



HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

14 December 2011

INCIVO 375 mg, film-coated tablet
B/4 bottles of 42 tablets (CIP code: 217 378-5)
B/1 bottle of 42 tablets (CIP code: 219 249-8)

Applicant: JANSSEN-CILAG

telaprevir
ATC Code: J05AE11 (protease inhibitor)

List I

Hospital prescription restricted to gastroenterology, hepatology, internal medicine or infectiology specialists.

Date of Marketing Authorisation (centralised European procedure):

Box of 4 bottles: 19/09/2011

Box of 1 bottle: 13/10/2011

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

telaprevir

1.2. Background

This is an NS3/4A protease inhibitor of the genotype 1 hepatitis C virus.

1.3. Indication

“INCIVO, in combination with peginterferon alfa and ribavirin, is indicated for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease (including cirrhosis):

- who are treatment-naive;
- who have previously been treated with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin, including relapsers, partial responders and null responders (see sections 4.4 and 5.1 of the SPC).”

1.4. Dosage

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

INCIVO, 750 mg dose of INCIVO (two 375 mg film-coated tablets) should be taken orally every 8 hours with food (the total daily dose is 6 tablets (2,250 mg)).

Taking INCIVO without food or without regard to the dosing interval may result in decreased plasma concentrations of telaprevir which could reduce the therapeutic effect of INCIVO.

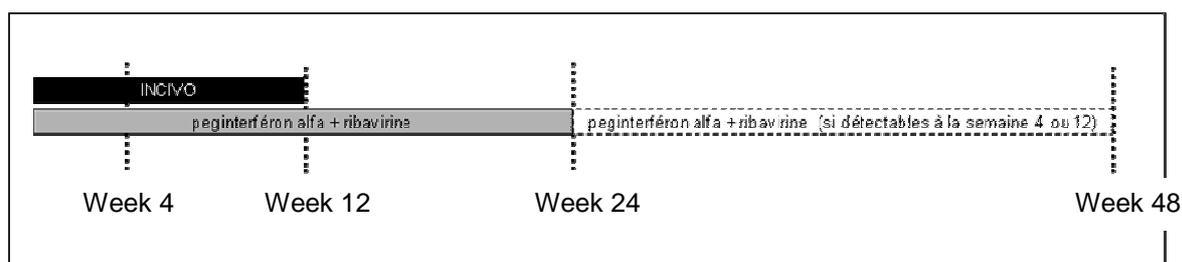
INCIVO should be administered in conjunction with ribavirin and peginterferon alfa-2a or -2b. Please consult sections 4.4 and 5.1 regarding the selection of peginterferon alfa-2a or -2b. For specific dosage instructions for peginterferon alfa and ribavirin, the Summary of Product Characteristics (SPC)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

Duration of the treatment - Treatment-naive adults and prior treatment relapsers

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

- Patients with undetectable hepatitis C virus ribonucleic acid (HCV RNA) at weeks 4 and 12 receive an additional 12 weeks of peginterferon alfa and ribavirin alone for a total treatment duration of 24 weeks.
- Patients with detectable HCV RNA at either week 4 or 12 receive an additional 36 weeks of peginterferon alfa and ribavirin alone for a total treatment duration of 48 weeks.
- For all patients with cirrhosis irrespective of undetectable HCV RNA at weeks 4 or 12, an additional 36 weeks of peginterferon alfa and ribavirin alone for a total treatment duration of 48 weeks is recommended (see section 5.1).

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



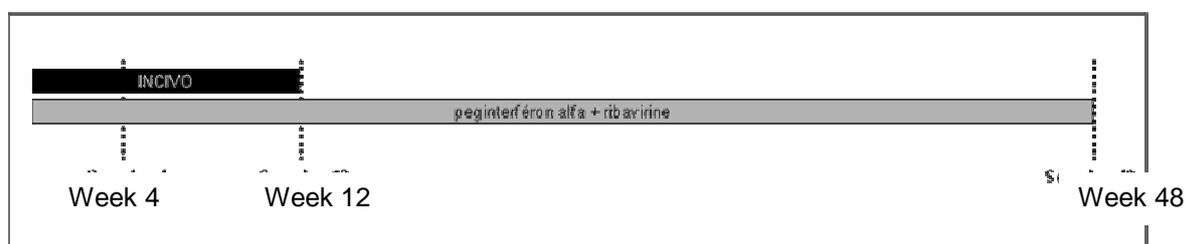
si détectables à la semaine 4 ou 12 = if detectable at week 4 or 12

HCV RNA levels should be monitored at weeks 4 and 12 to determine treatment duration. In phase 3 studies, a sensitive real-time PCR assay with a limit of quantification of 25 IU/ml and a limit of detection of 10-15 IU/ml was used to determine whether HCV RNA levels were undetectable (see section 5.1). Detectable HCV RNA below the lower limit of assay quantification should not be used as a substitute for “undetectable”, for making decisions on treatment duration, as this may lead to an insufficient duration of therapy and higher relapse rates. See table 1 for guidelines for discontinuation of INCIVO, peginterferon alfa and ribavirin treatment.

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

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

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



HCV RNA levels should be monitored at weeks 4 and 12. See table 1 for guidelines for discontinuation of INCIVO, peginterferon alfa and ribavirin treatment.

All patients

Since it is highly unlikely that patients with inadequate viral responses will achieve a sustained virologic response (SVR), it is recommended that patients with HCV RNA > 1,000 IU/ml at week 4 or week 12 discontinue therapy (refer to table 1).

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

Medicinal products	HCV RNA > 1,000 IU/ml at week 4 of treatment ^a	HCV RNA > 1,000 IU/ml at week 12 of treatment ^a
INCIVO	Permanently discontinue	INCIVO treatment completed
Peginterferon alfa and ribavirin	Permanently discontinue	

^a treatment with INCIVO, peginterferon alfa and ribavirin. These guidelines may not perform similarly when a lead-in treatment with peginterferon alfa and ribavirin has been used prior to starting INCIVO therapy (see section 5.1).

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

In prior null responders, consideration should be given to conduct an additional HCV RNA test between weeks 4 and 12. If the HCV RNA concentration is > 1,000 IU/ml, INCIVO, peginterferon alfa and ribavirin should be discontinued.

For patients receiving a total of 48 weeks of treatment, peginterferon alfa and ribavirin should be discontinued if HCV RNA is detectable at week 24 or week 36.

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

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

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

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

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

Special populations

Renal impairment

There are no clinical data on the use of INCIVO in HCV patients with moderate or severe renal impairment (CrCl ≤ 50 ml/min) (see section 4.4).

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

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

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

Hepatic impairment

INCIVO is not recommended in patients with moderate to severe hepatic impairment (Child-Pugh B or C, score ≥ 7) or decompensated liver disease (see section 4.4). Dose modification of INCIVO is not required when administered to hepatitis C patients with mild hepatic impairment (Child-Pugh A, score 5-6).

Refer also to the Summary of Product Characteristics for peginterferon alfa and ribavirin, which are contraindicated in Child-Pugh score ≥ 6 .

