75% had no cirrhosis (METAVIR fibrosis score F0-3) and 25% had cirrhosis (METAVIR fibrosis score F4); 78% had HCV genotype 1a of which 45% carried Q80K at baseline, and 22% had HCV genotype 1b; 86% had non-CC *IL28B* alleles (CT or TT); 76% were prior null responders to peginterferon alfa and ribavirin, and 24% were treatment-naïve.

Table 14 shows the response rates for patients without cirrhosis (METAVIR scores F0-3) receiving 12 weeks of simeprevir +sofosbuvir with or without ribavirin; extending treatment to 24 weeks did not increase response rates in comparison with 12 weeks treatment. Ribavirin use and prior treatment status (treatment-naïve and prior null responders) did not impact treatment outcome. The overall SVR12 rate was similar in patients receiving simeprevir + sofosbuvir with or without ribavirin. The response rates for patients with cirrhosis (METAVIR score F4) receiving 12 or 24 weeks of simeprevir + sofosbuvir are shown in table 15.

Table 14: Treatment outcome in HCV genotype 1 infected patients without cirrhosis receiving 12 weeks simeprevir + sofosbuvir, with or without ribavirin (study HPC2002)

Treatment outcome	simeprevir + sofosbuvir N = 21 % (n/N)	simeprevir + sofosbuvir + ribavirin N = 43 % (n/N)
SVR12	95% (20/21)	95% (41/43)
Outcome for patients without SVR12		
On-treatment failure	0% (0/21)	0% (0/43)
Viral relapse[1]	5% (1/21)	5%(2/43)

[1] Viral relapse rates are calculated with a denominator of patients with undetectable HCV RNA at EOT and with at least one follow-up HCV RNA assessment.

Table 15: Treatment outcome in HCV genotype 1 infected patients with cirrhosis receiving 12 or 24 weeks simeprevir + sofosbuvir with or without ribavirin (study HPC2002)

Treatment outcome	12 weeks		24 weeks	
	simeprevir + sofosbuvir N = 7 % (n/N)	simeprevir + sofosbuvir + ribavirin N = 11 % (n/N)	simeprevir + sofosbuvir N = 10 % (n/N)	simeprevir + sofosbuvir + ribavirin N = 13 % (n/N)
SVR12	86% (6/7)	91% (10/11)	100% (10/10)	92% (12/13)
Outcome for patients without SVR12				
On-treatment failure[1]	0% (0/7)	0% (0/11)	0% (0/10)	8% (1/13)
Viral relapse[2]	14% (1/7)	9% (1/11)	0% (0/10)	0% (0/12)

[1] The one patient with on-treatment failure discontinued treatment early due to an adverse event.

[2] Viral relapse rates are calculated with a denominator of patients with undetectable HCV RNA at EOT and with at least one follow-up HCV RNA assessment.

Efficacy in adults with HCV genotype 4

In study HPC2014 (OSIRIS), patients received simeprevir + sofosbuvir for 8 weeks (patients without cirrhosis) or 12 weeks (patients with or without cirrhosis) (see table 11). The 63 enrolled patients had a median age of 51 years (range 24 to 68 years; with 2% above 65 years); 54% were male; 43% had a BMI $\geq$ 30 kg/m^2; the median baseline HCV RNA level was 6.01 $\log_{10}$ IU/ml; 37% had cirrhosis; 30% had HCV genotype 4a, and 56% HCV genotype 4c or 4d; 79% had non-CC *IL28B* alleles (CT or TT); 52% were treatment-naïve, and 48% were treatment-experienced.

In study HPC3021 (PLUTO), patients received simeprevir + sofosbuvir for 12 weeks (see table 11). The 40 enrolled patients had a median age of 51 years (range 29 to 69 years; with 5% above 65 years); 73% were male; 18% had a BMI $\geq$ 30 kg/m^2; the median baseline HCV RNA level was 6.35 $\log_{10}$ IU/ml; 18% had cirrhosis; 25% had HCV genotype 4a, and 73% HCV genotype 4d; 85%

had non-CC *IL28B* alleles (CT or TT); 33% were treatment-naïve, and 68% were treatment-experienced.

The overall SVR12 rate for patients without cirrhosis receiving 8 weeks of simeprevir + sofosbuvir was 75% (15/20); all patients not achieving SVR12 had viral relapse (25%; 5/20). All patients with or without cirrhosis receiving 12 weeks of simeprevir + sofosbuvir achieved SVR12 (table 16).

Table 16: Treatment outcome in HCV genotype 4 infected patients receiving 12 weeks simeprevir + sofosbuvir (studies HPC2014 and HPC3021)

Treatment outcome	Study HPC2014 N = 43 % (n/N)	Study HPC3021 N = 40 % (n/N)
SVR12	100% (43/43)	100% (40/40)
without cirrhosis	100% (20/20)	100% (33/33)
with cirrhosis	100% (23/23)	100% (7/7)

Simeprevir in combination with peginterferon alfa and ribavirin

The efficacy of simeprevir in combination with peginterferon alfa and ribavirin was evaluated in patients with HCV genotype 1 or 4 infection, with or without HIV-1 co-infection, who were treatment-naïve or treatment-experienced (following prior interferon-based therapy) (tables 17 and 18).

