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

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

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

Table 5: Response rates: Study C211

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

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

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

[b] On-treatment-virologic failure includes patients who met a protocol-defined virologic stopping rule and/or had viral breakthrough.

[c] Relapse was defined as having less than 25 IU/ml at the planned end of treatment followed by HCV RNA ≥ 25 IU/ml at the last observation within the SVR follow-up visit window. The denominator when calculating the relapse rate represents the number of patients with end-of-treatment response (HCV RNA < 25 IU/ml).

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

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

Table 6: SVR rates for patient subgroups: Study C211

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

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

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

Study 108 (ADVANCE)
Study 108 was a randomised, double-blind, parallel-group, placebo-controlled, Phase 3 study conducted in treatment-naïve patients. INCIVO was given for the first 8 weeks of treatment (T8/PR regimen) or the first 12 weeks of treatment (T12/PR regimen) in combination with peginterferon alfa-2a and ribavirin for either 24 or 48 weeks. Patients who had undetectable HCV RNA (target not detected) at weeks 4 and 12 received 24 weeks of peginterferon alfa-2a and ribavirin treatment, and patients who did not have undetectable HCV RNA (target not detected) at week 4 and week 12 received 48 weeks of peginterferon alfa-2a and ribavirin treatment. The control regimen (Pbo/PR) had a fixed treatment duration of 48 weeks, with telaprevir-matching placebo for the first 12 weeks and peginterferon alfa-2a and ribavirin for 48 weeks.

The 1,088 enrolled patients had a median age of 49 years (range: 18 to 69); 58% of the patients were male; 23% had a body mass index ≥ 30 kg/m^2; 9% were Black; 11% were Hispanic or Latino; 77% had baseline HCV RNA levels ≥ 800,000 IU/ml; 15% had bridging fibrosis; 6% had cirrhosis; 59% had HCV genotype 1a; and 40% had HCV genotype 1b.

The SVR rate for the T8/PR group was 72% (261/364) ($P < 0.0001$ compared to Pbo/PR48 group). Table 7 shows the response rates for the recommended T12/PR and the Pbo/PR48 groups.

Table 7: Response rates: Study 108

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

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

[a] $P < 0.0001$, T12/PR compared to Pbo/PR48. The difference in SVR rates (95% confidence interval) between the T12/PR and Pbo/PR groups was 33 (26, 39).

[b] 95% confidence interval

SVR rates were higher (absolute difference of at least 28%) for the T12/PR group than for the Pbo/PR48 group across subgroups by sex, age, race, ethnicity, body mass index, HCV genotype subtype, baseline HCV RNA (< 800,000, ≥ 800,000 IU/ml), and extent of liver fibrosis. Table 8 shows SVR rates for patient subgroups.

Table 8: SVR rates for patient subgroups: Study 108

Subgroup	**T12/PR**	**Pbo/PR**
Men	78% (166/214)	46% (97/211)
45 to ≤ 65 years of age	73% (157/214)	39% (85/216)
Black	62% (16/26)	29% (8/28)
Hispanic Latino	77% (27/35)	39% (15/38)

BMI ≥ 30 kg/m^2	73% (56/77)	44% (38/87)
Baseline HCV RNA ≥ 800,000 IU/ml	77% (215/281)	39% (109/279)
HCV genotype 1a	75% (162/217)	43% (90/210)
HCV genotype 1b	84% (119/142)	51% (76/149)
Baseline liver fibrosis		
No fibrosis, minimal fibrosis, or portal fibrosis	82% (237/290)	49% (140/288)
Bridging fibrosis	63% (33/52)	35% (18/52)
Cirrhosis	71% (15/21)	38% (8/21)

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

Study 111 (ILLUMINATE)
Study 111 was a Phase 3, randomised, open label study conducted in treatment-naïve patients. The study was designed to compare SVR rates in patients with undetectable HCV RNA (target not detected) at weeks 4 and 12 who were treated with INCIVO for 12 weeks in combination with peginterferon alfa-2a and ribavirin for either 24 weeks (T12/PR24 regimen) or 48 weeks (T12/PR48 regimen). Patients with undetectable HCV RNA (target not detected) at weeks 4 and 12 were randomised at week 20 to receive either 24 weeks or 48 weeks of peginterferon alfa-2a and ribavirin treatment. The primary assessment was an evaluation of non-inferiority, using a margin of -10.5% of the 24-week regimen compared to the 48-week regimen in patients with undetectable HCV RNA (target not detected) at weeks 4 and 12.

