TRANSPARENCY COMMITTEE
Opinion
14 May 2014.

INCIVO 375 mg, coated tablet
4 bottles with child-proof closure containing 42 capsules (CIP: 34009 217 378 5 1)
1 bottle with child-proof closure containing 42 capsules (CIP: 34009 219 249 8 5)

Applicant: JANSSEN-CILAG

<table>
<thead>
<tr>
<th>INN</th>
<th>telaprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATC Code (2013)</td>
<td>J05AE11 (protease inhibitors)</td>
</tr>
</tbody>
</table>

Reason for the review

Re-assessment of the actual benefit and improvement in actual benefit at the request of the Transparency Committee in accordance with Article R 163-21 of the French Social Security Code

Change in the conditions for inclusion following amendments to the SPC

Lists concerned

National Health Insurance (French Social Security Code L.162-17)
Hospital use (French Social Security Code L.5123-2)

Indication concerned

“INCIVO, in combination with peginterferon alfa and ribavirin, is indicated in the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease (including cirrhosis):
- who are treatment-naïve;
- who have previously been treated with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin, including relapsers, partial responders, and null-responders.”
### Actual Benefit

**Substantial**

### Improvement in Actual Benefit

In the treatment of chronic hepatitis C due to genotype 1 HCV in adult patients with compensated liver disease, INCIVO in combination with dual therapy with peginterferon alfa and ribavirin provides a minor improvement in actual benefit (Level IV) in comparison with this dual therapy.

### Therapeutic use

In light of the safety profile, the risk of development of resistance, but above all the arrival of new treatments with a better profile in terms of efficacy, safety, resistance, and drug interactions, together with a shorter duration of treatment, the role of the first-generation protease inhibitors INCIVO and VICTRELIS in the treatment strategy is thus becoming very restricted.

### Recommendation

The Transparency Committee wishes to re-assess this medicinal product in the short term in the light of the changing clinical data and the changing approach to the management of chronic hepatitis C.
**01 ADMINISTRATIVE AND REGULATORY INFORMATION**

<table>
<thead>
<tr>
<th>Marketing Authorisation</th>
<th>Dates initiated (centralised procedure):</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- 19/09/2011: box with 4 HDPE bottles</td>
</tr>
<tr>
<td></td>
<td>- 13/10/2011: box with 1 HDPE bottle</td>
</tr>
<tr>
<td></td>
<td>Latest amendment, on 27/05/2013: dosage regimen of two daily intakes</td>
</tr>
<tr>
<td></td>
<td>The Marketing Authorisation is combined with a Risk Management Plan</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prescribing and dispensing conditions/special status</th>
<th>List I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital prescription restricted to specialists in gastroenterology and hepatology, internal medicine, and infectious diseases</td>
<td></td>
</tr>
<tr>
<td>Medicinal product authorised for dispensing to outpatients by hospital pharmacies (on ‘retrocession’ list)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ATC Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
</tr>
<tr>
<td>J</td>
</tr>
<tr>
<td>J05</td>
</tr>
<tr>
<td>J05A</td>
</tr>
<tr>
<td>J05AE</td>
</tr>
<tr>
<td>J05AE11</td>
</tr>
<tr>
<td>Antiinfectives for systemic use</td>
</tr>
<tr>
<td>Antivirals for systemic use</td>
</tr>
<tr>
<td>Direct acting antivirals</td>
</tr>
<tr>
<td>Protease inhibitors</td>
</tr>
<tr>
<td>telaprevir</td>
</tr>
</tbody>
</table>