Table 17: Studies conducted with simeprevir + peginterferon alfa + ribavirin: population and summary of study design

Study[1]	Population	Number of patients enrolled	Summary of study design
C208 - C216 (QUEST-1 and QUEST-2; Phase 3)	Genotype 1, treatment-naïve patients, with compensated cirrhosis or without cirrhosis	785	12 weeks SMV + peg-IFN-alfa + RBV, followed by 12 or 36 weeks peg-IFN-alfa + RBV[3]; control group: 48 weeks placebo + peg-IFN-alfa + RBV
HPC3007 (PROMISE; Phase 3)	Genotype 1, prior relapsers[2], with compensated cirrhosis or without cirrhosis	393	
C206 (ASPIRE; Phase 2)	Genotype 1 treatment-experienced[4] patients, with compensated cirrhosis or without cirrhosis	462	12, 24 or 48 weeks SMV in combination with 48 weeks peg-IFN-alfa + RBV; control group: 48 weeks placebo + peg-IFN-alfa + RBV
C212 (Phase 3)	Genotype 1, treatment-naïve or treatment-experienced[4], HCV/HIV-1 co-infected patients, with compensated cirrhosis or without cirrhosis	106	treatment-naïve patients or prior relapsers without cirrhosis: 12 weeks SMV + peg-IFN-alfa + RBV, followed by 12 or 36 weeks peg-IFN-alfa + RBV[3]; prior non-responder patients (partial and null responders) without cirrhosis and all treatment-naïve and treatment-experienced patients with cirrhosis: 12 weeks SMV + peg-IFN-alfa + RBV, followed by 36 weeks peg-IFN-alfa + RBV
HPC3011 (RESTORE; Phase 3)	Genotype 4, treatment-naïve or treatment-experienced[4] patients, with compensated cirrhosis or without cirrhosis	107	treatment-naïve patients or prior relapsers: 12 weeks SMV + peg-IFN-alfa + RBV, followed by 12 or 36 weeks peg-IFN-alfa + RBV[3]; prior non-responder patients (partial

			and null responders): 12 weeks SMV + peg-IFN-alfa + RBV, followed by 36 weeks peg-IFN-alfa + RBV

peg-IFN-alfa = peginterferon alfa; RBV = ribavirin (body-weight based twice daily ribavirin dosing, according to the Summary of Product Characteristics of ribavirin); SMV = simeprevir.

[1] Double-blind, randomised, placebo-controlled, except for studies C212 and HPC3011 which were open-label, single arm.

[2] Relapsers after prior interferon-based therapy.

[3] Overall treatment duration with peg-IFN-alfa and RBV was response-guided. The planned total duration of HCV treatment was 24 weeks if the following on-treatment protocol-defined response-guided therapy criteria were met: HCV RNA < 25 IU/ml detectable or undetectable at week 4 AND undetectable HCV RNA at week 12. Treatment stopping rules for HCV therapy were used to ensure that patients with inadequate on-treatment virologic response discontinued treatment in a timely manner.

[4] Includes relapsers, partial and null responders to prior treatment with peginterferon and ribavirin.

Table 18: Studies conducted with simeprevir + peginterferon alfa + ribavirin: demographics and baseline characteristics

	Pooled C208 and C216 N = 785	HPC3007 N = 393	C206 N = 462	C212[1] N = 106	HPC3011 N = 107
Age (years)					
median (range)	47 (18-73)	52 (20-71)	50 (20-69)	48 (27-67)	49 (27-69)
% above 65 yrs	2%	3%	3%	2%	5%
Male gender	56%	66%	67%	85%	79%
Race					
White	91%	94%	93%	82%	72%
Black/African American	7%	3%	5%	14%	28%
Asian	1%	2%	2%	1%	-
Hispanic	17%	7%	-	6%	7%
BMI ≥ 30 kg/m^2	23%	26%	25%	12%	14%
Baseline HCV RNA levels > 800,000 IU/ml	78%	84%	86%	86%	60%
METAVIR fibrosis score					
F0-2	74%	69%	63%	67%	57%
F3	16%	15%	19%	19%	14%
F4	10%	15%	18%	13%	29%
IL28B genotype					
CC	29%	24%	18%	27%	8%
CT	56%	64%	65%	56%	58%
TT	15%	12%	18%	17%	35%
HCV geno/subtype and presence of baseline Q80K polymorphism in HCV genotype 1a					
HCV genotype 1a	48%	42%	41%	82%	-
with Q80K	34%	31%	27%	34%	-
HCV genotype 1b	51%	58%	58%	17%	-
HCV genotype 4a - 4d	-	-	-	-	42% - 24%
Prior treatment history					
treatment-naïve	100%	-	-	50%	33%
treatment-experienced[2]	-				
prior relapser		100%	40%	14%	21%
prior partial responder		-	35%	9%	9%
prior null responder		-	25%	26%	37%

[1] HCV/HIV-1 co-infected patients.

[2] Treatment-experienced to prior treatment with peginterferon and ribavirin.

Efficacy in treatment-naïve patients with HCV genotype 1 infection

In studies C208 (QUEST-1) and C216 (QUEST-2), treatment-naïve patients received simeprevir (150 mg once daily) + peginterferon alfa + ribavirin for 12 weeks, followed by 12 or 36 additional

weeks of peginterferon alfa + ribavirin (see tables 17 and 18). In study C208, all patients received peginterferon alfa-2a; in study C216, 69% of the patients received peginterferon alfa-2a and 31% received peginterferon alfa-2b.

Table 19 shows the response rates in HCV genotype 1 infected treatment-naïve patients.

Table 19: Treatment outcome in treatment-naïve HCV genotype 1 infected patients (pooled data studies C208 and C216)

Treatment Outcome	**simeprevir + peginterferon + ribavirin N = 521 % (n/N)**	**placebo + peginterferon + ribavirin N = 264 % (n/N)**
Overall SVR12	80% (419/521)[1]	50% (132/264)
Outcome for patients without SVR12		
On-treatment failure	8% (42/521)	33% (87/264)
Viral relapse[2]	11% (51/470)	23% (39/172)
SVR12 rates for selected subgroups		
METAVIR fibrosis score		
F0-2	84% (317/378)	55% (106/192)
F3-4	68% (89/130)	36% (26/72)
F4	60% (29/48)	34% (11/32)
IL28B genotype		
CC	95% (144/152)	80% (63/79)
CT	78% (228/292)	41% (61/147)
TT	61% (47/77)	21% (8/38)
HCV geno/subtype and presence of Q80K polymorphism in HCV genotype 1a		
Genotype 1a	75% (191/254)	47% (62/131)
with Q80K	58% (49/84)	52% (23/44)
without Q80K	81% (138/165)	43% (36/83)
Genotype 1b	85% (228/267)	53% (70/133)

[1] $p < 0.001$.