Elderly

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

Paediatric population

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

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification

J	Anti-infectives for systemic use
J05	Antivirals for systemic use
J05A	Direct-acting antivirals
J05AE	Protease inhibitors
J05AE11	Telaprevir

2.2. Medicines in the same therapeutic category

Comparator medicines

Another protease inhibitor indicated in the treatment of genotype 1 chronic hepatitis C has a Marketing Authorisation dated 18/07/2011: VICTRELIS (boceprevir).

2.3. Medicines with a similar therapeutic aim

These are other proprietary medicinal products indicated in the treatment of chronic hepatitis C with wider indications (HIV co-infection, other genotypes, children depending on the proprietary medicinal products).

The actual benefit of these proprietary medicinal products is important.

➤ ribavirin:

COPEGUS, film-coated tablets 200 mg and 400 mg

REBETOL hard capsules, 200 mg and 40 mg/ml oral solution
and the generics

➤ peginterferon alfa:

PEGASYS (peginterferon alfa-2a) 135 µg, 180 µg, injectable solution in a prefilled syringe

VIRAFERONPEG (peginterferon alfa-2b) 50 µg, 80 µg, 100 µg, 120 µg, 150 µg, powder and solvent for injectable solution in prefilled pen and 50 µg, powder and solvent for injectable solution in a bottle

➤ non-pegylated interferon alfa:

ROFERON-A (interferon alfa-2a) 3, 4, 5, 6 and 9 million IU, injectable solution in a prefilled syringe

INTRONA (interferon alfa-2b) 10 and 18 million IU, injectable solution and 18, 30 and 60 million IU, injectable solution in a pen

3. ANALYSIS OF AVAILABLE DATA

The file submitted has three phase III studies evaluating telaprevir in combination with peginterferon alfa-2a and ribavirin versus peginterferon alfa-2a and ribavirin, in the absence of liver decompensation:

- the ADVANCE and ILLUMINATE studies in previously untreated adults;
- the REALIZE study on patients in whom prior treatment failed, i.e. relapsers and non-responders (partial responders and null responders).

The data presented do not involve special populations, such as transplant patients, patients co-infected with HIV or the hepatitis B virus and children.

3.1. Efficacy

3.1.1 Previously untreated adults

ADVANCE study (study 108)

A randomised, double-blind placebo-controlled study, whose main aim was to evaluate the efficacy of two treatment regimens of telaprevir (8 or 12 weeks) combined with peginterferon alfa-2a and ribavirin (for a total duration of 24 or 48 weeks) versus peginterferon alfa-2a and ribavirin (48 weeks) in adults infected with genotype 1 chronic hepatitis C and not previously treated with interferon alfa.

Main inclusion criteria:

- adults aged between 18 and 70 infected with genotype 1 chronic hepatitis C with a detectable viral load,
- availability of a liver biopsy,
- for patients with fibrosis or cirrhosis: no diagnosed or suspected hepatocellular carcinoma.

Main non-inclusion criteria:

- patients co-infected with HIV or hepatitis B virus,
- previously treated for their hepatitis C,
- patients with a history of organ transplant (except for corneal and skin grafts),
- decompensated liver disease.

Treatment: the patients were randomised (1:1:1) into three groups.

Randomisation was stratified by HCV genotype (1a or 1b) and RNA-HCV viral load (< 800,000 IU/ml versus \geq 800,000 IU/ml).

In each of the groups, the dosages of the pegylated bi-therapy were as follows:

- peginterferon alfa-2a: 180 μ g/week by the subcutaneous route
- ribavirin: 1,000 mg/day (patients weighing less than 75 kg) or 1,200 mg/day (\geq 75 kg) by the oral route in two doses.

The dosage of telaprevir was 750 mg every 8 hours (i.e. 2 tablets 3 times/day) by the oral route.

The patients were treated with one of the following three regimens:

1. Group PR (N=361):

placebo combined with the bi-therapy (peginterferon alfa-2a and ribavirin) for 12 weeks followed by 36 additional weeks of bi-therapy, i.e. a total treatment period of 48 weeks of bi-therapy.

2. Group T8-PR-TGR (Response-Guided Therapy) (N=364):

tri-therapy for 8 weeks combining telaprevir, peginterferon alfa-2a and ribavirin then placebo combined with the bi-therapy (peginterferon alfa-2a and ribavirin) for 4 weeks then bi-therapy for 12 or 36 additional weeks depending on negativation of the viral load at week 4 and week 12:

- extended rapid virologic response (eRVR+)¹: bi-therapy for 12 additional weeks, i.e. a total treatment period of 24 weeks
- absence of extended rapid virologic response (eRVR-): bi-therapy for 36 additional weeks, i.e. a total treatment period of 48 weeks.

3. Group T12-PR-TGR (Response-Guided Therapy) (N=363):

tri-therapy for 12 weeks combining telaprevir, peginterferon alfa-2a and ribavirin then bi-therapy (peginterferon alfa-2a and ribavirin) for 12 or 36 additional weeks depending on negativation of the viral load at week 4 and week 12:

- extended rapid virologic response (eRVR+)¹: bi-therapy for 12 additional weeks, i.e. a total treatment period of 24 weeks
- absence of extended rapid virologic response (eRVR-): bi-therapy for 36 additional weeks, i.e. a total treatment period of 48 weeks.

In the case of plasma HCV RNA > 1 000 IU/ml at week 4, telaprevir was stopped.

Following amendments to the protocol, a reduction in the doses of ribavirin was considered whilst administration of erythropoietin for anaemia management was prohibited.

Primary efficacy endpoint: achieving a sustained virologic response (SVR), defined as an undetectable HCV RNA viral load at the 24th week of follow-up after the end of the planned 24 or 48 weeks of treatment, in the FAS (Full Analysis Set) population including all of the randomised patients who received at least one treatment (peginterferon alfa-2a, ribavirin or telaprevir/placebo).

The main analysis involved a comparison between the groups T8-PR-TGR versus PR and T12-PR-TGR versus PR.

Secondary endpoints, in particular:

- sustained virologic response (SVR) at week 72, i.e. at the 24th week of follow-up after the end of the 48-week treatment and at the 48th week of follow-up after the end of the 24-week treatment
- rapid virologic response (RVR) defined by a viral load undetectable at week 4
- extended rapid virologic response (eRVR+) defined by a viral load undetectable at week 4 and week 12.

Results:

Of the 1,095 randomised patients, 1,088 received at least one dose of telaprevir (FAS population).

About 90% of the patients were Caucasian. The median age of the patients was 49 (18-69) years and 58% of the patients were male. The majority (59%) of the patients were infected with genotype 1a HCV and 40% by genotype 1b HCV. Most of the patients (77%) had a very high initial viral load ($\geq 800,000$ IU/ml). Approximately 15% of the patients had severe fibrosis (METAVIR score F3²). Cirrhosis (METAVIR score F4) was present in 6% (68/1088) of the patients.

