alfa-2a and ribavirin for either 24 or 48 weeks. Subjects who had undetectable HCV RNA at weeks 4 and 12 (extended rapid viral response; eRVR)received 24 weeks of peginterferon alfa-2a and ribavirin treatment, and subjects who did not have undetectable HCV RNA at week 4 and week 12 (no eRVR) 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 subjects had a median age of 49 years (range: 18 to 69); 58% of the subjects were male; 23% had a body mass index ≥30 kg/m$^2$; 9% were Black; 11% were Hispanic or Latino; 2% were Asian; 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 2 shows the response rates for the recommended T12/PR and the Pbo/PR48 groups.

| **Table 2: 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 at weeks 4 and 12 (eRVR)** | 58% (212/363) | 8% (29/361) |
| SVR in eRVR subjects | 92% (195/212) | 93% (27/29) |
| **No eRVR** | 42% (151/363) | 92% (332/361) |
| SVR in no eRVR subjects | 60% (90/151) | 42% (139/332) |
| **Undetectable HCV RNA 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 3 shows SVR rates for subject subgroups.

| **Table 3: SVR rates for patient subgroups: Study 108 (ADVANCE)** | | |
|---|---|---|
| **Subgroup** | **T12/PR** | **Pbo/PR** |
| Men | 78% (166/214) | 46% (97/211) |
| 45 to ≤ 65 years of age | 73% (157/214) | 39% (85/216) |
| Black | 62% (16/26) | 29% (8/28) |
| Hispanic Latino | 77% (27/35) | 39% (15/38) |
| BMI≥ 30 kg/m$^2$ | 73% (56/77) | 44% (38/87) |
| Baseline HCV RNA ≥ 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 subjects. The study was designed to compare SVR rates in subjects with undetectable HCV RNA at weeks 4 and 12 (extended rapid viral response; eRVR) who were treated with INCIVO for 12 weeks in combination with peginterferon alfa-2a and ribavirin for either 24 weeks (T12/PR24 regimen) or 48 weeks (T12/PR48 regimen). Subjects with undetectable HCV RNA at weeks 4 and 12 (eRVR) 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 subjects with undetectable HCV RNA at weeks 4 and 12.

The 540 enrolled subjects had a median age of 51 years (range: 19 to 70); 60% of the subjects were male; 32% had a body mass index ≥30 kg/m$^2$; 14% were Black; 10% were Hispanic or Latino; 2% were Asian; 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%) subjects had undetectable HCV RNA at weeks 4 and 12 (eRVR). Table 4 shows response rates. In subjects who had undetectable HCV RNA at weeks 4 and 12 (eRVR), 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 4: Response rates: Study 111 (ILLUMINATE)**

| | **Subjects with undetectable HCV RNA at weeks 4 and 12 (eRVR)** | | **T12/PR** |
|---|---|---|---|
| **Treatment outcome** | **T12/PR24 N = 162** | **T12/PR48 N = 160** | **All Subjects[a] N=540** |
| **SVR** | 92% (149/162) (87%, 96%)[b] | 90% (144/160) (84%, 94%)[b] | 74% (398/540) (70%, 77%)[b] |
| **Undetectable HCV RNA 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 subjects includes the 322 subjects with undetectable HCV RNA at weeks 4 and 12 and the 218 other subjects treated in the study (118 who did not have undetectable HCV RNA at 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 subjects was 62% (45/73).

Table 5 shows SVR rates by extent of liver fibrosis at baseline.

**Table 5: SVR rates by extent of liver fibrosis at baseline: Study 111 (ILLUMINATE)**

| | Subjects with undetectable HCV RNA at weeks 4 and 12 (eRVR) | | T12/PR All Subjects[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 subjects includes the 322 subjects with undetectable HCV RNA at weeks 4 and 12 and the 218 other subjects treated in the study (118 who did not have undetectable HCV RNA at weeks 4 and 12 and 100 who discontinued the study before week 20, when randomisation occurred)

***Efficacy in previously treated adults***

***Study C216 (REALIZE)***

Study C216 was a randomised, double-blind, placebo-controlled, Phase 3 study conducted in subjects (relapsers, partial responders, and null responders) who did not achieve SVR with prior treatment with peginterferon alfa-2a and ribavirin or peginterferon alfa-2b and ribavirin.

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

SVR rates for the T12(DS)/PR group were 88% (124/141) for prior relapsers, 56% (27/48) for prior partial responders, and 33% (25/75) for prior null responders. Table 6 shows the response rates for the recommended simultaneous start (T12/PR48) and the Pbo/PR48 arms.

**Table 6: Response rates: Study C216 (REALIZE)**

| 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] |
| **Undetectable HCV RNA at End of Treatment** | | |
| Prior relapsers | 87% (126/145) | 63% (43/68) |
| 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 7 shows SVR rates by extent of liver fibrosis.

| **Table 7: SVR rates by extent of liver fibrosis at baseline: Study C216 (REALIZE)** | | |
|---|---|---|
| **Extent of liver fibrosis** | **T12/PR** | **Pbo/PR48** |
| **Prior relapsers** | | |
| No or minimal fibrosis or portal fibrosis | 84% (68/81) | 32% (12/38) |
| Bridging fibrosis | 86% (31/36) | 13% (2/15) |
| Cirrhosis | 82% (23/28) | 7% (1/15) |
| **Prior partial responders** | | |
| No or minimal fibrosis or portal fibrosis | 79% (19/24) | 18% (3/17) |
| Bridging fibrosis | 71% (5/7) | 0 (0/5) |
| Cirrhosis | 33% (6/18) | 20% (1/5) |
| **Prior null responders** | | |
| No or minimal fibrosis or portal fibrosis | 31% (9/29) | 6% (1/18) |
| Bridging fibrosis | 47% (8/17) | 0 (0/9) |
| Cirrhosis | 19% (5/26) | 10% (1/10) |

T12/PR48: INCIVO for 12 weeks followed by placebo for 4 weeks, in combination with peginterferon alfa-2a and ribavirin for 48 weeks;
Pbo/PR48: placebo for 16 weeks in combination with peginterferon alfa-2a and ribavirin for 48 weeks

***Study 106 (PROVE 3) and Study 107***

Study 106 was a randomised, double-blind, placebo-controlled, Phase 2 study that enrolled subjects who had failed prior treatment with peginterferon alfa-2a and ribavirin or peginterferon alfa-2b and ribavirin. Among prior relapsers in the T12/PR24 treatment group who had undetectable HCV RNA at weeks 4 and 12 of treatment (extended rapid viral response; eRVR), the SVR rate was 89% (25/28) and the relapse rate was 7%.

Study 107 was an open label, rollover study for subjects who were treated in the control group (placebo, peginterferon alfa-2a, and ribavirin) of a Phase 2 study of INCIVO and who did not achieve SVR in the Phase 2 study. Among prior relapsers in the T12/PR24 treatment group who had undetectable HCV RNA at week 4 and 12 of treatment (extended rapid viral response; eRVR), 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 subjects.