**02 BACKGROUND**

In 2011, two first-generation hepatitis C virus (HCV) protease inhibitors, INCIVO (telaprevir) and VICTRELIS (boceprevir), obtained centralised Marketing Authorisation for the treatment of genotype 1 chronic hepatitis C in combination with pegylated interferon + ribavirin dual therapy. In its opinion of 14 December 2011, the Transparency Committee considered that, “taking into account:  
- the degree of virological efficacy achieved by the addition of telaprevir to the dual therapy peginterferon alfa/ribavirin, particularly in patients whose dual therapy failed and for whom no alternative treatment is available,  
- the possible reduction in the total treatment duration of 48 weeks (dual therapy) to 24 weeks (triple therapy) in some patients (previously untreated, non-cirrhotic patients or relapsers achieving a rapid response during treatment) but considering  
- the increased toxicoderma, particularly severe toxicoderma including DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) and Stevens-Johnson syndrome,  
- the sub-optimal level of proof of the data supporting the decision on treatment regimens, particularly in non-cirrhotic patients and relapsers after prior treatment achieving rapid response during treatment,  
the addition of telaprevir to the dual therapy with peginterferon/ribavirin provides, compared with this dual 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.”
In this opinion, the Transparency Committee pointed out that: “Considering the data available, the complexity of treatment regimens for the management of patients infected with hepatitis C, possible performance of not-yet routine IL28 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.”

In conclusion, the Transparency Committee indicated that it wished to re-assess the proprietary medicinal product INCIVO within one year, with updated clinical data, including those relating to cutaneous safety.

This document is based on the analysis of recent clinical and pharmacovigilance data provided by the company in response to the Transparency Committee’s request for a re-assessment of the proprietary medicinal product INCIVO.

## 03 DEFINITIONS

In accordance with the international terminology used, non-responder patients are patients who have not obtained HCV-RNA negativation at the end of treatment. These patients may be divided into:

- Partial responders: patients whose viral load decreased by at least 2 log IU/ml without obtaining negativation during the course of treatment;
- Null-responders: patients whose viral load decreased by less than 2 log IU/ml during a treatment period of at least 12 weeks.

Relapsers are patients whose HCV-RNA was negativated during treatment and whose viral load reappeared after discontinuation of treatment.

## 04 THERAPEUTIC 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-naïve;
- who have previously been treated with interferon alfa and ribavirin (pegylated or non-pegylated) alone or in combination with ribavirin, including relapsers, partial responders, and null-responders.”

## 05 DOSAGE

A dosage regimen consisting of two daily intakes was added to the Summary of Product Characteristics (SPC) in May 2013.

“INCIVO, 1125 mg dose (three 375 mg film-coated tablets) should be taken orally twice daily (b.i.d.) with food. Alternatively, 750 mg (two 375 mg tablets) can be taken orally every 8 hours (q8h) with food. The total daily dose is 6 tablets (or 2250 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 SPCs for these medicinal products should be consulted.

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

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

- Patients with undetectable hepatitis C virus ribonucleic acid (HCV-RNA) (target not detected) at weeks 4 and 12 receive an additional 12 weeks of peginterferon alfa and ribavirin alone for a total treatment duration of 24 weeks.
- Patients with detectable HCV-RNA at either 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 (target not detected) at week 4 or 12, an additional 36 weeks of peginterferon alfa and ribavirin alone for a total treatment duration of 48 weeks is recommended.

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

HCV-RNA levels should be monitored at weeks 4 and 12 to determine treatment duration. […]

**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.”
Hepatitis C is a serious condition owing to the fact that it frequently turns chronic, which in the long term can (in 10 to 20% of cases) lead to cirrhosis after a median period of between 10 and 30 years, depending on the presence or otherwise of various concomitant aggravating factors (male sex, alcohol, HIV co-infection and level of immunosuppression and HIV replication, fatty liver, age at time of infection, etc.), or even hepatocellular carcinoma (1 to 5% of cases of cirrhosis annually).

There are six genotypes of HCV, and subjects are generally infected with a single genotype. In France, genotype 1 (1a and especially 1b) is the most common (61.1%), followed by genotype 3 (18.6%); genotypes 2 (8.7%), 4 (9.1%), 5 (1.9%), and 6 (0.6%) are rarer. Genotypes 1 and 4 are associated with inferior treatment response, and genotype 3 with a higher risk of fatty liver.