[2] Viral relapse rates are calculated with a denominator of patients with undetectable HCV RNA at actual EOT. Includes 4 simeprevir-treated patients who experienced relapse after SVR12.

Eighty-eight percent (459/521) of the simeprevir-treated patients were eligible for a total treatment duration of 24 weeks; in these patients the SVR12 rate was 88%. Seventy-nine percent (404/509) of simeprevir-treated patients had undetectable HCV RNA at week 4; in these patients the SVR12 rate was 90%. The proportion of simeprevir-treated patients with HCV RNA < 25 IU/ml detectable at week 4 was 14% (70/509); 67% achieved SVR12.

In the pooled analysis of studies C208 and C216, 69% (58/84) of the simeprevir-treated HCV genotype 1a infected patients with Q80K polymorphism at baseline were eligible for a total treatment duration of 24 weeks; in these patients the SVR12 rate was 78%. Sixty-five percent (53/81) of the simeprevir-treated HCV genotype 1a infected patients with Q80K polymorphism had undetectable HCV RNA at week 4; in these patients the SVR12 rate was 79%.

SVR12 rates were statistically significantly higher for patients receiving simeprevir with peginterferon alfa-2a or peginterferon alfa-2b and ribavirin (88% and 78%, respectively) compared to patients receiving placebo with peginterferon alfa-2a or peginterferon alfa-2b and ribavirin (62% and 42%, respectively) (study C216).

Efficacy in treatment-experienced patients with HCV genotype 1 infection
In study HPC3007 (PROMISE), patients who relapsed after prior IFN-based therapy received simeprevir (150 mg once daily) + peginterferon alfa-2a + ribavirin for 12 weeks, followed by 12 or 36 additional weeks of peginterferon alfa-2a + ribavirin (see tables 17 and 18).

In study C206 (ASPIRE), patients who failed prior peg-IFN/RBV therapy received 12, 24 or 48 weeks simeprevir (100 mg or 150 mg once daily) in combination with 48 weeks of peginterferon alfa-2a + ribavirin (see tables 17 and 18).

Table 20 shows the response rates in treatment-experienced patients with HCV genotype 1 infection. Table 21 shows the SVR rates for selected subgroups for study HPC3007.

Table 20: Treatment outcome in treatment-experienced[1] HCV genotype 1 infected patients (studies HPC3007 and C206)

Treatment Outcome	Study HPC3007		Study C206	
	simeprevir % (n/N)	placebo % (n/N)	150 mg simeprevir 12 weeks % (n/N)	placebo % (n/N)
SVR[2]				
Prior relapsers	79% (206/260)[3]	37% (49/133)	77% (20/26)	37% (10/27)
Prior partial responders	-	-	65% (15/23)	9% (2/23)
Prior null responders	-	-	53% (9/17)	19% (3/16)
Outcome for patients without SVR				
On-treatment failure				
Prior relapsers	3% (8/260)	27% (36/133)	8% (2/26)	22% (6/27)
Prior partial responders	-	-	22% (5/23)	78% (18/23)
Prior null responders	-	-	35% (6/17)	75% (12/16)
Viral relapse[4]				
Prior relapsers	19% (46/249)	48% (45/93)	13% (3/23)	47% (9/19)
Prior partial responders	-	-	6% (1/17)	50% (2/4)
Prior null responders	-	-	18% (2/11)	25% (1/4)

1 Treatment-experienced to prior treatment with peginterferon and ribavirin.

2 SVR: SVR12 for study HPC3007 and SVR24 for study C206.

3 $p < 0.001$.

4 Viral relapse rates are calculated with a denominator of patients with undetectable HCV RNA at EOT and with at least one follow-up HCV RNA assessment. Study HPC3007: includes 5 simeprevir-treated patients who experienced relapse after SVR12.

Table 21: SVR12 rates for selected subgroups (study HPC3007)

Subgroup	simeprevir + peginterferon + ribavirin % (n/N)	placebo + peginterferon + ribavirin % (n/N)
METAVIR fibrosis score		
F0-2	82% (137/167)	41% (40/98)
F3-4	73% (61/83)	24% (8/34)
F4	74% (29/39)	26% (5/19)
IL28B genotype		
CC	89% (55/62)	53% (18/34)
CT	78% (131/167)	34% (28/83)
TT	65% (20/31)	19% (3/16)
HCV geno/subtype and presence of Q80K polymorphism in HCV genotype 1a		
Genotype 1a	70% (78/111)	28% (15/54)
with Q80K	47% (14/30)	30% (6/20)
without Q80K	79% (62/79)	26% (9/34)
Genotype 1b	86% (128/149)	43% (34/79)

In study HPC3007, 93% (241/260) of the simeprevir-treated patients were eligible for a total treatment duration of 24 weeks; in these patients the SVR12 rate was 83%. Seventy-seven percent (200/259) of simeprevir-treated patients had undetectable HCV RNA at week 4; in these patients the SVR12 rate

was 87%. The proportion of simeprevir-treated patients with HCV RNA < 25 IU/ml detectable at week 4 was 18% (47/259); 60% achieved SVR12.