The 540 enrolled patients had a median age of 51 years (range 19 to 70); 60% of the patients were male; 32% had a body mass index ≥ 30 kg/m^2; 14% were Black; 10% were Hispanic or Latino; 82% had baseline HCV RNA levels > 800,000 IU/ml; 16% had bridging fibrosis; 11% had cirrhosis; 72% had HCV genotype 1a; and 27% had HCV genotype 1b.

A total of 352 (65%) patients had undetectable HCV RNA (target not detected) at weeks 4 and 12. Table 9 shows response rates. In patients who had undetectable HCV RNA (target not detected) at weeks 4 and 12, there was no additional benefit to extending peginterferon alfa-2a and ribavirin treatment to 48 weeks (difference in SVR rates of 2%; 95% confidence interval: -4%, 8%).

Table 9: Response rates: Study 111

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

T12/PR24: INCIVO for 12 weeks with peginterferon alfa-2a and ribavirin for 24 weeks;
T12/PR48: INCIVO for 12 weeks with peginterferon alfa-2a and ribavirin for 48 weeks

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

[b] 95% confidence interval

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

Table 10: SVR rates by extent of liver fibrosis at baseline: Study 111			
	Patients with undetectable HCV RNA (target not detected) at weeks 4 and 12		T12/PR All Patients[a]
Subgroup	T12/PR24	T12/PR48	
No fibrosis, minimal fibrosis, or portal fibrosis	96% (119/124)	91% (115/127)	77% (302/391)
Bridging fibrosis	95% (19/20)	86% (18/21)	74% (65/88)
Cirrhosis	61% (11/18)	92% (11/12)	51% (31/61)

T12/PR24: INCIVO for 12 weeks with peginterferon alfa-2a and ribavirin for 24 weeks;
T12/PR48: INCIVO for 12 weeks with peginterferon alfa-2a and ribavirin for 48 weeks

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

Efficacy in previously treated adults

Study C216 (REALIZE)

Study C216 was a randomised, double-blind, placebo-controlled, Phase 3 study conducted in patients who did not achieve SVR with prior treatment with peginterferon alfa-2a and ribavirin or peginterferon alfa-2b and ribavirin. The study enrolled prior relapsers (patients with HCV RNA undetectable at end of treatment with a pegylated interferon-based regimen but HCV RNA detectable within 24 weeks of treatment follow-up) and prior non-responders (patients who did not have undetectable HCV RNA levels during or at the end of a prior course of at least 12 weeks of treatment). The non-responder-population was comprised of 2 subgroups: prior partial responders (greater than or equal to 2 $\log_{10}$ reduction in HCV RNA at week 12, but not achieving HCV RNA undetectable at end of treatment with a peginterferon and ribavirin) and prior null responders (less than 2 $\log_{10}$ reduction in HCV RNA at week 12 of prior treatment with peginterferon and ribavirin).

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

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

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

Table 11: Response rates: Study C216		
Treatment outcome	T12/PR48 % (n/N)	Pbo/PR48 % (n/N)
SVR		
Prior relapsers[a]	84% (122/145) (77%, 90%)[b]	22% (15/68) (13%, 34%)[b]
Prior partial responders[a]	61% (30/49) (46%, 75%)[b]	15% (4/27) (4%, 34%)[b]
Prior null responders[a]	31% (22/72) (20%, 43%)[b]	5% (2/37) (1%, 18%)[b]
HCV RNA < 25 IU/ml at End of Treatment		
Prior relapsers	87% (126/145)	63% (43/68)

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

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

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

[b] 95% confidence interval

For all populations in the study (prior relapsers, prior partial responders, and prior null responders), SVR rates were higher for the T12/PR group than for the Pbo/PR48 group across subgroups by sex, age, race, ethnicity, body mass index, HCV genotype subtype, baseline HCV RNA level, and extent of liver fibrosis. Table 12 shows SVR rates by extent of liver fibrosis.

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

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

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

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

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

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

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

Study 106 and Study 107

Study 106 was a randomised, double-blind, placebo-controlled, Phase 2 study that enrolled patients who had failed prior treatment with peginterferon alfa-2a and ribavirin or peginterferon alfa-2b and ribavirin. Among prior relapsers in the T12/PR24 treatment group who had undetectable HCV RNA

(target not detected) at weeks 4 and 12 of treatment, the SVR rate was 89% (25/28) and the relapse rate was 7%.