¹ Patients with an HCV RNA level undetectable at week 4 and which was also undetectable at week 12

² The METAVIR score evaluates the severity of hepatitis. The fibrosis stage is graduated from F0 (absence of fibrosis) to F4 (cirrhosis)

- main efficacy endpoint:

The percentage of patients who achieved a sustained virologic response at the 24th week of follow-up was 43.8% (158/361) in the PR group, 68.7% (250/364) in the T8-PR-TGR group and 74.7% (271/363) in the T12-PR-TGR group, i.e. an absolute increase of 24.9% between the T8-PR-TGR and PR groups (p<0.0001) and an absolute increase of 30.9% between the T12-PR-TGR and PR groups (p<0.0001) in the FAS population.

The treatment regimen involving 12 weeks of telaprevir was the one adopted in the Marketing Authorisation.

- Other endpoints:

The SVR at week 72 was 43.8% (158/361) in the PR group, 66.8% (243/364) in the T8-PR-TGR group and 73% (265/363) in the T12-PR-TGR group, i.e. an increase of 23% between the T8-PR-TGR and PR groups (p<0.0001) and an increase of 39.2% between the T12-PR-TGR and PR groups (p<0.0001).

A rapid virologic response defined by a viral load undetectable at week 4 was observed in 9.4% (34/361) of the patients of the PR group, in 66.5% (242/364) of the T8-PR-TGR group and in 67.8% (246/363) of the T12-PR-TGR group.

An extended rapid virologic response (eRVR+) defined by a viral load undetectable at week 4 and week 12 was observed in 8% (29/361) of the patients of the PR group, in 56.9% (207/364) of the T8-PR-TGR group and in 58.4% (212/363) of the T12-PR-TGR group. Around 60% of the patients of the T8-PR-TGR and T12-PR-TGR groups were therefore eligible for a total treatment duration of 24 weeks.

The RVR at the 24th week of follow-up was more frequent amongst those with a viral load undetectable at week 4 and at week 12 (eRVR+) and was between 83% and 97% depending on the groups (see table 2).

Table 2: SVR at the 24th week of follow-up depending on detectability of the viral load at week 4 and week 12: ADVANCE study

SVR at the 24 th week of follow-up	PR Group (N=361)	T8-PR-TGR Group (N=364)	T12-PR-TGR Group (N=363)
eRVR+	28/29 (96.6%)	171/207 (82.6%)	189/212 (89.2%)
eRVR-	130/332 (39.2%)	79/157 (50.3%)	82/151 (54.3%)

eRVR: viral load undetectable at week 4 and week 12

The percentage of relapse³ was 27.9% (64/229) in the PR group, 9.5% (28/295) in the T8-PR-TGR group and 8.6% (27/314) in the T12-PR-TGR group.

The percentages of patients who relapsed out of those with a viral load undetectable at week 4 and week 12 (eRVR+) were 0% (0/28) in the PR group, 9.3% (18/194) in the T8-PR-TGR group and 6.8% (14/207) in the T12-PR-TGR group.

Some analyses in sub-groups were carried out, particularly according to parameters with a potential impact on sustained virologic response, i.e. genotype, initial viral load and fibrosis stage.

The sustained virologic response was more frequent in the genotype 1b patients, with an initial viral load < 800,000 IU/ml and in the patients without cirrhosis.

It should, however, be noted that the number of patients with cirrhosis (METAVIR score F4) was very small (6%) in this study.

³ Proportion of subjects with an HCV RNA level undetectable at the end of the treatment but detectable at the end of follow-up.

ILLUMINATE study (study 111)

A randomised, open-label study, whose main aim was to demonstrate the non-inferiority of telaprevir combined with peginterferon and ribavirin for 24 weeks (T12-PR24) or for 48 weeks (T12-PR48) in terms of sustained virologic response in adults infected with genotype 1 chronic hepatitis C and not previously treated with interferon alfa amongst those achieving an extended rapid virologic response (eRVR) defined by an HCV RNA viral load undetectable at weeks 4 and 12.

The inclusion and non-inclusion criteria were similar to those of the ADVANCE study described above.

Treatment:

Randomisation, carried out at week 20, was stratified by HCV genotype (1a or 1b) and HCV RNA viral load (< 800,000 IU/ml versus \geq 800,000 IU/ml).

For the first 12 weeks, all the patients were treated with telaprevir (750 mg every 8 hours, i.e. 2 tablets 3 times a day), peginterferon alfa-2a (180 μ g/week subcutaneously) and ribavirin (1000 mg/day for patients weighing less than 75 kg or 1,200 mg/day if \geq 75 kg by the oral route in two doses).

Then, the bi-therapy (peginterferon and ribavirin) was administered for 12 or 36 additional weeks depending on detectability of the viral load at weeks 4 and 12 (eRVR) and the randomisation carried out at week 20.

At week 20, the patients who had continued the treatment and who achieved an extended rapid virologic response (eRVR+)⁴ were randomised to stop the bi-therapy at week 24, i.e. a total treatment period of 24 weeks (group T12-PR24, N=162) or continue it until week 48 (T12-PR48 group, N=160).

The patients who did not achieve an extended rapid virologic response (eRVR-) were treated for a total treatment period of 48 weeks (N=118).

In the case of plasma HCV RNA > 1,000 IU/ml at week 4, telaprevir was stopped.

Following amendments to the protocol, a reduction in the doses of ribavirin was considered whilst administration of erythropoietin for anaemia management was prohibited.

Primary efficacy endpoint: achieving a sustained virologic response (SVR), defined as an HCV RNA viral load undetectable at the 24th week of follow-up after the end of the 24 weeks (T12-PR24) or 48 weeks (T12-PR48) of treatment amongst the patients who had an extended rapid virologic response (eRVR+)⁴ in the FAS (Full Analysis Set) population including all of the randomised patients who received at least one treatment (peginterferon alfa-2a, ribavirin or telaprevir).

The statistical analysis was based on the following hypothesis: non-inferiority was established if the lower limit of the 95% confidence interval of the difference between the percentages of SVR (T12-PR24 less T12-PR48) was greater than -10.5%.

Results:

The patients' characteristics were overall similar to those of the ADVANCE study, except for a higher proportion of black subjects, patients with cirrhosis and genotype 1a.

In all, 540 patients were included: 352 (65%) achieved an extended rapid virologic response (eRVR+) and were randomised, 118 patients did not achieve an extended rapid virologic response (eRVR-) and 100 others stopped the study before the randomisation carried out at week 20.

⁴ Patients with an HCV RNA level undetectable at week 4 and which were also undetectable at week 12

Of the 352 patients who had achieved an extended rapid virologic response (eRVR+), the percentage of SVR at the 24th week of follow-up (primary endpoint) was 92% (144/156) in the T12-PR24 group and 88% (139/158) in the T12-PR48 group.

The lower limit of the 95% confidence interval of the difference in the percentages of SVR between the T12-PR24 and T12-PR48 groups in the eRVR+ patients was higher than the non-inferiority of -10.5% defined in the protocol in the per protocol population (4.5% CI_{95%} [-2.1%; 11.1%]). Similar results were observed in ITT analysis.