In study HPC3007, 80% (24/30) of the simeprevir-treated HCV genotype 1a infected patients with Q80K polymorphism at baseline were eligible for a total treatment duration of 24 weeks; in these patients the SVR12 rate was 58%. Forty-five percent (13/29) of the simeprevir-treated HCV genotype 1a infected patients with Q80K polymorphism had undetectable HCV RNA at week 4; in these patients the SVR12 rate was 77%.

Efficacy in patients with HCV genotype 1 and HIV-1 co-infection
In study C212, patients with HIV-1 co-infection who were treatment-naïve or failed prior peg-IFN/RBV therapy received simeprevir (150 mg once daily) + peginterferon alfa-2a + ribavirin for 12 weeks, followed by 12 or 36 additional weeks of peginterferon alfa-2a + ribavirin (see tables 17 and 18). Eighty-eight percent (n = 93) of the patients were on HIV therapy, most commonly with 2 NRTIs + raltegravir. The median baseline CD4+ cell count in patients on highly active antiretroviral therapy (HAART) was 561 x 10^6 cells/ml (range: 275-1,407 x 10^6 cells/ml).

Table 22 shows the response rates in HCV genotype 1 infected patients with HIV-1 co-infection.

Table 22: Treatment outcome in HCV genotype 1 infected patients with HIV-1 co-infection (study C212)

Treatment outcome	Treatment-naïve patients N = 53 % (n/N)	Prior relapsers N = 15 % (n/N)	Prior partial responders N = 10 % (n/N)	Prior null responders N = 28 % (n/N)
SVR12	79% (42/53)[1]	87% (13/15)	70% (7/10)	57% (16/28)[1]
Outcome for patients without SVR12				
On-treatment failure	9% (5/53)	0% (0/15)	20% (2/10)	39% (11/28)
Viral relapse[2]	10% (5/48)	13% (2/15)	0% (0/7)	12% (2/17)
SVR12 rates for selected subgroups				
METAVIR fibrosis score				
F0-2	89% (24/27)	78% (7/9)	50% (1/2)	57% (4/7)
F3-4	57% (4/7)	100% (2/2)	67% (2/3)	60% (6/10)
F4	100% (2/2)	100% (1/1)	100% (1/1)	60% (3/5)
IL28B genotype				
CC	100% (15/15)	100% (7/7)	100% (1/1)	80% (4/5)
CT	70% (19/27)	100% (6/6)	71% (5/7)	53% (10/19)
TT	80% (8/10)	0% (0/2)	50% (1/2)	50% (2/4)
HCV geno/subtype and presence of Q80K polymorphism in HCV genotype 1a				
Genotype 1a	77% (33/43)	83% (10/12)	67% (6/9)	54% (13/24)
with Q80K	86% (12/14)	33% (1/3)	100% (1/1)	50% (6/12)
without Q80K	72% (21/29)	100% (9/9)	63% (5/8)	58% (7/12)
Genotype 1b	90% (9/10)	100% (3/3)	100% (1/1)	75% (3/4)

[1] $p < 0.001$ compared to historical control of peginterferon alfa and ribavirin.

[2] Viral relapse rates are calculated with a denominator of patients with undetectable HCV RNA at actual EOT and with at least one follow-up HCV RNA assessment. Includes one prior null responder who experienced relapse after SVR12, who was considered to have an HCV re-infection (based on phylogenetic analyses).

Eighty-nine percent (54/61) of the simeprevir-treated treatment-naïve patients and prior relapsers without cirrhosis were eligible for 24 weeks of treatment; in these patients the SVR12 rate was 87%. Seventy-one percent (37/52), 93% (14/15), 80% (8/10) and 36% (10/28) of simeprevir-treated treatment-naïve patients, prior relapsers, prior partial responders and prior null responders had undetectable HCV RNA at week 4. In these patients the SVR12 rates were 89%, 93%, 75% and 90%, respectively.

Two patients had HIV virologic failure defined as confirmed HIV-1 RNA ≥ 200 copies/ml after previous < 50 copies/ml; these failures occurred 36 and 48 weeks after end of simeprevir treatment.

Efficacy in patients with HCV genotype 4 infection
In study HPC3011 (RESTORE), patients who were treatment-naïve or failed prior peg-IFN/RBV therapy received simeprevir (150 mg once daily) + peginterferon alfa-2a + ribavirin for 12 weeks, followed by 12 or 36 additional weeks of peginterferon alfa-2a + ribavirin (see tables 17 and 18).

Table 23 shows the response rates in HCV genotype 4 infected patients.

Table 23: Treatment outcome in HCV genotype 4 infected patients (study HPC3011)

Treatment outcome	**Treatment-naïve patients N = 35 % (n/N)**	**Prior relapsers N = 22 % (n/N)**	**Prior partial responders N = 10 % (n/N)**	**Prior null responders N = 40 % (n/N)**
SVR12	83% (29/35)	86% (19/22)	60% (6/10)	40% (16/40)
Outcome for patients without SVR12				
On-treatment failure	9% (3/35)	9% (2/22)	20% (2/10)	45% (18/40)
Viral relapse[1]	9% (3/35)	5% (1/22)	20% (2/10)	15% (6/40)
SVR12 rates for selected subgroups				
METAVIR fibrosis score				
F0-2	85% (22/26)	91% (10/11)	100% (5/5)	47% (8/17)
F3-4	78% (7/9)	82% (9/11)	20% (1/5)	35% (7/20)
F4	50% (1/2)	78% (7/9)	20% (1/5)	36% (5/14)
IL28B genotype				
CC	100% (7/7)	100% (1/1)	-	-
CT	82% (14/17)	82% (14/17)	60% (3/5)	41% (9/22)
TT	80% (8/10)	100% (4/4)	60% (3/5)	39% (7/18)

[1] Viral relapse rates are calculated with a denominator of patients with undetectable (or unconfirmed detectable) HCV RNA at actual EOT.