At the time of diagnosis, the initial assessment includes, in particular, a virological workup (HCV genotyping) and a clinical, biological, morphological, and radiological workup looking for signs of severity. The HCV genotype influences therapeutic management and treatment response. The liver histology helps differentiate less active forms of hepatitis from chronic active hepatitis and to arrive at a histological diagnosis of cirrhosis. The METAVIR score separately assesses the degree of inflammation (A0 to A3) and the degree of fibrosis (F0 to F4).

The therapeutic objective is to cure the infection, defined by the sustained virological response (SVR), i.e. a viral load (HCV-RNA) undetectable 24 weeks (or 12 weeks) after the end of treatment. In sum, treatment of chronic hepatitis C is proposed in the following situations:
- In cases where the HCV genotype is predictive of a good treatment response (2 or 3) regardless of the degree of liver fibrosis;
- In cases of genotype 1 or 4, in the presence of septal fibrosis (F ≥ 2) or portal fibrosis (F1) accompanied by signs of major activity (A2 or A3);
- In cases of acute hepatitis;
- In cases of compensated cirrhosis;
- In cases of HIV-HCV co-infection with the same indications as in mono-infected patients;
- In cases of severe extrahepatic manifestations, including cryoglobulinaemia;
- In the event of planned virus eradication, especially at the patient’s request or in the context of medically-assisted procreation or pregnancy;
- In transplant patients. It should be noted that recurrence of HCV is almost constant in these patients, and that treatment for HCV may be proposed in this context.

---

7 The METVAR score measures the histological status of the liver. The F classification (F0 to F4) measures fibrosis. Stages F3-F4 designate a pre-cirrhotic to cirrhotic stage.
8 The sustained virologic response corresponds to undetectability of HCV RNA 24 weeks after the end of treatment.
Currently, treatment of chronic hepatitis C is based on the use of interferon alfa and ribavirin, with or without a combined protease inhibitor (boceprevir or telaprevir in genotype 1 patients). There is not currently any treatment strategy that does not involve interferon.

Until 2011, pegylated alfa interferon/ribavirin (PEG-IFN/RBV) dual therapy for 24 to 48 weeks was the reference treatment for hepatitis C. This treatment leads to a mean SVR of 65%, depending on the viral genotype (genotype 1 patients being the most difficult to treat: approximately 50% of SVR versus 80 to 85% for genotypes 2-3). The factors associated with poor response to dual therapy are a high viral load, genotype 1 or 4, and co-infection with HIV. It should be noted that interferon is poorly tolerated (flu-like symptoms, depression, etc.) and tolerability decreases with age and in cases of advanced fibrosis. Intolerance leads to treatment being discontinued in 10 to 30% of cases within the first 6 months. The main and almost invariable adverse effect of ribavirin is a fall in haemoglobin (by about 13% in the first two months) due to haemolysis.

In patients infected with genotype 1 HCV, the advent of direct acting compounds (HCV protease inhibitors: boceprevir and telaprevir)\textsuperscript{9,10} has led to a change in management strategy since 2011. In this population, triple therapy (peginterferon + ribavirin + protease inhibitor) constitutes a therapeutic approach suited to certain profiles of patients not treated previously (in particular patients not having factors predictive of a good response to peginterferon + ribavirin dual therapy) and represents the reference treatment in certain patients in whom peginterferon + ribavirin dual therapy has failed. Triple therapy (peginterferon + ribavirin + protease inhibitor) increases the efficacy of antiviral treatment of genotype 1 hepatitis C, enabling a cure (SVR) to be obtained in 65 to 75% of patients, sometimes with a 24-week treatment period (particularly in non-cirrhotic patients, not previously treated or relapsers obtaining rapid response during treatment). Even in the presence of factors predictive of poor response (IL28B non-CC genotype, with a fibrosis score of F3-F4), the chances of cure with triple therapy remain high and above 50%, with a substantial benefit for patients in comparison to dual therapy. However, the adverse effects associated with interferon and ribavirin are potentiated with this triple therapy (increased haematological toxicity in particular), accompanied by more frequent treatment discontinuations. Managing adverse effects and possible drug interactions requires closer patient surveillance by the doctor and the various actors involved in the care pathway.