Consequently, the non-inferiority of a treatment regimen combining telaprevir with a bi-therapy for 24 weeks (T12-PR24) compared with a bi-therapy for 48 weeks (T12-PR48) was demonstrated in terms of sustained virologic response in the patients who had achieved an extended rapid virologic response (eRVR+).

In all, in previously untreated, non-cirrhotic adults, the duration of the bi-therapy with peginterferon alfa and ribavirin validated in the Marketing Authorisation following the 12 weeks of tri-therapy depends on detectability of the viral load during the treatment at week 4 and week 12. When an extended rapid virologic response is achieved, 12 additional weeks of bi-therapy are recommended, i.e. a total treatment period of 24 weeks. On the other hand, when the viral load is detectable at week 4 or at week 12, 36 additional weeks of bi-therapy are recommended, i.e. a total treatment period of 48 weeks.

In previously untreated cirrhotic patients for whom the data are limited, the treatment regimen validated conservatively in the Marketing Authorisation involves tri-therapy for 12 weeks combining telaprevir, peginterferon alfa-2a and ribavirin followed by 36 additional weeks of bi-therapy, irrespective of non-detectability of the viral load at week 4 and week 12, i.e. a total treatment period of 48 weeks.

For information, of the 30 cirrhotic patients who achieved an eRVR+ in the ILLUMINATE study, 12/18 achieved an SVR in the group involving a total treatment period of 24 weeks and 11/12 with a total treatment period of 48 weeks.

3.1.2 Adults whose prior treatment failed

REALIZE study (study C216)

A randomised, double-blind versus placebo study, whose main aim was to evaluate the efficacy of two treatment regimens of telaprevir combined with peginterferon alfa-2a and ribavirin (simultaneous TPR and deferred TPR) versus peginterferon alfa-2a and with ribavirin (PR) in adults infected with genotype 1 chronic hepatitis C whose bi-therapy failed (peginterferon alfa-2a or 2b and ribavirin).

Main inclusion criteria:

- adults aged between 18 and 70 infected with genotype 1 chronic hepatitis C who have not achieved a sustained virologic response:
 - relapser patients: the relapse was defined by a viral load undetectable at the end of the prior treatment then detectable during the follow-up period of 24 weeks;
 - non-responder patients: non-response was defined by the persistence of viral RNA at the end of the prior treatment of at least 12 weeks. Non-responder patients involved two sub-groups:
 - non-responders with partial response: reduction in the viral load $\geq 2 \log_{10}$
 - non-responders with null response: reduction in the viral load $< 2 \log_{10}$
- availability of a liver biopsy,
- for patients with fibrosis or cirrhosis: no diagnosed or suspected hepatocellular carcinoma.

Main non-inclusion criteria:

- patients co-infected with HIV or hepatitis B virus,
- decompensated liver disease,
- patients with a history of organ transplant (except for corneal and skin grafts),
- patients not responding to prior treatment, defined by a viral load undetectable then again detectable during prior treatment.

Treatment: the patients were randomised (1: 2: 2) into three groups.

Randomisation was stratified by HCV RNA viral load (< 800,000 IU/ml versus ≥ 800,000 IU/ml) and response to prior treatment (relapsers versus non-responders). In non-responder patients, an additional stratification was carried out between non-responders with partial response and non-responders with null response.

All the treatment groups were involved in pegylated bi-therapy for 48 weeks combining peginterferon alfa-2a (180 µg/week subcutaneously) and ribavirin (1,000 mg/day for patients weighing less than 75 kg or 1,200 mg/day if ≥ 75 kg by the oral route in two doses).

The telaprevir was administered for 12 weeks at a dose of 750 mg every 8 hours (i.e. 2 tablets 3 times/day), i.e. from the start of the treatment in the simultaneous TPR group, i.e. after an initial bi-therapy of 4 weeks in the deferred TPR group.

1. PR group (N=132):

bi-therapy with peginterferon alfa-2a and ribavirin for 48 weeks combined with placebo for the 16 first weeks.

2. Simultaneous TPR group (N=266): simultaneous combination of

- telaprevir for 12 weeks then placebo for 4 weeks
- bi-therapy with peginterferon alfa-2a and ribavirin for 48 weeks.

3. Deferred TPR group (initial bi-therapy of 4 weeks) (N=264): combination of

- placebo for 4 weeks then telaprevir for 12 weeks (from week 5 to week 16)
- bi-therapy with peginterferon alfa-2a and ribavirin for 48 weeks.

In the case of plasma HCV RNA >100 IU/mL at week 4, week 6 and week 8 after the start of treatment with telaprevir, telaprevir was stopped and the peginterferon and ribavirin were continued.

Following amendments to the protocol, a reduction in the doses of ribavirin was considered whilst administration of erythropoietin for anaemia management was prohibited.

Primary efficacy endpoint: achieving a sustained virologic response (SVR), defined as an HCV RNA viral load undetectable at the 24th week of follow-up after the end of the planned 48 weeks of treatment, in the FAS (Full Analysis Set) population including all of the randomised patients who received at least one treatment (peginterferon alfa-2a, ribavirin or telaprevir/placebo).

The main analysis involved a comparison between the simultaneous TPR versus PR groups and deferred TPR versus PR groups.

If the superiority of the simultaneous TPR and deferred TPR groups over the PR group was demonstrated, an analysis of non-inferiority between the simultaneous TPR and deferred TPR groups was scheduled.

The statistical analysis was based on the following hypothesis: non-inferiority was established if the lower limit of the 95% confidence interval of the difference between the percentages of SVR (simultaneous TPR less deferred TPR) was greater than -10%.

Secondary endpoints, in particular:

- SVR amongst the patients with a rapid virologic response (RVR) defined by an HCV RNA viral load undetectable 4 weeks after the start of the treatment with telaprevir or with placebo;
- SVR amongst the patients with an extended rapid virologic response (eRVR) defined by an HCV RNA viral load undetectable 4 and 12 weeks after the start of the treatment with telaprevir or with placebo;
- percentage relapse at week 72 defined by the proportion of subjects with an HCV RNA level undetectable at the end of the treatment but detectable at the end of follow-up.

Results:

In all, 662 patients were included. Around 93% of the patients were Caucasian. The median age of the patients was 51 years (21-70 years) and 70% of the patients were male. A little over half (54%) of the patients were infected with a genotype 1a HCV and 46% with genotype 1b HCV. Most of the patients (89%) had a very high initial viral load ($\geq 800,000$ IU/ml). The percentage of patients with a METAVIR² fibrosis score of F0/1/2 was 52%. Cirrhosis (METAVIR score F4) was present in 26% (169/662) of the patients.

About half (53.5%) of the patients included were relapsers after prior treatment, 18.7% were partial non-responders and 27.8% were null responders.