Eighty-nine percent (51/57) of the simeprevir-treated treatment-naïve patients and prior relapsers were eligible for a total treatment duration of 24 weeks; in these patients the SVR12 rate was 94%. Eighty percent (28/35), 90% (18/20), 40% (4/10) and 49% (19/39) of simeprevir-treated treatment-naïve patients, prior relapsers, prior partial responders and prior null responders, respectively, had undetectable HCV RNA at week 4. In these patients the SVR12 rates were 96%, 94%, 100% and 68%, respectively.

Viral breakthrough rates were 24% (11/45), 20% (5/25) and 11% (4/36) in patients with genotype 4a, 4d and 4/other, respectively. The clinical relevance of this difference in viral breakthrough rates is unknown.

Clinical study examining QT interval
The effect of simeprevir 150 mg once daily and 350 mg once daily for 7 days on the QT interval was evaluated in a randomised, double-blind, placebo- and positive-controlled (moxifloxacin 400 mg once daily), 4-way cross-over study in 60 healthy subjects. No meaningful changes in QTc interval were observed with either the recommended dose of 150 mg once daily or the supratherapeutic dose of 350 mg once daily.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with simeprevir in one or more subsets of the paediatric population from 3 years to less than 18 years of age in the treatment of chronic viral hepatitis C (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetic properties of simeprevir have been evaluated in healthy adult subjects and in adult HCV infected patients. Plasma exposure of simeprevir (AUC) in HCV infected patients was about 2- to 3-fold higher compared to that observed in healthy subjects. Plasma C_{max} and AUC of simeprevir were similar during co-administration of simeprevir with peginterferon alfa and ribavirin compared with administration of simeprevir alone.

Absorption
The mean absolute bioavailability of simeprevir following a single oral 150 mg dose of simeprevir in fed conditions is 62%. Maximum plasma concentrations (C_{max}) are typically achieved between 4 to 6 hours post dose.

In vitro experiments with human Caco-2 cells indicated that simeprevir is a substrate of P-gp.

Effect of food on absorption
Compared to intake without food, administration of simeprevir with food to healthy subjects increased the AUC by 61% after a high-fat, high-caloric (928 kcal) and 69% after a normal caloric (533 kcal) breakfast, and delayed the absorption by 1 hour and 1.5 hours, respectively.

Simeprevir must be taken with food (see section 4.2). The type of food does not affect exposure to simeprevir.

Distribution
Simeprevir is extensively bound to plasma proteins (> 99.9%), primarily to albumin and, to a lesser extent, alfa-1-acid glycoprotein. Plasma protein binding is not meaningfully altered in patients with renal or hepatic impairment.

Biotransformation
Simeprevir is metabolised in the liver. *In vitro* experiments with human liver microsomes indicated that simeprevir primarily undergoes oxidative metabolism by the hepatic CYP3A4 system. Involvement of CYP2C8 and CYP2C19 cannot be excluded. Moderate or strong inhibitors of CYP3A4 significantly increase the plasma exposure of simeprevir, and moderate or strong inducers of CYP3A4 significantly reduce plasma exposure of simeprevir. Simeprevir does not induce CYP1A2 or CYP3A4 *in vitro*. Simeprevir is not a clinically relevant inhibitor of cathepsin A enzyme activity.

In vitro experiments show that simeprevir is a substrate for the drug transporters P-glycoprotein (P-gp), MRP2, OATP1B1/3 and OATP2B1. Simeprevir inhibits the uptake transporters OATP1B1/3 and NTCP and the efflux transporters P-gp/MDR1, MRP2, BCRP and BSEP. OATP1B1/3 and MRP2 are involved in the transport of bilirubin into and out of hepatocytes. Simeprevir does not inhibit OCT2 *in vitro*.

Following a single oral administration of 200 mg ^{14}C-simeprevir to healthy subjects, the majority of the radioactivity in plasma (up to 98%) was accounted for by unchanged drug and a small part of the radioactivity in plasma was related to metabolites (none being major metabolites). Metabolites identified in faeces were formed via oxidation at the macrocyclic moiety or aromatic moiety or both and by O-demethylation followed by oxidation.

Elimination
Elimination of simeprevir occurs via biliary excretion. Renal clearance plays an insignificant role in its elimination. Following a single oral administration of 200 mg ^{14}C-simeprevir to healthy subjects, on average 91% of the total radioactivity was recovered in faeces. Less than 1% of the administered dose was recovered in urine. Unchanged simeprevir in faeces accounted for on average 31% of the administered dose.

The terminal elimination half-life of simeprevir was 10 to 13 hours in healthy subjects and 41 hours in HCV infected patients receiving 200 mg simeprevir.

Linearity/non-linearity
Plasma C_{max} and the area under the plasma concentration time curve (AUC) increased more than dose proportional after multiple doses between 75 mg and 200 mg once daily, with accumulation occurring following repeated dosing. Steady-state was reached after 7 days of once daily dosing.

Special populations
Elderly (above 65 years of age)
There is limited data on the use of simeprevir in patients older than 65 years. Age (18-73 years) had no clinically meaningful effect on the pharmacokinetics of simeprevir based on a population pharmacokinetic analysis (n = 21, age above 65 years) of HCV infected patients treated with simeprevir. No dose adjustment of simeprevir is required in elderly patients (see section 4.2).

Renal impairment
Renal elimination of simeprevir is negligible. Therefore, it is not expected that renal impairment will have a clinically relevant effect on the exposure to simeprevir.