Study 107 was an open label, rollover study for patients who were treated in the control group (placebo, peginterferon alfa-2a, and ribavirin) of a Phase 2 study of telaprevir and who did not achieve SVR in the Phase 2 study. Among prior relapsers in the T12/PR24 treatment group who had undetectable HCV RNA (target not detected) at week 4 and 12 of treatment, the SVR rate was 100% (24/24).

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

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

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

Table 14: Pooled response rates: Study C208

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

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

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

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

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

<u>*Efficacy in adults with HCV/HIV-1 co-infection*</u>
Study 110
Study 110 was a phase II randomised, double-blind, placebo-controlled study conducted in patients with chronic genotype 1 HCV/HIV co-infection who were treatment-naïve for hepatitis C. Patients were either not on antiretroviral therapy (CD4 count ≥ 500 cells/mm^3), or had stable controlled HIV (HIV RNA < 50 copies/ml, CD4 count ≥ 300 cells/mm^3) being treated with efavirenz or atazanavir/ritonavir in combination with tenofovir disoproxil fumarate and emtricitabine or lamivudine. Patients were randomised to 12 weeks of INCIVO (750 mg every 8 hours if taken in

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

Table 15: Response Rates: Study 110

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

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

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

Study HPC3008

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

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

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

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

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

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

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

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

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

Liver transplant recipients

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

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

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

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

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

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

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

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

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

Clinical Studies Examining QT Interval

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

Paediatric population

No clinical studies have been performed in paediatric patients.

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

5.2 Pharmacokinetic properties

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

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

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

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

The exposure to telaprevir was increased by 20% when taken following a high-fat caloric meal (56 g fat, 928 kcal) compared to an intake following a standard normal caloric meal (21 g fat, 533 kcal). When compared to administration following a standard normal caloric meal, exposure (AUC) decreased by 73% when telaprevir was taken on an empty stomach, by 26% following a low-calorie high-protein meal (9 g fat, 260 kcal), and by 39% following a low-calorie low-fat meal (3.6 g fat, 249 kcal). Therefore, telaprevir should be taken with food.

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

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

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

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

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

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

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

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

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

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

Elimination
Following administration of a single oral dose of 750 mg ^{14}C-telaprevir in healthy subjects, 90 % of total radioactivity was recovered in faeces, urine and expired air within 96 hours post-dose. The median recovery of the administered radioactive dose was approximately 82% in the faeces, 9% in exhaled air and 1% in urine. The contribution of unchanged ^{14}C – telaprevir and VRT-127394 towards total radioactivity recovered in faeces was 31.8% and 18.7%, respectively.

After oral administration, the apparent total clearance (Cl/F) was estimated to be 32.4 l/h with an inter-individual variability of 27.2%. The mean elimination half-life after single-dose oral administration of telaprevir 750 mg typically ranged from about 4.0 to 4.7 hours. At steady-state, the effective half-life is about 9-11 hours.

Linearity/non-linearity
The exposure (AUC) to telaprevir increased slightly greater than proportionally to the dose after single-dose administration of 375 up to 1,875 mg with food, possibly due to saturation of metabolic pathways or efflux transporters.

An increase in dose from 750 mg every 8 hours to 1,875 mg every 8 hours in a multiple-dose study resulted in a less than proportional increase (i.e., about 40%) in telaprevir exposure.

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

Renal impairment
The pharmacokinetics of telaprevir were assessed after administration of a single dose of 750 mg to HCV-negative subjects with severe renal impairment (CrCl < 30 ml/min). The mean telaprevir C_{max} and AUC were 10% and 21% greater, respectively, compared to healthy subjects (see section 4.2).

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

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

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

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

5.3 Preclinical safety data

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

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

Impairment of fertility
Telaprevir had no effects on fertility or fecundity when evaluated in rats.

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

Excretion into milk
When administered to lactating rats, levels of telaprevir and its major metabolite were higher in milk compared to those observed in plasma. Rat offspring exposed to telaprevir in utero showed normal body weight at birth. However, when fed via milk from telaprevir-treated dams, body weight gain of rat pups was lower than normal (likely due to taste aversion). After weaning, rat pup body weight gain returned to normal.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
hypromellose acetate succinate
calcium hydrogen phosphate (anhydrous)
microcrystalline cellulose
silica colloidal anhydrous
sodium lauryl sulphate
croscarmellose sodium
sodium stearyl fumarate

Tablet film-coat
polyvinyl alcohol

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle containing 42 film-coated tablets and fitted with polypropylene (PP) child resistant closure and induction seal liner. Desiccant (one pouch or two pouches) is added.