- primary endpoint:

The percentage of patients who achieved a sustained virologic response at the 24th week of follow-up was 16.7% in the PR group, 64.3% in the simultaneous TPR group and of 66.3% in the deferred TPR group, i.e. an absolute increase of 46.8% between the simultaneous TPR and PR groups ($p < 0.001$) and an absolute increase of 49.8% between the deferred TPR and PR groups ($p < 0.001$) in the FAS population.

The difference in SVR between the groups including telaprevir compared with the PR group depending on the response to prior treatment was (simultaneous TPR vs PR and deferred TPR vs PR):

- relapser patients: 60.5% (83.4% vs 23.5%) and 64.9% (87.9% vs 23.5%);
- non-responder patients: 35% between each of the groups (41.3% vs 9.4% and 41.5% vs 9.4%).

The SVR at the 24th week of follow-up in the relapser patients sub-group proved to be superior to that achieved in the non-responders (see table 3). The percentage of SVR was the lowest (approximately 30%) in the stratum of patients who were null responders to prior treatment with peginterferon alfa and ribavirin.

Table 3: SVR depending on the response to prior treatment: REALIZE study

SVR at the 24 th week of follow-up	PR group (N=132)	Simultaneous TPR group (N=266)	Deferred TPR group (N=264)
Response to prior treatment			
Relapsers	16/68 (23.5%)	121/145 (83.4%)	124/141 (87.9%)
Non-responders:	6/64 (9.4%)	50/121 (41.3%)	51/123 (41.5%)
- partial responders	4/27 (14.8%)	29/49 (59.2%)	26/48 (54.2%)
- null responders	2/37 (5.4%)	21/72 (29.2%)	25/75 (33.3%)

- other endpoints:

The SVR at the 24th week of follow-up was more frequent amongst the patients who achieved an RVR⁵ or an eRVR⁶ (see table 4).

Table 4: SVR depending on the RVR or the eRVR: REALIZE study

SVR at the 24 th week of follow-up	PR group (N=132)	Simultaneous TPR group (N=266)	Deferred TPR group (N=264)
Patients who achieved an RVR			
Relapsers	2/2 (100%)	91/101 (90%)	116/126 (92%)
Non-responders	1/1 (100%)	33/51 (65%)	39/62 (63%)
Patients who achieved an eRVR			
Relapsers	2/2 (100%)	91/95 (96%)	116/123 (94%)
Non-responders	1/1 (100%)	33/46 (72%)	38/57 (67%)

5 Rapid virologic response: viral load HCV RNA undetectable 4 weeks after the start of the treatment with telaprevir or placebo

6 Extended rapid virologic response: viral load HCV RNA undetectable 4 and 12 weeks after the start of the treatment with telaprevir or placebo

The SVR was observed more frequently when the reduction in the viral load at the 4th week of treatment was $\geq 1 \log_{10}$ compared with a reduction $< 1 \log_{10}$ in particular (see table 5). It should, however, be noted that the numbers in several sub-groups were very small, particularly in the PR group.

Table 5: SVR depending on the reduction in viral load at week 4 and depending on the response to prior treatment: REALIZE study

SVR at the 24 th week of follow-up	PR group (N=132)	Simultaneous TPR group (N=266)	Deferred TPR group (N=264)
Reduction in viral load $< 1 \log_{10}$ at week 4			
Relapsers	0/6 (0%)	-	8/13 (62%)
Non-responders	0/31 (0%)	0/2 (0%)	16/59 (27%)
Reduction in viral load $\geq 1 \log_{10}$ at week 4			
Relapsers	15/55 (27%)	114/133 (86%)	106/113 (94%)
Non-responders	6/29 (21%)	48/110 (44%)	31/55 (57%)

Amongst the patients with a viral load undetectable at the end of the treatment, the percentage of relapse at week 72 was of the same order between the simultaneous TPR (19.5%) and deferred TPR (17%) groups. The relapser patients after prior treatment relapsed less frequently than the non-responder patients (7% vs 21-27%), see table 6.

Table 6: Percentage of relapse at week 72 depending on the response to prior treatment: REALIZE study

Percentage of relapse at week 72	PR group (N=132)	Simultaneous TPR group (N=266)	Deferred TPR group (N=264)
Relapsers	30/46 (65%)	10/135 (7%)	9/138 (7%)
Non-responders:	3/9 (33%)	16/69 (23%)	18/72 (25%)
- partial responders	0/4 (0%)	8/39 (21%)	9/36 (25%)
- null responders	3/5 (60%)	8/30 (27%)	9/36 (25%)

Analyses in sub-groups were carried out, particularly according to parameters with a potential impact on sustained virologic response, i.e. genotype, initial viral load and the fibrosis stage.

Amongst the relapser patients, the SVR in the groups involving telaprevir was of the same order whatever the genotype sub-type (1a or 1b), the initial viral load and the stage of fibrosis (grouped TPR groups: F0-2: 86%, F3: 85%, F4: 84%; PR group: F0-2: 32%, F3: 13%, F4: 13%).

Amongst the partial responder and null responder patients, the SVR in the groups involving telaprevir was more frequent in the genotype 1b patients with a high initial viral load ($< 800,000$ IU/ml vs $\geq 800,000$ IU/ml) and in the patients with less fibrosis:

- partial responders: grouped TPR groups: F0-2: 72%, F3: 56%, F4: 34%; PR group: F0-2: 18%, F3: 0%, F4: 20%;
- null responders: grouped TPR groups: F0-2: 41%, F3: 39%, F4: 14%; PR group: F0-2: 6%, F3: 0%, F4: 10%.

It should, however, be noted that the patients with an initial viral load $<$ than 800,000 IU/ml represented 11% of the patients included and that the number of patients per METAVIR fibrosis score was small in each of the treatment groups ($<$ 30).

Decision on the treatment regimens:

Since superiority of the two telaprevir treatment groups over placebo was demonstrated, the consecutive non-inferiority analysis laid down in the protocol was carried out.

The lower limit of the confidence interval of the difference in the percentages of SVR was lower than the predefined limit of - 10% for the whole of the population (-3,0% CI_{95%} [-13%; 7%]) and for each of the sub-groups depending on the response to prior treatment: relapsers: -4.3% [-12.6%, 3.9%] and null responders: -0.4% [-13.6%, 12.9%].

Consequently, the non-inferiority of the simultaneous TPR group compared with the deferred TPR group was not demonstrated in terms of SVR at week 72.

Although non-inferiority was not demonstrated between the simultaneous TPR and deferred TPR groups, considering there was no significant difference in terms of relapse, virologic failure during the treatment and the emergence of HCV-resistant variants, the treatment regimen combining telaprevir with peginterferon alfa and ribavirin was the one immediately adopted in the Marketing Authorisation (simultaneous TPR group).

In all, in the non-responder patients (partial responders and null responders), the validated treatment regimen involves 12 weeks of tri-therapy (telaprevir, peginterferon and ribavirin) followed by 36 weeks of peginterferon and ribavirin, i.e. a total treatment period of 48 weeks (which corresponds to the regimen evaluated in the simultaneous TPR group).