Compared to healthy subjects with normal renal function (classified using the Modification of Diet in Renal Disease [MDRD] eGFR formula; eGFR ≥ 80 ml/min), the mean steady-state AUC of simeprevir was 1.62-fold higher (90% confidence interval: 0.73-3.6) in subjects with severe renal impairment (eGFR below 30 ml/min). As exposure may be increased in HCV infected patients with severe renal impairment, caution is recommended when prescribing simeprevir to these patients (see section 4.2).

As simeprevir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

Refer to the respective Summary of Product Characteristics of the medicinal products used in combination with simeprevir regarding their use in patients with renal impairment.

Hepatic impairment
Simeprevir is primarily metabolised by the liver.
Plasma exposure of simeprevir in HCV infected patients was about 2- to 3-fold higher compared to that observed in healthy subjects.

Compared to healthy subjects with normal hepatic function, the mean steady-state AUC of simeprevir was 2.4-fold higher in non-HCV infected subjects with moderate hepatic impairment (Child-Pugh B) and 5.2-fold higher in non-HCV infected subjects with severe hepatic impairment (Child-Pugh C).

No dose adjustment of simeprevir is necessary in patients with mild hepatic impairment. The safety and efficacy of simeprevir have not been established in HCV infected patients with moderate or severe hepatic impairment (Child-Pugh B or C). OLYSIO is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh B or C) (see sections 4.2 and 4.4).

Refer to the respective Summary of Product Characteristics of the medicinal products used in combination with simeprevir regarding their use in patients with hepatic impairment.

Gender
No dose adjustment is necessary based on gender. Gender had no clinically relevant effect on the pharmacokinetics of simeprevir based on a population pharmacokinetic analysis of HCV infected patients treated with simeprevir in combination with peginterferon alfa and ribavirin.

Body weight
No dose adjustment is necessary based on body weight or body mass index. These characteristics have no clinically relevant effect on the pharmacokinetics of simeprevir based on a population pharmacokinetic analysis of HCV infected patients treated with simeprevir in combination with peginterferon alfa and ribavirin.

Race
Population pharmacokinetic estimates of exposure of simeprevir were comparable between Caucasian and Black/African American HCV infected patients treated with simeprevir in combination with peginterferon alfa and ribavirin.

In a phase 3 study conducted in China and South-Korea, the mean plasma exposure of simeprevir in Asian HCV infected patients was 2.1-fold higher compared to non-Asian HCV infected patients in a pooled phase 3 population from global studies.

No dose adjustment is necessary based on race.

Patients co-infected with HIV-1
Pharmacokinetic parameters of simeprevir were comparable between patients with HCV genotype 1 infection with or without HIV-1 co-infection.

Paediatric population
The pharmacokinetics of simeprevir in children aged below 18 years have not been investigated.

5.3 Preclinical safety data

In rodents, simeprevir elicited toxic effects in the liver, pancreas and gastrointestinal systems. Dosing of animals resulted in similar (dogs) or lower (rats) exposures than those observed in humans at the recommended dose of 150 mg once daily. In dogs, simeprevir was associated with a reversible multifocal hepatocellular necrosis with associated increases in ALT, AST, alkaline phosphatase and/or bilirubin. This effect was observed at higher systemic exposures (14-fold) than those in humans at the recommended dose of 150 mg once daily.

Simeprevir *in vitro* was very mildly irritating to the eyes. *In vitro*, simeprevir induced a phototoxic response on BALB/c 3T3 fibroblasts after UVA exposure, in the absence and presence of protein supplements. Simeprevir was not irritating to rabbit skin, and is not likely to cause skin sensitisation.

There were no adverse effects of simeprevir on vital functions (cardiac, respiratory and central nervous system) in animal studies.

Carcinogenicity and mutagenicity
Simeprevir was not genotoxic in a series of *in vitro* and *in vivo* tests. Carcinogenicity studies with simeprevir have not been conducted.

Reproductive toxicology
Studies carried out in rats did not reveal significant findings on fertility, embryo-fetal development or pre- and post-natal development at any of the tested doses (corresponding to a systemic exposure in rats similar or lower than that observed in humans at the recommended dose of 150 mg once daily). Supernumerary ribs and delayed ossification were reported in mice at 4-fold higher exposures than those observed in humans at the recommended dose of 150 mg once daily.

In pregnant rats, simeprevir concentrations in placenta, fetal liver and foetus were lower compared to those observed in blood. When administered to lactating rats, simeprevir was detected in plasma of suckling rats likely due to excretion of simeprevir via milk.

Environmental Risk Assessment (ERA)
Simeprevir is classified as a PBT (persistent, bioaccumulative and toxic) substance (see section 6.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Sodium lauryl sulfate
Magnesium stearate
Colloidal anhydrous silica
Croscarmellose sodium
Lactose monohydrate

Capsule shell
Gelatin
Titanium dioxide (E171)

Black printing ink
Shellac (E904)
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package in order to protect from light.
This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Opaque polyvinylchloride/polyethylene/polyvinylidenechloride (PVC/PE/PVDC) aluminium push-through blister strips of 7 capsules.

Pack sizes of 7 or 28 capsules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

This medicinal product may pose a risk to the environment (see section 5.3). 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/1/14/924/001 (7 capsules)

EU/1/14/924/002 (28 capsules)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 May 2014

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. MANUFACTURER 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 responsible for batch release

Janssen-Cilag SpA
Via C. Janssen
Borgo San Michele
04100 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 requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
In order to evaluate the recurrence of hepatocellular carcinoma associated with OLYSIO, the MAH shall conduct and submit the results of a prospective safety study using data deriving from a cohort of a well-defined group of patients, based on an agreed protocol. The final study report shall be submitted by:	Q2 2021

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

OLYSIO 150 mg hard capsules
simeprevir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains simeprevir sodium equivalent to 150 mg simeprevir.