It should be pointed out that interferon alfa is contraindicated in the following situations:
- autoimmune hepatitis,
- transplantation patients under treatment with immunosuppressants,
- psychiatric and decompensated thyroid disorders,
- severe renal impairment,
- decompensated cirrhosis.

In view of these limitations, medicinal products at least as effective as those employed in current treatment strategies (based on the use of interferon and ribavirin) need to be available, with a better safety and resistance profile, enabling strategies to be developed that do not include interferon (or even ribavirin) and offering the possibility of extending cover to patients with a greater medical need (in particular patients who are ineligible for or do not respond to interferon).

\textsuperscript{9} Opinion of the Transparency Committee of 14 December 2011 relating to VICTRELIS (boceprevir). Available at \url{www.has-sante.fr/}.

\textsuperscript{10} Opinion of the Transparency Committee of 14 December 2011 relating to INCIVO (telaprevir). Available at \url{www.has-sante.fr/}.
07 CLINICALLY RELEVANT COMPARATORS

07.1 Medicinal products

Currently, treatment of hepatitis C, irrespective of the genotype considered, is based on the use of the pegylated interferon + ribavirin (PEG-INF+RBV) combination.

Since 2011, in the case of patients with genotype 1 virus, two HCV protease inhibitors (boceprevir and telaprevir) are indicated in combination with PEG-INF+RBV.

In January 2014, sofosbuvir, a new antiviral agent active against all hepatitis C virus genotypes, the first representative of a new therapeutic category (nucleotide analogue specific for HCV, NS5B polymerase inhibitor) obtained Marketing Authorisation in the treatment of chronic hepatitis C.

<table>
<thead>
<tr>
<th>NAME (INN) Company</th>
<th>Indication</th>
<th>Date of opinion/AB/IAB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SOVALDI</strong> (sofosbuvir) Gilead</td>
<td>“SOVALDI is indicated in combination with other medicinal products for the treatment of chronic hepatitis C in adults”</td>
<td>Under assessment</td>
</tr>
<tr>
<td><strong>VICTRELIS</strong> (boceprevir) MSD</td>
<td>“VICTRELIS is indicated for the treatment of chronic hepatitis C genotype 1 HCV infection, in combination with pegylated interferon alfa and ribavirin, in adult patients with compensated liver disease who are previous untreated or who have failed previous therapy”</td>
<td>Transparency Committee opinion of 14/12/2011 AB: substantial IAB: “The Transparency Committee considers that, compared with peginterferon/ribavirin dual therapy alone, the addition of boceprevir to this dual therapy provides: - a minor improvement in actual benefit (level IV) in previously untreated adults, - moderate improvement (level III) in adults whose treatment for chronic hepatitis C genotype 1 has failed, in the absence of hepatic decompensation.”</td>
</tr>
<tr>
<td><strong>PEGASYS</strong> (pegylated interferon alfa 2a) Roche</td>
<td>“PEGASYS is indicated for the treatment of chronic hepatitis C in adults who are positive for serum HCV-RNA, including patients with compensated cirrhosis and/or co-infected with HIV (stable HIV infection)”</td>
<td>Transparency Committee opinion of 20/11/2002 AB: substantial IAB: “Pegylated interferon alfa-2a (PEGASYS) shares the improvement in actual benefit of pegylated interferon alfa-2b in contrast to standard (non-pegylated) interferon.” Transparency Committee opinion of 6/07/2005 AB: substantial IAB: “In genotype 1 patients with normal transaminase levels, PEGASYS combined with ribavirin provides a moderate improvement in actual benefit (IAB III) in terms of efficacy in comparison to the present strategy.” “In genotype 2-3 patients with normal transaminase levels, PEGASYS combined with ribavirin provides a minor improvement in actual benefit (level IV) in terms of efficacy in comparison with the present strategy.” Transparency Committee opinion of 10/03/2010 AB: substantial IAB: “No improvement in actual benefit (level V) in the management of patients with chronic hepatitis C whose previous treatment with interferon alfa (whether pegylated or not) alone or in combination with ribavirin had failed.”</td>
</tr>
<tr>
<td><strong>VIRAHERON PEG</strong> (pegylated interferon alfa 2b) MSD</td>
<td>“VIRAHERONPEG is indicated for the treatment of adult patients with chronic hepatitis C who are positive for RNA-HCV, including patients with compensated liver disease”</td>
<td>Transparency Committee opinion of 10/10/2001 AB: substantial IAB: As dual therapy “For all patients: VIRAHERONPEG/ribavirin dual therapy offers a simplified administration regimen and represents a minor (level IV) improvement in actual benefit.”</td>
</tr>
</tbody>
</table>
cirrhosis and/or patients with clinically stable HIV.”