All subjects received 12 weeks of INCIVO in combination with the peginterferon alfa/ribavirin standard therapy. Subjects were randomised to 1 of 4 treatment groups:

- INCIVO 750 mg every 8 hours with peginterferon alfa-2a 180 μg/week and ribavirin 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 Prescribing Information.

At Week 12, INCIVO dosing ended and subjects continued on standard therapy only. The percentage of subjects with SVR in the pooled peginterferon alfa-2a group was 83.8%, in the pooled peginterferon alfa-2b group 81.5% with a 95% confidence interval for the difference of (-10.8, 12.1)

*Long-term efficacy data*

***Study 112 (EXTEND)***

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

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. Data indicate that the QTcF effects of telaprevir are more pronounced in males. In addition, mean increases in heart rate, which persisted until 24 hours after last intake, were observed following regimens of both 750 mg and 1875 mg telaprevir. The mechanism behind this observation is not known.

## 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 Pharmacodynamics: Clinical Experience, Efficacy in Previously Treated Adults).

## CONTRAINDICATIONS

Hypersensitivity to telaprevir or to any of the excipients.

Concomitant administration of INCIVO with active substances that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events (narrow therapeutic index) is contraindicated. 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) and orally administered midazolam[#] and triazolam.

Concomitant administration of INCIVO with any Class Ia or III antiarrhythmics, except for intravenous lidocaine, is contraindicated.

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 is contraindicated.

INCIVO in combination with peginterferon alfa and ribavirin is contraindicated in:

- women who are or may become pregnant. Ribavirin may cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug treatment, the patient should be apprised of the potential hazard to a fetus (see PRECAUTIONS, Use in pregnancy and contraception requirements).
- men whose female partners are pregnant.

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

## PRECAUTIONS

Severe rash

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

5.8% of patients discontinued INCIVO alone due to rash events and 2.6% of patients discontinued INCIVO combination treatment for rash events compared to none 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**. 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

#Preparations with these active substances may not be approved for use in Australia

take several weeks to resolve. Other drugs 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.

For additional information on mild to moderate rash, see ADVERSE EFFECTS.

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: localized 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. |
| 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.<br><br>For moderate rash that progresses, permanent discontinuation of INCIVO should be considered. If the rash does not improve<br><br>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.<br><br>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 significant systemic symptoms, mucous membrane ulceration, target lesions, epidermal detachment | Permanently discontinue INCIVO immediately.<br><br>Consultation with a specialist in dermatology is recommended.<br><br>Monitor for progression or systemic symptoms until the rash is resolved.<br><br>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. |
| Suspicion or diagnosis of generalized bullous eruption, DRESS, Stevens-Johnson syndrome/toxic epidermal necrolysis. acute generalized exanthematous pustulosis, erythema multiforme | Permanent and immediate discontinuation of INCIVO, peginterferon alfa, and ribavirin. Consult with a specialist in dermatology. |

INCIVO must not be restarted if discontinued. Refer also to the Product Information 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. Haemoglobin levels decrease sharply during the first 4 weeks of therapy, with lowest values reached at the end of INCIVO dosing. Hemoglobin values gradually improve after INCIVO dosing completion.

In subjects receiving INCIVO combination treatment, 1.9% discontinued INCIVO alone, 0.9% discontinued INCIVO combination treatment and 27.6% underwent ribavirin dose modification (reduction, interruption or discontinuation) due to anaemia. In subjects treated with peginterferon alfa and ribavirin alone, there were 0.5% discontinuations and 11% underwent ribavirin dose modifications due to anaemia.

Haemoglobin should be monitored prior to and at least every 4 weeks during INCIVO combination treatment (see PRECAUTIONS: Laboratory tests).

Initiation of INCIVO combination treatment is not recommended if baseline haemoglobin is < 12 g/dl (females) or < 13 g/dl (males).

For the management of anaemia, refer to the Product Information for ribavirin for its dose reduction guidelines. Ribavirin dose should be reduced if the haemoglobin level is < 10 g/dl and ribavirin should be discontinued if the haemoglobin level is < 8.5 g/dl. 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.

Drug interactions

Refer to CONTRAINDICATIONS for a listing of medicinal products that are contraindicated for use with INCIVO due to potentially life-threatening adverse events or potential loss of therapeutic effect to INCIVO. Refer to PRECAUTIONS: Interactions with other medicines for established and other potentially significant drug-drug interactions.

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 PHARMACOLOGY: Pharmacodynamics). Exposure at this dose was comparable to the exposure in HCV-infected patients dosed at 750 mg INCIVO every 8 hours plus peginterferon alfa and ribavirin. The potential clinical significance of these findings is uncertain.

Caution is recommended when prescribing INCIVO concurrently with medicinal products known to induce QT prolongation and which are CYP3A substrates such as erythromycin, clarithromycin, telithromycin, posaconazole, voriconazole, ketoconazole, tacrolimus, salmeterol, vardenafil (see PRECAUTIONS: Interactions with other medicines). INCIVO co-administration with domperidone should be avoided (see PRECAUTIONS: Interactions with other medicines). INCIVO may increase concentrations of the co-administered medicinal product and this may result in an increased risk of

their associated cardiac adverse events. In the event that co-administration of such medicinal products with INCIVO is judged strictly necessary, clinical monitoring including ECG assessments is recommended. See CONTRAINDICATIONS for medicinal products with a narrow therapeutic index which are contraindicated with INCIVO.

Use of INCIVO should be avoided in patients with congenital QT prolongation, or a family history of congenital QT prolongation or sudden death. In the event that treatment with INCIVO in such patients is judged strictly necessary, patients should be closely monitored, including ECG assessments.

Use INCIVO with caution in patients with:

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

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

General

INCIVO must not be administered as monotherapy and must only be prescribed in combination with both peginterferon alfa and ribavirin. The Product Information for peginterferon alfa and ribavirin must therefore be consulted before starting therapy with INCIVO.

There are no clinical data on re-treating patients who have failed an HCV NS3-4A protease inhibitor-based therapy (see PHARMACOLOGY - Pharmacodynamics) or on use of repeated courses of INCIVO.

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.

Inadequate virologic response

Patients with inadequate viral response are unlikely to achieve SVR and may develop treatment-emergent resistance substitutions (see Pharmacodynamics). Discontinuation of therapy is recommended in all patients with HCV RNA levels > 1000 IU/ml at treatment Week 4. Patients with detectable HCV RNA at week 12 or week 24 should discontinue peginterferon alfa and ribavirin (see DOSAGE AND ADMINISTRATION).