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Janssen Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 September 2011

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

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

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

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

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

- **Risk Management Plan (RMP)**

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

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

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

- **Additional risk minimisation measures**

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

The Physician Leaflet should contain the following key elements:

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (1-bottle pack)

1. NAME OF THE MEDICINAL PRODUCT

INCIVO 375 mg film-coated tablets
telaprevir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 375 mg of telaprevir.

3. LIST OF EXCIPIENTS

Contains sodium.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

42 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/11/720/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

incivo 375 mg

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL (1-bottle pack)

1. NAME OF THE MEDICINAL PRODUCT

INCIVO 375 mg film-coated tablets
telaprevir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 375 mg of telaprevir.

3. LIST OF EXCIPIENTS

Contains sodium.

4. PHARMACEUTICAL FORM AND CONTENTS

42 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not remove the desiccant.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/11/720/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (4-bottle pack)

1. NAME OF THE MEDICINAL PRODUCT

INCIVO 375 mg film-coated tablets
telaprevir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 375 mg of telaprevir.

3. LIST OF EXCIPIENTS

Contains sodium.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

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

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/11/720/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

incivo 375 mg

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL (4-bottle pack)

1. NAME OF THE MEDICINAL PRODUCT

INCIVO 375 mg film-coated tablets
telaprevir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 375 mg of telaprevir.

3. LIST OF EXCIPIENTS

Contains sodium.

4. PHARMACEUTICAL FORM AND CONTENTS

42 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not remove the desiccant.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/11/720/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

B. PACKAGE LEAFLET

Package leaflet: Information for the user

INCIVO 375 mg film-coated tablets
telaprevir

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

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

What is in this leaflet

1. What INCIVO is and what it is used for
2. What you need to know before you take INCIVO
3. How to take INCIVO
4. Possible side effects
5. How to store INCIVO
6. Contents of the pack and other information

1. What INCIVO is and what it is used for

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

2. What you need to know before you take INCIVO

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3. How to take INCIVO

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

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

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

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

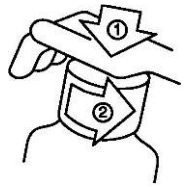
break, or dissolve the tablets before you swallow them. Tell your health care provider if you have problems swallowing whole tablets.

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

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

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

Removing the child resistant cap



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

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

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

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

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

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

4. Possible side effects

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

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

Contact your doctor immediately if you get a skin rash.

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

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

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

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

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

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

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

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

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

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

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

5. How to store INCIVO

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

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

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

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

6. Contents of the pack and other information

What INCIVO contains
The active substance is telaprevir. Each tablet of INCIVO contains 375 mg of telaprevir.
The other ingredients are:
Tablet core
hypromellose acetate succinate, calcium hydrogen phosphate (anhydrous), microcrystalline cellulose, silica colloidal anhydrous, sodium lauryl sulphate, croscarmellose sodium, sodium stearyl fumarate

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

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

Marketing Authorisation Holder
Janssen Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

Manufacturer
Janssen-Cilag SpA,
Via C. Janssen,
04100 Borgo San Michele,
Latina, Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Janssen-Cilag NV
Antwerpseweg 15-17
B-2340 Beerse
Tel/Tél: +32 14 64 94 11

Lietuva
UAB „Johnson & Johnson“
Geležinio Vilko g. 18A
LT-08104 Vilnius
Tel: +370 5 278 68 88

България
„Джонсън & Джонсън България” ЕООД
ж.к. Младост 4
Бизнес Парк София, сграда 4
София 1766
Тел.: +359 2 489 94 00

Luxembourg/Luxemburg
Janssen-Cilag NV
Antwerpseweg 15-17
B-2340 Beerse
Belgique/Belgien
Tél/Tel: +32 14 64 94 11

Česká republika
Janssen-Cilag s.r.o.
Karla Engliše 3201/06
CZ-150 00 Praha 5 - Smíchov
Tel: +420 227 012 227