benefit in comparison with dual therapy with non-pegylated interferon alfa-2b/ribavirin.”

“In genotype 1 patients with a small viral load, VIRADERPEN/ribavirin dual therapy offers a simplified administration regimen and represents a minor (level IV) improvement in actual benefit in comparison with dual therapy with non-pegylated interferon alfa-2b/ribavirin.”

Transparency Committee opinion of 10/12/2008
AB: substantial
IAB: “No improvement in actual benefit in chronic hepatitis C patients in whom treatment with alfa interferon + ribavirin had failed.”

COPEGUS (ribavirin) Roche

COPEGUS is indicated for the treatment of chronic hepatitis C and must only be used as part of a combination regimen with peginterferon alfa-2a (PEGASYS) or with IFN alfa-2a.”

Transparency Committee opinion of 02/07/2003
AB: substantial
IAB: “No improvement in actual benefit compared with ribavirin (REBETOL).”

Transparency Committee opinion of 20/10/2010
AB: substantial
IAB: “No improvement in actual benefit (level V) in the management of patients with chronic hepatitis C whose previous treatment with interferon alfa (whether pegylated or not) alone or in combination with ribavirin had failed.”

REBETOL (ribavirin) MSD

“REBETOL is indicated for the treatment of chronic hepatitis C and must only be used as part of a combination regimen with peginterferon alfa-2b interferon alfa-2b”

Transparency Committee opinion of 11/07/2001
AB: substantial
IAB: nd

Transparency Committee opinion of 10/12/2008
AB: substantial
IAB: “No improvement in actual benefit in non-responders to dual therapy or relapsers.”

07.2 Other information

Two medicinal products are currently on a temporary authorisation for use by a cohort:
- simeprevir\(^{11}\) in combination with other medicinal products, for the treatment of chronic hepatitis C due to the genotype 1 or 4 virus in adults in an advanced stage of the disease (with liver fibrosis F3/F4 or presenting extrahepatic manifestations of HCV) and for whom there are no suitable treatment alternatives;
- daclatasvir\(^{12}\) in combination with sofosbuvir for the treatment of chronic hepatitis C due to virus genotypes 1,2,3,4
  o for patients in an advanced stage of the disease (with liver fibrosis F3/F4 or presenting extrahepatic manifestations of HCV) and for whom there are no suitable treatment alternatives
  o or on the waitinglist for a liver or kidney transplant
  o or having undergone a liver transplant and presenting recurrence of the HCV infection.

\(\text{Conclusion}\)

The clinically relevant comparators of telaprevir (INCIVO) are the other antivirals that can be used in combination with pegylated interferon and ribavirin dual therapy in the treatment of chronic hepatitis C due to HCV genotype 1: boceprevir (VICTRELIS) or sofosbuvir (SOVALDI).

\(^{11}\) ANSM. http://ansm.sante.fr/var/ansm_site/storage/original/application/3d90458534c4c3c236c3bce9c9a98cbc.pdf.