3. LIST OF EXCIPIENTS

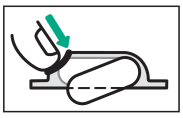
Contains lactose monohydrate

4. PHARMACEUTICAL FORM AND CONTENTS

7 hard capsules
28 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use



Press edge of pocket

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 package in order to protect from light.

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

Disposal: Read the package leaflet.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/924/001 (7 capsules)
EU/1/14/924/002 (28 capsules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

olysis 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

OLYSIO 150 mg capsules
simeprevir

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon
Tue
Wed
Thu
Fri
Sat
Sun

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

OLYSIO 150 mg hard capsules
simeprevir

▼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 OLYSIO is and what it is used for

What OLYSIO is
- OLYSIO contains the active substance 'simeprevir'. It acts against the virus that causes hepatitis C infection, called 'hepatitis C virus' (HCV).
- OLYSIO must not be used by itself. OLYSIO must always be used as part of a course of treatment with other medicines for treating chronic hepatitis C infection. It is therefore important that you also read the package leaflets that are provided with these other medicines before you start taking OLYSIO. If you have any further questions about any of these medicines, ask your doctor or pharmacist.

What OLYSIO is used for
OLYSIO is used with other medicines to treat chronic (long-term) hepatitis C infection in adults.

How OLYSIO works
OLYSIO helps to fight against hepatitis C infection by preventing HCV from multiplying. When used together with other medicines to treat chronic hepatitis C infection, OLYSIO helps to clear HCV from your body.

2. What you need to know before you take OLYSIO

Do not take OLYSIO if you are allergic to simeprevir or any of the other ingredients of this medicine (listed in section 6). Do not take OLYSIO if this applies to you. If you are not sure, talk to your doctor or pharmacist before taking OLYSIO.

Warnings and precautions
Talk to your doctor or pharmacist about all your medical conditions before taking OLYSIO in particular if:
- you have hepatitis C that is not 'genotype 1' or 'genotype 4';

- you have ever taken any medicines to treat hepatitis C;
- you have any other liver problems in addition to hepatitis C;
- you have a current or previous infection with the hepatitis B virus, since your doctor may want to monitor you more closely;
- you have had or are going to have an organ transplant.

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking OLYSIO.

When taking OLYSIO combination treatment, tell your doctor if you have the following symptoms as they may be a sign of worsening liver problems:
- notice yellowing of your skin or eyes
- your urine is darker than normal
- notice swelling of your stomach area.

This is particularly significant if these are accompanied by either of the following symptoms:
- feel sick (nauseous), are sick (vomit) or lose your appetite
- confusion.

OLYSIO combination treatment with sofosbuvir may result in slowing of the heart rate (pulse) along with other symptoms when taken with amiodarone, a medicine used to treat irregular heart beat.
Tell your doctor if any of the following applies:
- you currently take, or have taken in the last few months, the medicine amiodarone (your doctor may consider alternative treatments if you have taken this medicine)
- you take other medicines to treat irregular heart beat or high blood pressure.

Tell your doctor immediately if you are taking OLYSIO with sofosbuvir and any medicines for heart problems, and during treatment you experience:
- shortness of breath
- light-headedness
- palpitations
- fainting.

<u>Sensitivity to sunlight</u>
You may be more sensitive to sunlight (photosensitivity) when taking OLYSIO (see section 4 for information about side effects).
During your treatment with OLYSIO, use appropriate sun protection (such as a sun hat, sunglasses and sunscreen). Especially avoid intense or prolonged exposure to sunlight (including tanning devices).
If you develop a photosensitivity reaction during treatment, contact your doctor immediately.

<u>Rash</u>
You may experience a rash during treatment with OLYSIO. Rash may become severe.
If you develop a rash during treatment, contact your doctor immediately.

<u>Blood tests</u>
Your doctor will test your blood before you start your treatment and regularly during your treatment. These blood tests help your doctor to
- check if the treatment is working for you
- check your liver function.

Children and adolescents
OLYSIO must not be used in children and adolescents (under 18 years of age) because it has not been studied in this age group.

Other medicines and OLYSIO
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because OLYSIO and other medicines may interact with each other.

In particular tell your doctor or pharmacist if you take any of the following medicines:

- digoxin, disopyramide, flecainide, mexiletine, propafenone or quinidine (when taken by mouth) or amiodarone to treat irregular heart beat
- clarithromycin, erythromycin (when taken by mouth or given by injection) or telithromycin to treat bacterial infections
- warfarin and other similar medicines called vitamin K antagonists used to thin the blood. Your doctor may need to increase the frequency of your blood tests to check how well your blood can clot.
- carbamazepine, oxcarbazepine, phenobarbital or phenytoin to prevent seizures
- astemizole or terfenadine to treat allergies
- itraconazole, fluconazole, ketoconazole, posaconazole or voriconazole (when taken by mouth or given by injection) to treat fungal infections
- rifabutin, rifampicin or rifapentine to treat infections like tuberculosis
- amlodipine, bepridil, diltiazem, felodipine, nicardipine, nifedipine, nisoldipine or verapamil (when taken by mouth) to decrease blood pressure
- dexamethasone (when given by injection or taken by mouth) to treat asthma or inflammation and auto-immune diseases
- cisapride to treat stomach problems
- milk thistle (a herbal medicine) for liver problems
- St John's wort (*Hypericum perforatum*, a herbal medicine) for anxiety or depression
- ledipasvir to treat hepatitis C infection
- cobicistat to increase levels of some medicines used to treat HIV infection
- atazanavir, darunavir, delavirdine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir or tipranavir to treat HIV infection
- atorvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin or simvastatin to lower cholesterol levels
- ciclosporin, sirolimus or tacrolimus to lower immune response or prevent organ transplant failures
- sildenafil or tadalafil to treat 'pulmonary arterial hypertension'
- midazolam or triazolam (when taken by mouth) to help you sleep or for anxiety

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking OLYSIO.