On the other hand, in non-cirrhotic patients and relapsers after prior treatment, a treatment duration different from that studied in the REALIZE study has been validated when the viral load is undetectable at week 4 and week 12. This response-guided treatment regimen involves 12 weeks of tri-therapy (telaprevir, peginterferon and ribavirin) followed by 12 weeks of peginterferon and ribavirin, i.e. a total treatment duration of 24 weeks. When the viral load is detectable at week 4 or at week 12, the treatment regimen is identical to the one validated in the non-responder patients.

3.2. Adverse effects

3.2.1 Tolerance data from the phase II and III studies (see SPC)

The adverse events linked with telaprevir combined with the peginterferon and ribavirin most frequently reported (frequency $\geq 1/10$) were: anaemia, nausea, diarrhoea, vomiting, haemorrhoids, proctalgia, pruritus, skin rash.

The adverse events of moderate or more severe intensity (\geq grade 2) were more frequent in patients treated with telaprevir and peginterferon and ribavirin than in those treated with peginterferon and ribavirin.

During the treatment phase with telaprevir/placebo, the adverse events of grades ≥ 3 most frequently reported in the telaprevir group (frequency $\geq 1\%$) were: anaemia, skin rash, thrombopenia, lymphopenia, pruritus and nausea.

Particular adverse events

Skin rash

In the phase II and III clinical studies versus placebo, skin rash was more severe and more frequent (55% vs 33%) with the combination of telaprevir with peginterferon alfa and ribavirin than with the bi-therapy.

Severe skin rash (mainly of the eczematous and pruriginous type and covering more than 50% of the body surface) was reported in 4.8% of the patients who received treatment with telaprevir in combination with peginterferon alfa and ribavirin versus 0.4% of the patients who received only peginterferon alfa and ribavirin.

An improvement in the skin rash occurred after the end of the treatment or after stopping the treatment with telaprevir; however, it may take several weeks for the skin rash to disappear.

Cases of DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) occurring in the form of a skin rash combined with eosinophilia with one or more of the following signs: fever, lymphadenopathy, oedema of the face, and internal organ disorders (hepatic, renal, pulmonary) were suspected in 0.4% of the patients. Stevens-Johnson syndrome was observed in fewer than 0.1% of the patients. All of these reactions disappeared when the treatment was stopped.

Because of the occurrence of skin rash, 5.8% of the patients stopped the telaprevir and 2.6% stopped the tri-therapy versus 0% in the patients treated only with bi-therapy (peginterferon alfa and ribavirin).

Anaemia

In the phase II and III clinical studies versus placebo, anaemia (defined as a haemoglobin concentration < 10 g/dl) was more frequent with the combination of telaprevir with peginterferon alfa and ribavirin than with peginterferon alfa and ribavirin: 32.1% vs 14.8% (whose haemoglobin concentration < 8.5 g/dl: 8% vs 2%).

Management of the anaemia involved, more frequently in the patients treated with telaprevir combined with the bi-therapy than in those treated with bi-therapy alone:

- reductions in the dose of ribavirin (when the haemoglobin concentration was between 8.5 and 10 g/dl): 21.6% vs 9.4%;
- transfusions: 2.5% vs 0.7% during the treatment phase with telaprevir/placebo and 4.6% vs 1.6% throughout the study.

The administration of erythropoietin was not authorised in the studies.

Because of the occurrence of anaemia, 1.9% of the patients stopped the treatment with telaprevir and 0.9% stopped the tri-therapy versus 0.5% in the patients treated only with bi-therapy (peginterferon alfa and ribavirin).

Anorectal signs and symptoms

The majority of these events (haemorrhoids, anorectal discomfort, anal pruritus and sensation of anal burning) were of light to moderate intensity; very few led to the treatment being stopped and they disappeared when the treatment with telaprevir had ended.

3.2.2 Tolerance data from the phase III studies: ADVANCE, ILLUMINATE and REALIZE

➤ Previously untreated adults

ADVANCE study (study 108)

Discontinuation of treatment because of adverse events was reported in 3.6% of the patients of the PR group, 7.7% of the T8-PR-TGR group and 6.9% of the T12-PR-TGR group. The adverse events which led to the treatments being stopped included: anaemia, fatigue, nausea and skin rash.

Serious adverse events were observed in 6.6% of the patients of the PR group, 8.5% of the T8-PR-TGR group and 9.1% of the T12-PR-TGR group.

ILLUMINATE study (study 111)

Of the patients who achieved an extended rapid virologic response (eRVR+), stoppage of treatment (telaprevir) because of adverse events was reported in 13% of the patients of the T12-PR24 group and 13.8% of the T12-PR48 group. In the group of the patients who had not achieved an extended rapid virologic response (eRVR-), stoppage of treatment because of adverse events was reported in 11% of the patients. Adverse events that led to discontinuation of the treatments included: skin rash, fatigue, anaemia, nausea and vomiting. Serious adverse events were observed in 2.5% of the patients of the T12-PR24 (eRVR+) group and in 10% of the T12-PR48 (eRVR+) group.

➤ Adults whose prior treatment failed: REALIZE study (study C216)

Discontinuation of treatment because of adverse events was reported in 3% of the patients of the PR group and in 12.8% of the grouped TPR group. Adverse events that led to discontinuation of the treatment included: anaemia, skin rash.

Serious adverse events were observed in 5.3% of the patients of the PR group and in 12.3% of the group TPR groups.

3.3. Other data

3.3.1 Long-term follow-up

Long-term follow-up (3 years) is in progress to evaluate maintenance of the virologic response and changes in HCV-variants in the subjects who had not achieved an SVR (*EXTEND study or 112*).

The intermediate results involving 123 patients showed that 99% (122/123) of the patients maintained their SVR status throughout the available follow-up period (median duration of 22 months).

3.3.2 Resistance

According to the SPC, of 1,169 patients included in phase III studies and treated following a regimen consisting of 12 weeks of telaprevir combined with peginterferon alfa and ribavirin, 125 presented with virologic failure during the treatment and 90 relapsed.

The emergence of telaprevir-resistant HCV variants was detected more frequently in the patients with virologic failure (105/125, i.e. 84%) than in relapse patients (55/90, i.e. 61%).

Virologic failure during treatment with telaprevir was more frequent amongst null responders to prior treatment than amongst previously untreated patients and relapsers or partial responders to prior treatment.

Of 255 patients included in the phase III studies (108, 111 and C216) in whom telaprevir-resistant variants appeared during the treatment, 152 patients (60%) no longer presented with resistant variants (median follow-up of 10 months).

3.3.3 Efficacy and tolerance of telaprevir in combination with peginterferon alfa-2b

No data on the efficacy and tolerance of telaprevir in combination with peginterferon alfa-2b are available in patients whose prior treatment failed.

The only data available are based on a phase II, open-label study carried out in previously untreated patients. The SVR was comparable between the group involving peginterferon alfa-2a (N=80) and the one involving peginterferon alfa-2b (N=81). However, in patients treated with peginterferon alfa-2b, virologic escape was observed more frequently and eligibility for a shorter total treatment duration (24 weeks) was less frequent (see SPC Special warnings section).