A high proportion of previous null responders (less than 2 $\log_{10}$ reduction in HCV RNA at week 12 of prior treatment with peginterferon and ribavirin), particularly those with cirrhosis, did not achieve sustained virologic response (SVR) and had telaprevir resistance-associated substitutions emerge on treatment with INCIVO.

Use of INCIVO in treatment of other HCV genotypes

There is 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.

Use in patients with hepatic impairment

INCIVO is not recommended for patients with moderate or severe hepatic impairment (Child-Pugh B or C, score ≥ 7) or patients with decompensated liver disease.

INCIVO has not been studied in patients with severe hepatic impairment (Child-Pugh C, score ≥ 10) or decompensated liver disease and is not recommended in these populations.

In subjects with moderate hepatic impairment (Child-Pugh B, score 7-9), exposure to steady state INCIVO was decreased by approximately 46% compared to healthy individuals. As the appropriate dose of INCIVO in hepatitis C-infected patients with moderate hepatic impairment has not been determined, INCIVO is not recommended in these patients (see DOSAGE AND ADMINISTRATION and PHARMACOLOGY – Pharmacokinetics).

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

Organ transplant patients

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

HCV/HIV (human immunodeficiency virus) co-infection

There is limited clinical data assessing INCIVO in combination with peginterferon and ribavirin in HCV treatment naïve patients who were either not on HIV antiretroviral therapy or were being treated with efavirenz or atazanavir/ritonavir in combination with tenofovir disoproxil fumarate and emtricitabine or lamivudine (see PRECAUTIONS: Interactions with other medicines).

HCV/HBV (hepatitis B virus) co-infection

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

Use in 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.

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.

Effects on fertility

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

No human data on the effect of INCIVO on fertility are available. Telaprevir had no effect on the fertility of male and female rats at oral doses up to 300 and 500 mg/kg/day, respectively (less than

the anticipated clinical exposure based on AUC). Degenerative testicular changes and testicular weight loss were noted in male rats at doses of 300 mg/kg/day. These changes were generally reversible and not observed in dogs following repeated dosing at higher exposure levels (based on AUC). Early embryonic effects (including increased pre-plantation loss and/or nonviable embryos) were observed in male rats given 300 mg/kg/day paired with untreated and treated (500 mg/kg/day) female rats prior to and during mating. While these effects were likely associated with the testicular toxicity observed in males, contributions from the female cannot be ruled out.

*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 rats, telaprevir caused degenerative changes in testes which were reversible and did not affect fertility.

Use in 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 treatment. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients.

*INCIVO/Peginterferon Alfa/Ribavirin Combination Treatment (Category X)*

Animal studies have shown that ribavirin causes birth defects and/or fetal deaths while peginterferon alfa is abortifacient. See the prescribing information for ribavirin.

Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin; and therefore ribavirin is contraindicated in women who are pregnant and in the male partners of women who are pregnant (see CONTRAINDICATIONS and ribavirin prescribing information). Interferons have abortifacient effects in animals and should be assumed to have abortifacient potential in humans (see peginterferon alfa prescribing information).

Extreme caution must be taken to avoid pregnancy in female patients and female partners of male patients while taking this combination. Women of childbearing potential and their male partners should not receive ribavirin unless they are using effective contraception (two reliable forms) during treatment with ribavirin and for 4 months after treatment. Systemic hormonal contraceptives may not be as effective in women while taking INCIVO. Therefore, two alternative effective methods of contraception, including intrauterine devices and barrier methods, should be used in women during treatment with INCIVOand concomitant ribavirin.

*INCIVO (telaprevir) Tablets (Category B2)*

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

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. As any birth control method can fail, at least 2 reliable forms of effective contraception must be used. Refer also to the Product Information for ribavirin.

Female patients of childbearing potential and their male partners as well as male patients and their female partners must use 2 effective contraceptive methods during treatment and for 4 months after all treatment has ended.

*Female patients:*

INCIVO combination therapy should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Pregnancy testing should occur monthly during INCIVO combination therapy and for 4 months after all therapy has stopped.

Hormonal contraceptives may not be reliable during INCIVO dosing (see PRECAUTIONS: Interactions with other medicines). Therefore, female patients of childbearing potential should use 2 additional methods of effective birth control during INCIVO dosing and for 2 months after the last intake of INCIVO. Examples of non-hormonal methods of contraception include a male condom OR female condom (a combination of a male condom and a female condom is not suitable), a diaphragm with spermicidal jelly, or a cervical cap with spermicidal jelly. As of 2 months after completion of INCIVO treatment, hormonal contraceptives can again be used as one of the 2 required effective methods of birth control; however, specific Product Information recommendations should be respected.

Refer also to the Product Information for ribavirin.

*Male patients and their female partners:*

Male patients and their female partners of childbearing potential must use 2 effective contraceptive methods during treatment and for 7 months after all treatment has ended. INCIVO in combination with peginterferon alfa and ribavirin is contraindicated in the male partners of women who are pregnant. Pregnancy testing in non-pregnant female partners is recommended before INCIVO combination therapy, every month during INCIVO combination therapy, and for 7 months after ribavirin therapy has ended.

Refer also to the Product Information for ribavirin.

Use in lactation

It is not known whether telaprevir is excreted in human breast milk. When administered to lactating rats, levels of telaprevir and its major metabolite were two-fold 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 at doses ≥ 150 mg/kg/day PO (less than the anticipated clinical telaprevir exposure, based on AUC), body weight gain of rat pups was lower than normal . After weaning, rat pup body weight gain returned to normal. Because of the potential for adverse reactions in breastfed infants, breast-feeding must be discontinued prior to initiation of therapy. See also the Product Information for ribavirin and peginterferon alfa.

Laboratory tests

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

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

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

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

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

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

Refer to the Product Information for peginterferon alfa and ribavirin, including pregnancy testing requirements (see PRECAUTIONS: Use in pregnancy and contraception requirements).

Carcinogenicity

No carcinogenicity studies were performed with telaprevir. See also the Product Information for ribavirin and peginterferon alfa.

Genotoxicity

Telaprevir was not mutagenic nor clastogenic in a standard battery of *in vitro* (bacterial mutation and chromosomal aberration) and *in vivo* (mouse micronucleus) assays. See also the Product Information for ribavirin and peginterferon alfa.

## INTERACTIONS WITH OTHER MEDICINES

Telaprevir is primarily metabolised in the liver by CYP3A and is a P-glycoprotein (P-gp) substrate. Co-administration of INCIVO and medicinal products that induce CYP3A and/or P-gp may decrease telaprevir plasma concentrations. Co-administration of INCIVO and medicinal products that inhibit CYP3A and/or P-gp may increase telaprevir plasma concentrations. Administration of INCIVO may increase systemic exposure to medicinal products that are substrates of CYP3A or P-gp, which could increase or prolong their therapeutic effect and adverse reactions.

Interaction studies have only been performed in adults.