Magyarország
Janssen-Cilag Kft.
Nagyenyed u. 8-14
H-Budapest, 1123
Tel: +36 1 884 2858

Danmark
Janssen-Cilag A/S
Bregnerødvej 133
DK-3460 Birkerød
Tlf: +45 45 94 82 82

Malta
AM MANGION LTD.
Mangion Building, Triq Ġdida fi Triq Valletta
MT-Ħal-Luqa LQA 6000
Tel: +356 2397 6000

Deutschland
Janssen-Cilag GmbH
Johnson & Johnson Platz 1
D-41470 Neuss
Tel: +49 2137 955-955

Nederland
Janssen-Cilag B.V.
Dr. Paul Janssenweg 150
NL-5026 RH Tilburg
Tel: +31 13 583 73 73

Eesti
Janssen-Cilag Polska Sp. z o.o. Eesti filiaal
Lõõtsa 2
EE-11415 Tallinn
Tel: +372 617 7410

Norge
Janssen-Cilag AS
Postboks 144
NO-1325-Lysaker
Tlf: +47 24 12 65 00

Ελλάδα
Janssen-Cilag Φαρμακευτική Α.Ε.Β.Ε.
Λεωφόρος Ειρήνης 56
GR-151 21 Πεύκη, Αθήνα
Τηλ: +30 210 80 90 000

España
Janssen-Cilag, S.A.
Paseo de las Doce Estrellas, 5-7
E-28042 Madrid
Tel: +34 91 722 81 00

France
Janssen-Cilag
1, rue Camille Desmoulins, TSA 91003
F-92787 Issy Les Moulineaux, Cedex 9
Tél: 0 800 25 50 75 / +33 1 55 00 40 03

Hrvatska
Johnson & Johnson S.E. d.o.o.
Oreškovićeva 6h
10010 Zagreb
Tel: +385 1 6610 700

Ireland
Janssen-Cilag Ltd.
50-100 Holmers Farm Way
High Wycombe
Buckinghamshire HP12 4EG
United Kingdom
Tel: +44 1 494 567 444

Ísland
Janssen-Cilag AB
c/o Vistor hf.
Hörgatúni 2
IS-210 Garðabær
Sími: +354 535 7000

Italia
Janssen-Cilag SpA
Via M Buonarroti, 23
I-20093 Cologno Monzese MI
Tel: +39 02 2510 1

Κύπρος
Βαρνάβας Χατζηπαναγής Λτδ,
Λεωφόρος Γιάννου Κρανιδιώτη 226
Λατσιά
CY-2234 Λευκωσία
Τηλ: +357 22 207 700

Österreich
Janssen-Cilag Pharma GmbH
Vorgartenstraße 206B
A-1020 Wien
Tel: +43 1 610 300

Polska
Janssen-Cilag Polska Sp. z o.o.
ul. Iłżecka 24
PL-02-135 Warszawa
Tel: +48 22 237 60 00

Portugal
Janssen-Cilag Farmacêutica, Lda.
Estrada Consiglieri Pedroso, 69 A
Queluz de Baixo
PT-2734-503 Barcarena
Tel: +351 21 43 68 835

România
Johnson & Johnson România SRL
Str. Tipografilor nr. 11-15
Clădirea S-Park, Corp A2, Etaj 5
013714 Bucureşti, ROMÂNIA
Tel: +40 21 207 1800

Slovenija
Johnson & Johnson d.o.o.
Šmartinska cesta 53
SI-1000 Ljubljana
Tel: +386 1 401 18 30

Slovenská republika
Johnson & Johnson s.r.o.
CBC III, Karadžičova 12
SK-821 08 Bratislava
Tel: +421 232 408 400

Suomi/Finland
Janssen-Cilag Oy
Vaisalantie/Vaisalavägen 2
FI-02130 Espoo/Esbo
Puh/Tel: +358 207 531 300

Sverige
Janssen-Cilag AB
Box 7073
SE-192 07 Sollentuna
Tel: +46 8 626 50 00

Latvija
Janssen-Cilag Polska Sp. z o.o. filiāle Latvijā
Mūkusalas iela 101
Rīga, LV-1004
Tel: +371 678 93561

United Kingdom
Janssen-Cilag Ltd.
50-100 Holmers Farm Way
High Wycombe
Buckinghamshire HP12 4EG - UK
Tel: +44 1 494 567 444

This leaflet was last revised in {MM/YYYY}.

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