In addition, tell your doctor if you take any medicines used to treat irregular heart beat or high blood pressure.

Pregnancy, contraception and breast-feeding

Pregnancy

If you are pregnant, think you might be pregnant or are planning to become pregnant, ask your doctor or pharmacist for advice before taking this medicine.

Pregnant women should not take OLYSIO unless specifically directed by the doctor.

When OLYSIO is used with ribavirin, please read the package leaflet for ribavirin for information regarding pregnancy. Ribavirin can affect your unborn baby.

- If you are a woman, you **must not become pregnant during treatment and for several months afterwards**.
- If you are a man, your female partner **must not become pregnant during your treatment and for several months afterwards.**

If pregnancy occurs during this period, you must contact your doctor straight away.

Contraception

Women must use an effective method of contraception during treatment with OLYSIO.

When OLYSIO is used with ribavirin, read the package leaflet for ribavirin for information regarding contraception requirements. You and your partner must use an effective method of contraception during treatment and for several months afterwards.

Breast-feeding
Talk to your doctor if you are breast-feeding before taking OLYSIO. This is important because it is not known whether simeprevir can pass into breast milk. The doctor will advise you to stop breast-feeding or to stop taking OLYSIO while breast-feeding.

Driving and using machines
Combination treatment of OLYSIO with other medicines used for treating your chronic hepatitis C infection may affect your ability to drive and use machines. Do not drive or use machines if you feel faint or have problems with your vision. Read the package leaflets for these other medicines for information regarding driving and using machines.

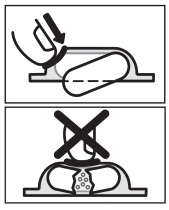
OLYSIO contains lactose
OLYSIO contains lactose (a type of sugar). If you have been told by your doctor that you have an intolerance to some sugars, talk to your doctor before taking this medicine.

3. How to take OLYSIO

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.
You must take OLYSIO as part of a course of treatment with other medicines for treating your chronic hepatitis C infection. A course of OLYSIO lasts for either 12 or 24 weeks but you may need to take the other medicines for longer, according to your doctor's instructions. Read the package leaflets for these medicines for their dosage and directions on 'how to take' them.

How to take
- The recommended dose of OLYSIO is one capsule (150 milligrams) once a day.
- The days of the week are printed on the blister strip - this will help you remember to take your capsule.
- Try to take OLYSIO at the same time each day.
- Always take OLYSIO with food. The type of food is not important.
- Take this medicine by mouth.
- Swallow the capsule whole.

How to remove capsule
Press either **edge** of the pocket to push the capsule through the foil, as shown.
Do not press the capsule from the center of the pocket. This can damage or break open the capsule.



If the capsule shell has been broken or opened, some medicine may be lost and you should take a new capsule. If the capsule shell is indented or bent - without being broken or opened - the capsule can still be used.

If you take more OLYSIO than you should
If you take more OLYSIO than you should, talk to your doctor or pharmacist immediately.

If you forget to take OLYSIO
- If it is more than 12 hours until your next dose, take the missed dose as soon as possible with food. Then continue taking OLYSIO at the usual scheduled time.
- If it is less than 12 hours until your next dose, skip the missed dose. Then take the next dose of OLYSIO at the usual scheduled time.
- Do not take a double dose to make up for a forgotten dose.

If you are not sure what to do, contact your doctor or pharmacist.

Do not stop taking OLYSIO
Do not stop taking OLYSIO unless your doctor tells you to. If you do, your medicine may not work properly.

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

4. Possible side effects

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

The following side effects may happen with **OLYSIO** when used **in combination with sofosbuvir**:
Common: may affect up to 1 in 10 people:
- itching of the skin
- skin rash*
- constipation
- being sensitive to sunlight (photosensitivity)
- increased 'bilirubin' levels in your blood (bilirubin is a pigment made by the liver).

* Skin rash may affect more than 1 in 10 people (very common) when OLYSIO is used in combination with sofosbuvir for 24 weeks.

The following side effects may happen with **OLYSIO** when used **in combination with peginterferon alfa and ribavirin**:
Very common: may affect more than 1 in 10 people:
- feeling sick (nausea)
- itching of the skin
- skin rash
- being short of breath.

Common: may affect up to 1 in 10 people:
- increased 'bilirubin' levels in your blood (bilirubin is a pigment made by the liver)*
- being sensitive to sunlight (photosensitivity)
- constipation.

* In a clinical study in Asian patients from China and South-Korea, increased blood 'bilirubin' levels were reported in more than 1 in 10 people (very common).

Read the package leaflets for the other medicines used for treating your hepatitis C infection for side effects reported with these medicines.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. 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.

5. How to store OLYSIO

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 carton and blister packaging after EXP. The expiry date refers to the last day of that month.
- This medicine does not require any special temperature storage conditions.
- Store in the original package in order to protect from light.
- This medicine may pose a risk to the environment. 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 OLYSIO contains
- The active substance is simeprevir. Each capsule contains simeprevir sodium equivalent to 150 milligrams of simeprevir.
- The other ingredients are sodium lauryl sulfate, magnesium stearate, colloidal anhydrous silica, croscarmellose sodium, lactose monohydrate, gelatin, titanium dioxide (E171), iron oxide black (E172) and shellac (E904).

What OLYSIO looks like and contents of the pack
The hard capsules are white, with 'TMC435 150' printed in black ink.
OLYSIO is supplied in push-through blister strips of 7 capsules. The days of the week are printed on the blister strip.
OLYSIO is available in packs containing 7 capsules (1 blister) or 28 capsules (4 blisters).
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, Borgo San Michele, 04100 Latina, Italy

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

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.