Associations contraindicated (see also CONTRAINDICATIONS)

*CYP3A substrates with a narrow therapeutic index*

INCIVO must not be administered concurrently with medicinal products with a narrow therapeutic window that are substrates of cytochrome P450 3A (CYP3A). Co-administration of INCIVO may increase the plasma concentration of these medicinal products, which may lead to serious and/or life-threatening adverse reactions such as cardiac arrhythmia (i.e., amiodarone, astemizole[#], bepridil, cisapride, 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., orally administered midazolam[#], triazolam), or hypotension or cardiac arrhythmia (i.e., alfuzosin and sildenafil for pulmonary arterial hypertension).

[#]Preparations with these active substances may not be approved for use in Australia

INCIVO must not be administered concurrently with any 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.

*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 should not be combined with INCIVO.

*Carbamazepine, phenytoin and phenobarbital*

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

*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.

Other combinations

Table 8 provides dosing recommendations as a result of drug interactions with INCIVO. These recommendations are based on either drug interaction studies (indicated with *) or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy.

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.

**Table 8 INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS**

| **Medicinal products by therapeutic areas** | **Effect on concentration of INCIVO or concomitant medicinal product** | **Clinical comment** |
|---|---|---|
| **ANTIARRHYTHMICS** | | |
| lidocaine<br><br>(intravenous) | ↑ lidocaine | Telaprevir may increase the concentrations of systemically administered lidocaine. Caution is warranted and clinical monitoring is recommended when intravenous lidocaine is administered for the treatment of acute ventricular arrhythmia. |

| | | |
|---|---|---|
| digoxin* | ↑ digoxin<br><br>AUC 1.85 (1.70-2.00)<br><br>$C_{max}$ 1.50 (1.36-1.65) | Concentrations of digoxin were increased when co-administered with telaprevir. The lowest dose of digoxin should be initially prescribed. The serum digoxin concentrations should be monitored and used for titration of digoxin dose to obtain the desired clinical effect. |
| **ANTIBACTERIALS** | | |
| clarithromycin<br><br>erythromycin<br><br>telithromycin<br><br>troleandomycin | ↑ telaprevir<br><br>↑ antibacterials | Concentrations of both telaprevir and the antibacterial may be increased during co-administration. Caution is warranted and clinical monitoring is recommended when co-administered with INCIVO.<br><br>QT interval prolongation and Torsade de Pointes have been reported with clarithromycin and erythromycin. QT interval prolongation has been reported with telithromycin. |
| **ANTICOAGULANT** | | |
| warfarin | ↑ or ↓ warfarin | Concentrations of warfarin may be altered when co-administered with telaprevir. It is recommended that the international normalised ratio (INR) be monitored when warfarin is co-administered with telaprevir. |
| dabigatran | ↑ dabigatran<br><br>↔ telaprevir | Caution is warranted, laboratory and clinical monitoring is recommended. |
| **ANTICONVULSANTS** | | |
| carbamazepine<br><br>phenobarbital<br><br>phenytoin | ↓ telaprevir<br><br>↑ carbamazepine<br><br>↑ or ↓ phenytoin<br><br>↑ or ↓ phenobarbital | Concentrations of the anticonvulsant may be altered and concentrations of telaprevir may be decreased. Co-administration with these agents is contraindicated. |
| **ANTIDEPRESSANTS** | | |
| escitalopram* | ↔ telaprevir<br><br>↓ escitalopram<br><br>AUC 0.65 (0.60-0.70)<br><br>$C_{max}$ 0.70 (0.65-0.76)<br><br>$C_{min}$ 0.58 (0.52-0.64) | Concentrations of escitalopram were decreased when co-administered with telaprevir. Selective serotonin reuptake inhibitors such as escitalopram have a wide therapeutic index, but doses may need to be increased when combined with telaprevir. |

| | | |
|---|---|---|
| desipramine<br><br>trazodone | ↑ desipramine<br><br>↑ trazodone | Concomitant use of trazodone or desipramine and telaprevir may increase plasma concentrations of trazodone or desipramine which may lead to adverse events such as nausea, dizziness, hypotension and syncope. If trazodone or desipramine is used with telaprevir, the combination should be used with caution and a lower dose of trazodone or desipramine should be considered. |
| **ANTIEMETICS** | | |
| domperidone | ↑ domperidone | Concentrations of domperidone may be increased when co-administered with telaprevir. Co-administration of domperidone with INCIVO should be avoided. |
| **ANTIFUNGALS** | | |
| ketoconazole*<br><br>itraconazole<br><br>posaconazole<br><br>voriconazole | ↑ ketoconazole<br><br>↑ telaprevir<br><br>AUC 1.62 (1.45-1.81)<br><br>$C_{max}$ 1.24 (1.10-1.41)<br><br>↑ itraconazole<br><br>↑ posaconazole<br><br>↑ or ↓ voriconazole | Ketoconazole increases the plasma concentrations of telaprevir. Concomitant systemic use of itraconazole or posaconazole with telaprevir may increase plasma concentration of telaprevir.<br><br>Plasma concentrations of itraconazole, ketoconazole, or posaconazole may be increased in the presence of 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.<br><br>QT interval prolongation and Torsade de Pointes have been reported with voriconazole and posaconazole. QT interval prolongation has been reported with ketoconazole.<br><br>Due to multiple enzymes involved with voriconazole metabolism, it is difficult to predict the interaction with telaprevir. Voriconazole should not be administered to patients receiving telaprevir unless an assessment of the benefit/risk ratio justifies its use. |

| | | |
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| **ANTI GOUT** | | |
| colchicine | ↑ colchicine | Patients with renal or hepatic impairment should not be given colchicine with INCIVO, due to the risk of colchicine toxicity. A reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with normal renal or hepatic function.<br><br><u>Treatment of gout flares: co-administration of colchicine in patients on INCIVO:</u><br><br>0.6 mg (1 tablet) for 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Not to be repeated before 3 days.<br><br><u>If used for prophylaxis of gout flares: co-administration of colchicine in patients on INCIVO:</u><br><br>If the original regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg once a day.<br><br>If the original regimen was 0.6 mg once a day, the regimen should be adjusted to 0.3 mg once every other day.<br><br><u>Treatment of familial Mediterranean fever (FMF): co-administration of colchicine in patients on INCIVO:</u><br><br>Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day). |
| **ANTIMYCOBACTERIAL** | | |
| rifabutin | ↓ telaprevir<br><br>↑ rifabutin | Concentrations of telaprevir may be decreased, while rifabutin concentrations may be increased during co-administration. Telaprevir may be less effective due to decreased concentrations. The concomitant use of rifabutin and telaprevir is not recommended. |