\(^{12}\) ANSM. http://ansm.sante.fr/var/ansm_site/storage/original/application/9dc54d141586170d08b13eaff20f05a.pdf.
### Summary of Previous Assessments

**Date of Opinion**

14 December 2011 (Inclusion for National Health Insurance and Hospital use)

**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 genotypes of hepatitis C virus, genotype 1 is predominant.
- These proprietary medicinal products fall within the category of first- or second-line triple therapy (in combination with peginterferon alfa and ribavirin).
- They are intended as curative therapy.

**Public Health Benefit:**

Hepatitis C represents a moderate public health burden. In the indication (treatment of patients infected with genotype 1 HCV, 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 Technical Group for the Definition of Objectives] 2003, 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-naive 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 IL28 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.**

**There is one treatment alternative validated in the Marketing Authorisation: VICTRELIS (boceprevir).**

**Consequently, the actual benefit of INCIVO is substantial.**

**Improvement in Actual Benefit**

Taking into account:
- the degree of virological efficacy achieved by the addition of telaprevir to the dual therapy peginterferon alpha/ribavirin dual therapy, particularly in patients whose dual therapy failed and for whom no alternative treatment is available,
- the possible reduction in the total treatment duration of 48 weeks (dual therapy) to 24 weeks (triple therapy) in some patients (previously untreated, non-cirrhotic patients or relapsers, achieving a rapid response during treatment)

**but considering,**

- the increased toxicoderma, particularly severe toxicoderma including DRESS and Stevens-Johnson syndrome,
- the sub-optimal level of proof of the data supporting the decision on treatment regimens, particularly in non-cirrhotic patients and relapers after prior treatment achieving a rapid response during treatment, the Transparency Committee considers that the addition of telaprevir to the dual therapy with peginterferon/ribavirin provides, compared with this dual therapy:
  - a level IV IAB (minor) in previously untreated adults,
  - a level III IAB (moderate) in adults whose treatment has failed,
  - in the treatment of genotype 1 chronic hepatitis C, in the absence of liver decompensation.

**Studies requested**

In view of the available data, the complexity of the treatment regimens for managing patients with hepatitis C, the possible application of the not-yet routine IL28 genotype test, the potential arrival of new compounds, additional data are expected on:
- the characteristics of patients treated for hepatitis C
- the conditions of use (therapeutic strategies set up, genotype testing before treatment, tests undertaken, etc.).

Use of the database on patients infected with hepatitis B and C, initiated by the ANRS (HEPATER study), which will be set up in 2012, could be considered.
Within the framework of this re-assessment of the improvement in actual benefit of the medicinal product INCIVO at the request of the Transparency Committee, the company presented:
- two open-label studies in patients who had participated in the clinical studies;
- two pharmacoepidemiology studies;
- one analysis of data obtained under a temporary authorisation for use (ATU);
- a literature review;
- a summary of pharmacovigilance data;
- usage/prescription data.

The company also provided the results of the study that led to the Marketing Authorisation being amended by the addition of a dosage regimen consisting of two daily intakes (C211 or OPTIMIZE study).

The double-blind, randomised, phase III comparative studies (ADVANCE\textsuperscript{13} and REALIZE\textsuperscript{14} studies) were presented in the previous Transparency Committee opinion dated 14 December 2011.

**Reminder of the Transparency Committee’s conclusions concerning these studies:**\textsuperscript{9}

“In the treatment of genotype 1 chronic hepatitis C virus infection, the efficacy and safety 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 Therapy: 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 triple therapy telaprevir/peginterferon alfa/ribavirin for 12 weeks followed by dual 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 dual therapy prior to the triple 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 \( \geq 2 \) and stoppage of treatment because of an adverse event. The adverse events of grades \( \geq 3 \) most frequently reported in the telaprevir group (frequency \( \geq 1\% \)) were: anaemia, skin rash, thrombocytopenia, 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;
- risk of anaemia (32% vs 15% with the dual 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."