3.4. Conclusion

In the treatment of genotype 1 chronic hepatitis C virus infection, the efficacy and adverse effects of telaprevir combined with peginterferon alfa-2a and ribavirin were evaluated versus peginterferon alfa-2a combined with ribavirin in randomised, double-blind studies on previously untreated adults or adults whose prior treatment with peginterferon combined with ribavirin failed, in the absence of liver decompensation.

The addition of telaprevir (750 mg 3 times/day) to peginterferon alfa-2a/ribavirin (TPR) resulted in an increase in the percentage of sustained virologic response (viral load undetectable at the 24th week of follow-up) compared with the combination peginterferon alfa-2a/ribavirin (PR):

- in previously untreated adults: T12-PR-Response-Guided Treatment: 74.7% versus PR: 43.8%, $p < 0.0001$, i.e. an absolute gain of 31% (ADVANCE study);

- in adults whose prior treatment failed: simultaneous TPR: 64.3% versus PR: 16.7%, $p < 0.0001$, i.e. an absolute gain of 47% (REALIZE study).

The sustained virologic response (SVR) observed 24 weeks after stoppage of the treatment was less frequent in:

- patients whose prior treatment failed than in treatment-naïve patients,
- non-responder patients than in relapser patients,
- null responder patients than in partial responder patients.

Furthermore, in null responders to prior treatment and cirrhotic patients (representing a small number of patients in the REALIZE study), only 14% had an SVR in the telaprevir treatment groups.

The data from a long-term follow-up study (in progress) will make it possible to evaluate amongst other things maintenance of the virologic response and viral resistance at 3 years.

The treatment regimen involves a phase of tri-therapy telaprevir/peginterferon alfa/ribavirin, for 12 weeks followed by a bi-therapy with peginterferon alfa/ribavirin. The total treatment duration is maintained at 48 weeks. It can be shortened to 24 weeks depending on the response achieved during treatment in the treatment-naïve, non-cirrhotic patients or patients whose prior treatment failed (although not evaluated in this sub-group in a phase III study) when the HCV RNA viral load is undetectable at the 4th and 12th week of treatment. The treatment regimen validated in the Marketing Authorisation does not make provision for 4 weeks of bi-therapy prior to the tri-therapy, although the non-inferiority analysis carried out on patients whose prior treatment failed was not conclusive.

In terms of tolerance, the addition of telaprevir to peginterferon alfa-2a/ribavirin increased:

- the adverse events, particularly grades ≥ 2 and stoppage of treatment because of an adverse event. The adverse events of grades ≥ 3 most frequently reported in the telaprevir group (frequency $\geq 1\%$) were: anaemia, skin rash, thrombopenia, lymphopenia, pruritus and nausea;
- cutaneous toxicity: skin rashes were more severe and more frequent with telaprevir. Cases of severe toxicoderma (Stevens-Johnson syndrome and DRESS) were observed with telaprevir combined with peginterferon alfa and ribavirin;
- the risk of anaemia (32% vs 15% with the bi-therapy). Reductions in the dose of ribavirin and/or transfusions were more frequent in the adults treated with telaprevir, whether or not they had been treated previously. The use of EPO was not permitted in the studies.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

The severity of hepatitis C is linked with its frequent progression to chronicity which can lead to long-term cirrhosis, hepatocellular insufficiency and hepatocellular carcinoma. Of the six hepatitis C virus genotypes, genotype 1 is predominant.

These proprietary medicinal products fall within the category of first- or second-line tri-therapy (in combination with peginterferon alfa and ribavirin).

They are intended as curative therapy.

The efficacy/adverse effects ratio is modest, particularly because of the cutaneous toxicity.

Public health benefit:

Hepatitis C represents a moderate public health burden. In the indication (treatment of patients infected with genotype 1 HCV virus hepatitis C, with compensated liver disease), the burden affects more particularly the population of pre-treated patients and remains moderate.

The reduction in morbidity and mortality attributable to chronic hepatitis C is a public health need that is consistent with an established priority (GTNDO*, National hepatitis B and C control plan, 2009-2012).

The data from clinical trials have shown a substantial impact of telaprevir treatment on the rate of sustained virologic response, particularly in pre-treated patients. The modelling results show that the antiproteases have an impact on the morbidity and mortality of the patients treated (progression towards chronicity, liver fibrosis, liver cancer, death). This impact is substantial in pre-treated patients and small in treatment-naïve patients.

The impact on quality of life and the organisation of care is not documented.

Transferability is questionable, particularly because of the complexity of the treatment regimen, the *not yet routine* performance of the IL-28 genotype test before treatment and the absence of data in patients co-infected with HIV.

The treatment with telaprevir, in combination with peginterferon alfa and ribavirin, therefore seems able to provide an additional partial response to the identified public health need.

Consequently, in the current state of knowledge, a moderate public health benefit is expected for INCIVO in this indication.

*GTNDO: Group technique national de définition des objectifs (DGS-2003) [= National Technical Group Defining Objectives]

There is a treatment alternative validated in the Marketing Authorisation, VICTRELIS (boceprevir).

Consequently, the actual benefit of INCIVO is substantial.

4.2. Improvement in actual benefit (IAB)

Taking into account:

- the degree of virologic efficacy achieved by the addition of telaprevir to the bi-therapy peginterferon alfa/ribavirin, particularly in patients whose bi-therapy failed for whom no alternative treatment is available,
- the possible reduction in the total treatment duration of 48 weeks (bi-therapy) to 24 weeks (tri-therapy) in some patients (previously untreated, non-cirrhotic patients or relapsers achieving a rapid response during treatment)

but considering,

- the increased cutaneous toxicity, particularly severe toxicoderma including DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) and Stevens-Johnson syndrome,
- the non-optimum level of proof of the data supporting the decision on treatment regimens, particularly in non-cirrhotic patients and relapsers after prior treatment achieving a rapid response during treatment

the Committee considers that the addition of telaprevir to the bi-therapy with peginterferon/ribavirin provides, compared with this bi-therapy,:

- a level IV IAB (minor) in previously untreated adults,
- a level III IAB (moderate) in adults whose treatment failed

in the treatment of genotype 1 chronic hepatitis C, in the absence of liver decompensation.

4.3. Therapeutic use

As the Consensus Conference on the treatment of hepatitis C in February 2002⁷ has not been updated, the therapeutic use of INCIVO in the management of patients infected with genotype 1 HCV is based on the ADVANCE, ILLUMINATE and REALIZE pivotal studies.

The aim of the treatment is eradication of the virus in order to prevent complications linked with the infection.

The decision to treat should take into account a set of criteria, including biochemical, virological and biological criteria, particularly the fibrosis stage.

The reference treatment of the chronic infection with the hepatitis C virus consists of a bi-therapy with pegylated interferon/ribavirin for 6 to 12 months. In the event of adverse effects or a contraindication to ribavirin, the pegylated interferon is used as a monotherapy. In the population of patients infected with genotype 1 HCV, this bi-therapy, as first-line treatment, results in therapeutic failure in more than 50% of the patients. The percentage of response is even smaller during a second treatment in patients whose treatment failed.