| | | |
|---|---|---|
| rifampicin* | ↓ telaprevir<br><br>AUC 0.08 (0.07-0.11)<br><br>$C_{max}$ 0.14 (0.11-0.18)<br><br>↑ rifampicin | Co-administration of rifampicin with telaprevir is contraindicated. |
| **BENZODIAZEPINES** | | |
| alprazolam* | ↑ alprazolam<br><br>AUC 1.35 (1.23-1.49)<br><br>$C_{max}$ 0.97 (0.92-1.03) | Concomitant use of alprazolam and telaprevir increased exposure to alprazolam by 35%. Clinical monitoring is warranted. |
| parenterally administered midazolam*[#] | ↑ midazolam<br><br>AUC 3.40 (3.04-3.79)<br><br>$C_{max}$ 1.02 (0.80-1.31) | Concomitant use of parenterally administered midazolam with telaprevir increased exposure to midazolam 3.4-fold. Co-administration should be done in a setting which ensures clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation.<br><br>Dose reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered.<br><br>Co-administration of oral midazolam with telaprevir is contraindicated. |
| zolpidem (non-benzodiazepine sedative)* | ↓ zolpidem<br><br>AUC 0.53 (0.45-0.64)<br><br>$C_{max}$ 0.58 (0.52-0.66) | Exposure to zolpidem was decreased by 47% when co-administered with telaprevir. Clinical monitoring and dose titration of zolpidem is recommended to achieve the desired clinical response. |
| **CALCIUM CHANNEL BLOCKERS** | | |
| amlodipine* | ↑ amlodipine<br><br>AUC 2.79 (2.58-3.01)<br><br>$C_{max}$ 1.27 (1.21-1.33) | Exposure to amlodipine was increased 2.8-fold when co-administered with telaprevir. Caution should be used and dose reduction for amlodipine should be considered. Clinical monitoring is recommended. |

| | | |
|---|---|---|
| diltiazem<br><br>felodipine<br><br>nicardipine<br><br>nifedipine<br><br>nisoldipine<br><br>verapamil | ↑ calcium channel blockers | Concentrations of other calcium channel blockers may be increased when telaprevir is co-administered.<br><br>Caution is warranted and clinical monitoring of patients is recommended. |
| **CORTICOSTEROIDS** | | |
| *Systemic*<br><br>dexamethasone | ↓ telaprevir | Systemic dexamethasone induces CYP3A and can thereby decrease telaprevir plasma concentrations. This may result in loss of therapeutic effect of telaprevir. Therefore this combination should be used with caution or alternatives should be considered. |
| *inhaled/nasal*<br><br>fluticasone<br><br>budesonide | ↑ fluticasone<br><br>↑ budesonide | Concomitant use of inhaled fluticasone or budesonide and telaprevir may increase plasma concentrations of fluticasone or budesonide resulting in significantly reduced serum cortisol concentrations. Co-administration of fluticasone or budesonide and telaprevir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects. |
| **ENDOTHELIN RECEPTOR ANTAGONIST** | | |
| bosentan | ↑ bosentan | Concentrations of bosentan may be increased when co-administered with telaprevir. Caution is warranted and clinical monitoring is recommended. |
| **HIV-ANTIVIRAL AGENTS: HIV-PROTEASE INHIBITORS (PIs)** | | |
| atazanavir/ritonavir* | ↓ telaprevir<br><br>AUC 0.80 (0.76-0.85)<br><br>$C_{max}$ 0.79 (0.74-0.84)<br><br>$C_{min}$ 0.85 (0.75-0.98)<br><br>↑ atazanavir<br><br>AUC 1.17 (0.97-1.43)<br><br>$C_{max}$ 0.85 (0.73-0.98)<br><br>$C_{min}$ 1.85 (1.40-2.44) | In a drug interaction study in healthy volunteers where telaprevir was co-administered with atazanavir/ritonavir, the steady-state telaprevir exposure was reduced by 20%, while the steady-state atazanavir exposure was increased by 17%. Clinical and laboratory monitoring for hyperbilirubinemia is recommended (see PRECAUTIONS: Laboratory tests). |

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|---|---|---|
| darunavir/ritonavir* | ↓ telaprevir<br>AUC 0.65 (0.61-0.69)<br>$C_{max}$ 0.64 (0.61-0.67)<br>$C_{min}$ 0.68 (0.63-0.74)<br>↓ darunavir<br>AUC 0.60 (0.57-0.63)<br>$C_{max}$ 0.60 (0.56-0.64)<br>$C_{min}$ 0.58 (0.52-0.63) | In a drug interaction study in healthy volunteers where telaprevir was co-administered with darunavir/ritonavir, the steady-state telaprevir exposure was reduced by 35%, while the steady-state darunavir exposure was reduced by 40%. It is not recommended to co-administer darunavir/ritonavir and telaprevir (see PRECAUTIONS for HIV/HCV patients). |
| fosamprenavir/ritonavir* | ↓ telaprevir<br>AUC 0.68 (0.63-0.72)<br>$C_{max}$ 0.67 (0.63-0.71)<br>$C_{min}$ 0.70 (0.64-0.77)<br>↓ amprenavir<br>AUC 0.53 (0.49-0.58)<br>$C_{max}$ 0.65 (0.59-0.70)<br>$C_{min}$ 0.44 (0.40-0.50) | In a drug interaction study in healthy volunteers where telaprevir was co-administered with fosamprenavir/ritonavir, the steady-state telaprevir exposure was reduced by 32%, while the steady-state amprenavir exposure was reduced by 47%. It is not recommended to co-administer fosamprenavir/ritonavir and telaprevir (see PRECAUTIONS for HIV/HCV patients). |
| lopinavir/ritonavir* | ↓ telaprevir<br>AUC 0.46 (0.41-0.52)<br>$C_{max}$ 0.47 (0.41-0.52)<br>$C_{min}$ 0.48 (0.40-0.56)<br>↔ lopinavir<br>AUC 1.06 (0.96-1.17)<br>$C_{max}$ 0.96 (0.87-1.05)<br>$C_{min}$ 1.14 (0.96-1.36) | In a drug interaction study in healthy volunteers where telaprevir was co-administered with lopinavir/ritonavir, the steady-state telaprevir exposure was reduced by 54%, while the steady-state exposure to lopinavir was not affected. It is not recommended to co-administer lopinavir/ritonavir and telaprevir (see PRECAUTIONS for HIV/HCV patients). |

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| **HIV-ANTIVIRAL AGENTS: REVERSE TRANSCRIPTASE INHIBITORS** | | |
| efavirenz* | ↓ telaprevir 1.125 mg q8h<br><br>AUC 0.82 (0.73-0.92)<br><br>$C_{max}$ 0.86 (0.76-0.97)<br><br>$C_{min}$ 0.75 (0.66-0.86)<br><br>↓ efavirenz (+ TVR 1.125 mg q8h)<br><br>AUC 0.82 (0.74-0.90)<br><br>$C_{max}$ 0.76 (0.68-0.85)<br><br>$C_{min}$ 0.90 (0.81-1.01) | In a drug interaction study in healthy volunteers where telaprevir (at a dose of 1,125 mg every 8 hours) was co-administered with efavirenz, the steady-state efavirenz exposure was reduced by 18%. The steady-state telaprevir exposure was reduced by 18% relative to telaprevir administered 750 mg every 8 hours. If co-administered, telaprevir 1,125 mg every 8 hours should be used (see PRECAUTIONS for HIV/HCV patients). |
| tenofovir disoproxil fumarate* | ↔ telaprevir<br><br>AUC 1.00 (0.94-1.07)<br><br>$C_{max}$ 1.01 (0.96-1.05)<br><br>$C_{min}$ 1.03 (0.93-1.14)<br><br>↑ tenofovir<br><br>AUC 1.30 (1.22-1.39)<br><br>$C_{max}$ 1.30 (1.16-1.45)<br><br>$C_{min}$ 1.41 (1.29-1.54) | In a drug interaction study in healthy volunteers co-administration of telaprevir and tenofovir led to an increase in tenofovir exposure by about 30%. Increased clinical and laboratory monitoring are warranted. |
| **HMG-CoA REDUCTASE INHIBITORS** | | |
| atorvastatin* | ↑ atorvastatin<br><br>AUC 7.88 (6.82-9.07)<br><br>$C_{max}$ 10.6 (8.74-12.85) | Exposure to atorvastatin was increased 8-fold when co-administered with telaprevir.<br><br>Co-administration of atorvastatin and telaprevir is contraindicated (see CONTRAINDICATIONS). |

| | | |
|---|---|---|
| **HORMONAL CONTRACEPTIVES/OESTROGEN** | | |
| ethinylestradiol*<br><br>norethindrone* | ↓ ethinylestradiol<br><br>AUC 0.72 (0.69-0.75)<br><br>$C_{max}$ 0.74 (0.68-0.80)<br><br>$C_{min}$ 0.67 (0.63-0.71)<br><br>↔ norethindrone<br><br>AUC 0.89 (0.86-0.93)<br><br>$C_{max}$ 0.85 (0.81-0.89)<br><br>$C_{min}$ 0.94 (0.87-1.00) | Exposure to ethinylestradiol was decreased by 28% when co-administered with telaprevir. Alternative methods of non-hormonal contraception should be used when hormonal contraceptives are co-administered with telaprevir.<br><br>Patients using oestrogens as hormone replacement therapy should be clinically monitored for signs of oestrogen deficiency.<br><br>Refer to PRECAUTIONS: Use in pregnancy and contraception requirements. |
| **IMMUNOSUPPRESSANTS** | | |
| cyclosporine*<br><br>sirolimus<br><br>tacrolimus* | ↑ cyclosporine<br><br>AUC 4.64 (3.90-5.51)<br><br>$C_{max}$ 1.32 (1.08-1.60)<br><br>↑ sirolimus<br><br>↑ tacrolimus<br><br>AUC 70.3 (52.9-93.4)<br><br>$C_{max}$ 9.35 (6.73-13.0) | Plasma concentrations of cyclosporine and tacrolimus are markedly increased when co-administered with telaprevir. Plasma concentration of sirolimus may be increased when co-administered with telaprevir, though this has not been studied. Significant dose reductions and prolongation of the dosing interval of the immunosuppressant to achieve the desired blood levels should be anticipated. Close monitoring of the immunosuppressant blood levels, and frequent assessments of renal function and immunosuppressant related side effects are recommended when co-administered with telaprevir. Tacrolimus may prolong the QT interval. The use of INCIVO in organ transplant candidates or patients is not recommended (see PRECAUTIONS: Organ transplant patients). |
| **INHALED BETA AGONIST** | | |
| salmeterol | ↑ salmeterol | Concentrations of salmeterol may be increased when co-administered with telaprevir. Concurrent administration of salmeterol and telaprevir is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia. |

| | | |
|---|---|---|
| **NARCOTIC ANALGESIC** | | |
| methadone* | ↓ R-methadone<br><br>AUC 0.71 (0.66-0.76)<br><br>$C_{max}$ 0.71 (0.66-0.76)<br><br>$C_{min}$ 0.69 (0.64-0.75) | Concentrations of methadone were reduced by 29% when co-administered with telaprevir. No adjustment of methadone dose is required when initiating co-administration of telaprevir. However, clinical monitoring is recommended as the dose of methadone during maintenance therapy may need to be adjusted in some patients.<br><br>QT interval prolongation and Torsade de Pointes have been reported with methadone. |
| **PDE-5 INHIBITORS** | | |
| sildenafil<br><br>tadalafil<br><br>vardenafil | ↑ PDE-5 inhibitors | Concentrations of PDE-5 inhibitors may be increased when co-administered with telaprevir. 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.<br><br>Co-administration of sildenafil or tadalafil and telaprevir in the treatment of pulmonary arterial hypertension is contraindicated. |
| **PROTON PUMP INHIBITORS** | | |
| esomeprazole* | ↔ telaprevir<br><br>AUC 0.98 (0.91-1.05)<br><br>$C_{max}$ 0.95 (0.86-1.06) | Since there was no effect of esomeprazole on the plasma concentrations of telaprevir, proton pump inhibitors can be used without dose modification. |
| * dosing recommendations are based on drug interaction studies<br><br>#Preparations with these active substances may not be approved for use in Australia | | |

*Paediatric population*

Interaction studies have only been performed in adults.

Effect on ability to drive or operate machinery

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

# ADVERSE EFFECTS

Clinical Trial Data

### *a. Summary of the safety profile*

Throughout this section, adverse reactions are reported. Adverse drug reactions (ADRs) are adverse events that were considered to be reasonably associated with the use of INCIVO in combination with peginterferon alfa and ribavirin-based on the comprehensive assessment of the available adverse event information. A causal relationship with INCIVO in combination with peginterferon alfa and ribavirin cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a medicinal product cannot be directly compared to rates in the clinical trials of another medicinal product and may not reflect the rates observed in clinical practice.

The overall safety profile of INCIVO is based on all available pooled Phase 2 and 3 clinical trial data (both controlled and uncontrolled) containing 2,641 subjects who received INCIVO combination treatment.

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

The incidence of ADRs of at least Grade 2 in severity was higher in the INCIVO group than in the placebo group.

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

### *b. Tabulated summary of adverse reactions*

ADRs to INCIVO of at least moderate intensity (≥Grade 2) are presented in Table 9.