In the studies carried out on mono-infected, non-transplant adults, undergoing first-line treatment or whose treatment failed with the combination peginterferon alfa-2a/ribavirin, in the absence of liver decompensation, an absolute gain in terms of sustained virologic response was of the order of 30% to 45% with the addition of telaprevir to the bi-therapy peginterferon/ribavirin compared with this bi-therapy alone.

After 12 weeks of treatment combining telaprevir, peginterferon alfa and ribavirin, the duration of the bi-therapy (peginterferon alfa/ribavirin) recommended in the Marketing Authorisation is:

- 12 weeks (i.e. a total treatment period of 24 weeks): in previously untreated patients or non-cirrhotic relapsers after prior treatment achieving an extended rapid virologic response (characterised by an HCV RNA viral load undetectable at the 4th and 12th weeks of treatment);
- 36 weeks (i.e. a total treatment period of 48 weeks):
 - in previously untreated patients or relapsers after prior treatment with an HCV RNA viral load detectable at week 4 or week 12,
 - in all the non-responder patients (partial or null responders),
 - in all the cirrhotic patients.

Monitoring the efficacy of the treatment is based on repeated measurement of the viral load. A viral load > 1,000 IU/ml at the 4th or to the 12th week of treatment requires the tri-therapy (telaprevir, peginterferon and ribavirin) to be stopped.

⁷ Consensus Conference on the treatment of hepatitis C. February 2002. Available on: http://www.infectiologie.com/site/medias/_documents/consensus/HCV-2002.pdf

Because of the worrying cutaneous toxicity of telaprevir, close monitoring of the skin rash and the specific rules on stopping treatment described in the SPC are essential. This identified risk is the subject of a risk minimisation plan.

A better knowledge of the predictive factors of response, particularly a rapid virologic response, the IL28B genotype, will make it possible to identify the patients who would not derive any significant benefit from the addition of a protease inhibitor to the bi-therapy. The therapeutic decision should also take into account the possibility of inclusion in clinical trials evaluating new molecules for the cirrhotic patients who are null responders after prior treatment, in view of the limited data and the small percentage of SVR observed.

A study comparing two protease inhibitors (boceprevir and telaprevir) is not available taking into account the concomitant clinical developments.

Furthermore, no clinical data are available concerning re-treatment of the patients whose treatment involving an NS3-4A protease inhibitor of HCV failed.

Therapeutic use of INCIVO

In the treatment of genotype 1 chronic hepatitis C virus infection, in the event of compensated liver disease, taking into account the levels of virologic efficacy which differ depending on the sub-populations evaluated and its adverse effects profile, telaprevir, and likewise boceprevir, in combination with the pegylated interferon and ribavirin,

- would constitute a new therapeutic method suited to some profiles of previously untreated patients,
- should represent the reference in some patients whose bi-therapy failed.

4.4. Target population

The target population is represented by previously untreated patients infected with genotype 1 chronic hepatitis C whose prior treatment failed, in the absence of liver decompensation.

The epidemiological data on hepatitis C come mainly from the prevalence survey carried out by the Health Monitoring Institute in 2004.⁸

The prevalence of anti-HCV antibody seropositivity was estimated in France at approximately 0.84% (95% CI: 0.65-1.10), i.e. 367,055 people (269,361-464,750).

In the people with anti-HCV antibodies, the prevalence of the chronic infection (RNA-positive) was estimated at 65% (95% CI: 50-78), which corresponds to a global prevalence in the population of 0.53% (95% CI: 0.40-0.70), i.e. 232,196 people (167,869-296,523) aged between 18 and 80.

Only 59.1% of these people are diagnosed, i.e. 137,228 patients (99,210-175,245) from which 23,000 people should be deducted because they are HIV carriers and co-infected with HCV,⁹ INCIVO not being indicated in patients co-infected with HIV, i.e. 114,228 (76,210-152,245).

Some of these cannot be treated because of a contraindication to the treatment (liver decompensation, for example). The population can be estimated at approximately 10%,¹⁰ i.e. 113,026 (68,589-137,020) people who are able to benefit from a treatment.

Approximately 60% of the cases of hepatitis C in France are genotype 1.¹¹

Consequently, the population able to receive treatment would be around 67,816 patients (41,153 to 82,212).

⁸ Meffre C, Le Strat Y, Delarocque-Astagneau E, Antona D, Desenclos JC. Prevalence of hepatitis B and C in France in 2004 - Health Monitoring Institute, InVS, Saint-Maurice, March 2007
http://www.invs.sante.fr/publications/2006/prevalence_b_c/vhb_france_2004.pdf

⁹ National hepatitis B and C control plan 2009-2012 http://www.sante.gouv.fr/IMG/pdf/Plan_national_Hepatitis.pdf

¹⁰ National hepatitis C monitoring on the basis of the voluntary reference centres 2001-2006. Health Monitoring Institute - April 2008. http://www.invs.sante.fr/surveillance/hepatitis_c/poleref_volontaire/stages_cliniques.pdf

¹¹ National hepatitis C monitoring on the basis of the reference centres Epidemiological data 2001-2007 INVS

As well as the cases already diagnosed, the new cases of hepatitis C which will be diagnosed during the year will have to be taken into account. This figure is estimated at 5,000 new cases per year in France,¹² i.e. approximately 3,000 new cases of genotype 1. In viraemic patients newly treated for hepatitis C in the reference centres in 2007, an antiviral treatment was instituted in 26% of the patients, was planned for 19% of the patients and not planned for 55% of the patients.¹³

Furthermore, in 2006, approximately 72,500 people affected with hepatitis C were included under Long-Term Diseases no. 6 “Chronic active diseases of the liver and cirrhosis”.¹⁵

Lastly, it should be possible to estimate the number of patients not previously treated or whose prior treatment failed who may benefit from the addition of a protease inhibitor in addition to the standard pegylated bi-therapy.

4.5. Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services.

The Committee would like to re-evaluate this medicine in one year in the light of the updated clinical data, particularly those relating to cutaneous tolerance.

4.5.1 Packaging: Appropriate for the prescription conditions

4.5.2 Reimbursement rate: 65%

Considering the data available, the complexity of the treatment regimens for management of the patients infected with hepatitis C, possible performance of not-yet routine IL-28 genotype testing and the potential arrival of new molecules, additional data are expected on:

- the characteristics of the patients treated for hepatitis C
- the conditions of use (therapeutic strategies set up, genotype testing before treatment, treatments undertaken, etc.).

Use of the database on patients infected with hepatitis B and C, initiated by the ANRS [National Aids Research Agency] (HEPATER study), which will be set up in 2012, could be considered.

¹² Roudot-Thoraval F. Development of the epidemiological characteristics of hepatitis C. *Gastroenterol Clin Biol* 2002; 26: B138-B143

¹³ Institution of an anti-viral treatment (a) in viraemic patients newly treated for hepatitis C in the reference centres - Data 2004-2007