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

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

| **System Organ Class**<br><br>Frequency category | **Adverse Drug Reaction** | **INCIVO, peginterferon alfa, and ribavirin combination therapy**<br><br>N = 1346 | **Placebo/peginterferon alfa and ribavirin**<br><br>N = 764 |
|---|---|---|---|
| ***Infections and infestations*** | | | |
| uncommon | Oral candidiasis | 9 (0.7) | 1 (0.1) |
| ***Blood and lymphatic system disorders*** | | | |
| very common | Anaemia | 282 (21.0) | 65 (8.5) |
| ***Endocrine disorders*** | | | |
| uncommon | Hypothyroidism | 5 (0.4) | 0 |
| ***Metabolism and nutrition disorders*** | | | |
| uncommon | Gout | 3 (0.2) | 0 |
| ***Nervous system disorders*** | | | |
| common | Dysgeusia | 16 (1.2) | 3 (0.4) |
| | Syncope | 13 (1.0) | 3 (0.4) |
| ***Eye disorders*** | | | |
| uncommon | Retinopathy | 3 (0.2) | 0 |
| ***Gastrointestinal disorders*** | | | |
| common | Nausea | 128 (9.5) | 43 (5.6) |
| | Diarrhoea | 84 (6.2) | 26 (3.4) |
| | Haemorrhoids | 56 (4.2) | 3 (0.4) |
| | Vomiting | 54 (4.0) | 18 (2.4) |
| | Proctalgia | 47 (3.5) | 5 (0.7) |
| | Anal pruritus | 17 (1.3) | 0 |
| uncommon | Rectal haemorrhage | 10 (0.7) | 3 (0.4) |
| | Anal fissure | 9 (0.7) | 0 |
| | Proctitis | 3 (0.2) | 0 |

| | | | |
|---|---|---|---|
| ***Skin and subcutaneous tissue disorders*** | | | |
| very common | Pruritus<br><br>Rash | 219 (16.3)<br><br>216 (16.0) | 32 (4.2)<br><br>37 (4.8) |
| common | Eczema | 25 (1.9) | 5 (0.7) |
| uncommon | Swelling face<br><br>Drug rash with eosinophilia and systemic symptoms<br><br>Urticaria<br><br>Exfoliative rash | 7 (0.5)<br><br>6 (0.4)<br><br><br><br>3 (0.2)<br><br>2 (0.1) | 0<br><br>0<br><br><br><br>1 (0.1)<br><br>0 |
| ***General disorders and administration site conditions*** | | | |
| uncommon | Oedema peripheral | 5 (0.4) | 0 |

ADRs related to laboratory findings were thrombocytopenia, lymphopenia, hyperuricaemia, hypokalaemia, hyperbilirubinaemia, and blood creatinine increased (see ADVERSE EFFECTS:

Laboratory abnormalities).

Stevens-Johnson syndrome (rare; < 0.1%) has been reported during clinical experience with INCIVO that resolved after treatment discontinuation (see PRECAUTIONS).

*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 subjects treated with INCIVO combination treatment from the pooled data from the placebo-controlled Phase 2 and Phase 3 trials are presented in Table 10:

**Table 10: Laboratory abnormalities, DAIDS Grade ≥ 2, considered adverse drug reactions, in HCV-infected subjects**

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

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

| **Laboratory parameter**<br><br>**%** | **DAIDS toxicity range*** | **INCIVO, peginterferon alfa, and ribavirin combination therapy** | **peginterferon alfa and ribavirin** |
|---|---|---|---|
| Absolute lymphocyte count, decrease | | | |
| Grade 2 | 500-599/$mm^3$ | 13.1% | 5.6% |
| Grade 3 | 350-499/$mm^3$ | 11.8% | 4.4% |
| Grade 4 | <350/$mm^3$ | 4.8% | <1% |
| Creatinine, increase | | | |
| Grade 2 | 1.4-1.8 x ULN | <1% | <1% |
| Grade 3 | 1.9-3.4 x ULN | <1% | 0% |
| Haemoglobin, decrease | | | |
| Grade 2 | 9.0-9.9 g/dl or any decrease 3.5-4.4 g/dl | 27.0% | 27.0% |
| Grade 3 | 7.0-8.9 g/dl or any decrease ≥4.5 g/dl | 51.1% | 24.0% |
| Grade 4 | <7.0 g/dl | 1.1% | 0% |
| Hyperbilirubinemia | | | |
| Grade 2 | 1.6-2.5 x ULN | 13.6% | 6.8% |
| Grade 3 | 2.6-5.0 x ULN | 3.6% | 1.1% |
| Grade 4 | >5.0 x ULN | <1% | <1% |
| Hyperuricaemia | | | |
| Grade 2 | 10.1-12.0 mg/dl | 17.9% | 2.6% |
| Grade 3 | 12.1-15.0 mg/dl | 4.6% | 0.5% |
| Grade 4 | >15.0 mg/dl | 1.1% | 0% |
| Hypokalaemia | | | |
| Grade 2 | 2.5-2.9 mEq/l | 1.6% | 0.3% |
| Grade 3 | 2.0-2.4 mEq/l | 0% | 0% |
| Low-density lipoprotein, increase | | | |
| Grade 2 | 4.13-4.90 mmol/l<br><br>160-190 mg/dl | 6.9% | 2.1% |
| Grade 3 | ≥4.91 mmol/l<br><br>≥191 mg/dl | 2.5% | 0.4% |
| Platelet count, decrease | | | |
| Grade 2 | 50,000-99,999/$mm^3$ | 24.4% | 15.6% |

| | | | |
|---|---|---|---|
| Grade 3 | 25,000-49,999/$mm^3$ | 2.8% | <1% |
| Grade 4 | <25,000/$mm^3$ | <1% | <1% |
| Total cholesterol, increase | | | |
| Grade 2 | 6.20-7.77 mmol/l<br>240-300 mg/dl | 15.4% | 1.6% |
| Grade 3 | >7.77 mmol/l<br>>300 mg/dl | 2.0% | <1% |

ULN = Upper Limit of Normal

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

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

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

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

***c. Description of selected adverse reactions***

*Rash*

Severe rash, Stevens-Johnson Syndrome and DRESS have been reported with INCIVO (see PRECAUTIONS). 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 PRECAUTIONS 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. Erythropoiesis-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 PRECAUTIONS).

*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.

## DOSAGE AND ADMINISTRATION

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

INCIVO, 750 mg (two 375 mg film-coated tablets) should be taken orally every 8 hours with food (the total daily dose is 6 tablets (2,250 mg)). Patients should be instructed to swallow the tablets whole (e.g., patients should not chew, break or dissolve the tablet).

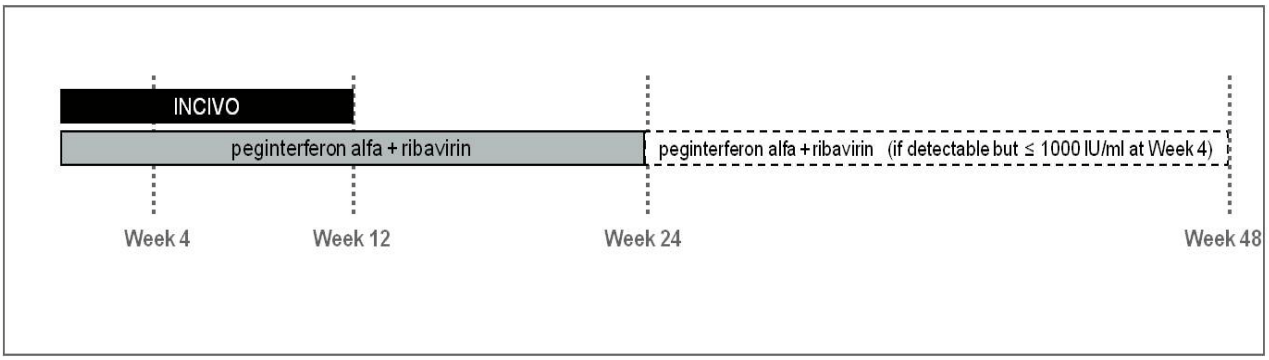
For specific dosage instructions for peginterferon alfa and ribavirin, consult the Product Information for these medicinal products.

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

Treatment with INCIVO must be initiated in combination with peginterferon alfa and ribavirin and administered for 12 weeks (see Figure 1 and Table 11).

- Patients with undetectable HCV RNA at weeks 4 and 12 receive an additional 12 weeks of peginterferon alfa and ribavirin alone for a total treatment duration of 24 weeks.
- Patients with detectable HCV RNA (but ≤ 1000 IU/mL) at week 4 receive an additional 36 weeks of peginterferon alfa and ribavirin alone for a total treatment duration of 48 weeks.
- For all patients with cirrhosis irrespective of undetectable HCV RNA at weeks 4 or 12, an additional 36 weeks of peginterferon alfa and ribavirin alone for a total treatment duration of 48 weeks is recommended (see PHARMACOLOGY - Pharmacodynamics).

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



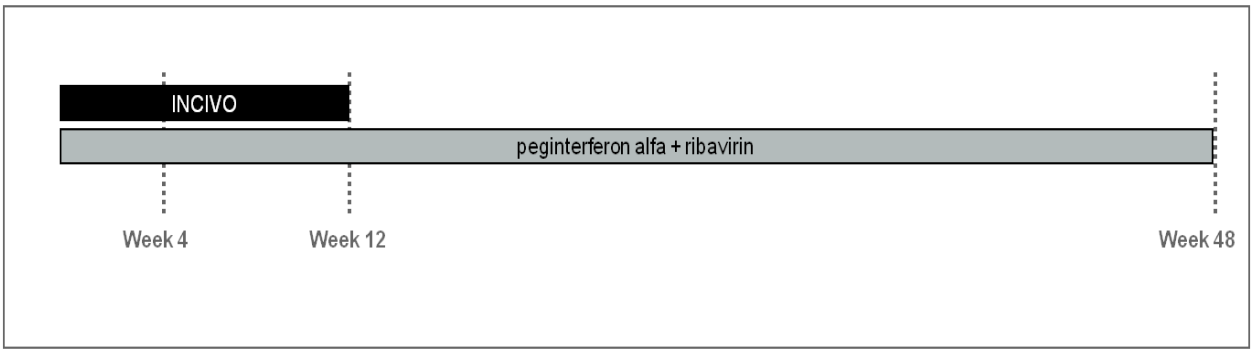

HCV RNA levels should be monitored by a quantitative assay at week 4 and a qualitative assay at week 12 to determine treatment duration. See Table 11 for Guidelines for Discontinuation of INCIVO, Peginterferon Alfa, and Ribavirin Treatment.

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.

*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 and Table 11).

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




HCV RNA levels should be monitored by a quantitative assay at week 4 and and a qualitative assay at week 12 to determine treatment duration. See Table 11 for Guidelines for Discontinuation of INCIVO, Peginterferon Alfa, and Ribavirin Treatment.

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 > 1000 IU/ml at week 4 discontinue INCIVO peginterferon alfa and ribavirin. Patients with detectable HCV RNA at week 12 or week 24 should discontinue peginterferon alfa and ribavirin (refer to Table 11).

**Table 11: Guidelines for discontinuation of INCIVO, Peginterferon Alfa, and Ribavirin treatment***

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

*These guidelines, including the use of a quantitative assay at week 4 and a qualitative assay at week 12, still apply if telaprevir is discontinued for an adverse event before week 12

INCIVO must be dosed with peginterferon alfa and ribavirin to prevent treatment failure.

The dose of INCIVO must not be reduced to prevent treatment failure.

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

There is no data on re-treating patients who have failed a course of HCV NS3-4A protease inhibitor-based therapy (see PHARMACOLOGY - Pharmacodynamics) with INCIVO.

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

In case a dose of INCIVO is missed within 4 hours of the time it is usually taken, patients should be instructed to take the prescribed dose of INCIVO with food as soon as possible. If the missed dose is noticed more than 4 hours after the time INCIVO should be taken, the missed dose should be skipped and the patient should resume the normal dosing schedule.

Special populations

*Renal impairment*

There are no clinical data on the use of INCIVO in HCV patients with moderate or severe renal impairment (CrCl ≤ 50 ml/min). No dose adjustment is recommended for INCIVO in HCV patients with mild, moderate or severe renal impairment (see PRECAUTIONS and PHARMACOLOGY - Pharmacokinetics). Ribavirin is contraindicated, or used with extreme cautions in patients with CrCl < 50 ml/min (see the Product Information for ribavirin).

Hepatic impairment

INCIVO is not recommended in patients with moderate to severe hepatic impairment (Child-Pugh B or C, score ≥ 7) or decompensated liver disease (see PRECAUTIONS). 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 Product Information for peginterferon alfa and ribavirin which are contraindicated in Child-Pugh score ≥ 6.

Elderly

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

Paediatric population

The safety and efficacy of INCIVO in children aged < 18 years have not yet been established.

No data are available.

## OVERDOSAGE

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.

Management of Overdosage

No specific antidote is available for overdose with INCIVO. Treatment of overdose with INCIVO consists of general supportive measures including monitoring of ECG and vital signs and observation of the clinical status of the patient. Administration of activated charcoal within one or two hours after ingestion may be used to aid in the removal of unabsorbed active substance.

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

Contact the Poisons Information Centre (telephone no. 13 11 26) for advice on management of overdosage.

## PRESENTATION AND STORAGE CONDITIONS

375 mg: Yellow, caplet-shaped, film-coated tablets of approximately 20 mm in length, marked with “T375” on one side.
Pack size: Bottle pack of 42 tablets.

Store below 25$^{o}$C.

## NAME AND ADDRESS OF THE SPONSOR

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## POISON SCHEDULE OF THE MEDICINE

S4 - Prescription Only Medicine

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG):
6 March 2012

Date of most recent amendment:

23 May 2012