09.1 Efficacy

The new data presented by the company were obtained from open-label follow-up studies, observational studies, and meta-analyses:
- Study C219: follow-up study that evaluated the efficacy and safety of telaprevir in control group patients in the REALIZE study and in patients who did not receive 12 weeks of treatment in the phase I studies. Given its methodology, this study is not relevant to this re-assessment;
- 112 or EXTEND study: long-term follow-up study to evaluate maintenance of the virologic response in subjects who achieved an SVR or changes in HCV-variants in the subjects who did achieve an SVR in an earlier clinical study;
- Early Access Program (EAP):\(^{15}\) early access program introduced in 16 countries in which telaprevir is not marketed, enabling patients with genotype 1 chronic hepatitis C to be treated who could not be included in a clinical study. Given the methodology of this study and in particular a dosage regimen that did not correspond to the one recommended in France, only the safety data will be given;
- CUPIC cohort (ANRS CO20):\(^{16,17}\) prospective French cohort monitored by the National Agency for Research on AIDS and viral hepatitis – ANRS, whose aim was to evaluate the efficacy and safety of protease inhibitors in patients treated under their temporary authorisation for use by a cohort (cirrhosis patients (stage F4) whose prior dual therapy treatment had failed);
- Temporary authorisation for use by a named person [ATU nominative in French] and temporary authorisation for use by a cohort: only the safety data will be given on account of the short patient follow-up period;
- Meta-analyses:\(^{18,19,20,21,22,23,24,25,26,27,28}\) 11 indirect comparison meta-analyses, in which the efficacy and safety of protease inhibitors (telaprevir and boceprevir) were assessed on the

---

\(^{16}\) Fontaine H, Hezode C, Dorival C et al. SVR12 rates and safety of triple therapy including telaprevir or boceprevir in 221 cirrhotic non responders treated in the French early access program (ANRS CO20-CUPIC). J. Hepatol. 2013 vol. 58: S25–S44.
basis of the results of phase II and III studies, were published. Their methodological weaknesses (disparate inclusion and exclusion criteria, SVR estimated at different times, variable treatment durations, etc.) do not allow a comparison of the two protease inhibitors to be made. Their conclusions (improved SVR and increased risk of anaemia in patients treated with protease inhibitors) are not likely to change the Transparency Committee’s previous opinion.

The company also presented the results of the open-label OPTIMIZE study, which compared the administration of telaprevir every 8 hours with twice daily administration in combination with peginterferon + ribavirin dual therapy.

9.1.1 EXTEND study

The EXTEND study is a long-term (3-year) follow-up study of phase II and III clinical studies whose main aim was to evaluate:
- the maintenance of virological response over time in patients who have achieved a SVR after telaprevir treatment (cohort A);
- changes in HCV variants in patients without a SVR who have developed resistance after telaprevir treatment (cohort B).

A total of 408 patients were included: 220 in cohort A and 188 in cohort B. The median age of patients was 55 years (26-70 years) and 16% of them had cirrhosis. The HCV was genotype 1a in 56% of patients, genotype 1b in 36%, and another genotype in 8%. At baseline, in the phase II or III studies, 40% of patients were treatment-naïve; the remaining patients (60%) were non-responders,29 8% of whom were partial responders,29 10% null-responders,29 and in 42% the profile was unspecified.

The results presented are taken from an interim analysis carried out on 24 June 2012:
- cohort A (n = 220): the elapsed time between SVR and the final assessment of the RNA-HCV levels available at that date was at least 25 months in 120 patients (55%) and at least 35 months in 92 patients (42%). None of the patients had a delayed relapse.
- cohort B (n = 188): the median duration of follow-up was 35.6 months. The resistance profile at the time of treatment failure was evaluable in 163 patients and enabled viral resistance to be identified at the time of treatment failure in 126 patients (77%). The

---

29 Non-responder patients are patients who have not obtained HCV RNA negativation at the end of treatment. These patients may be divided into:
- Partial responders: patients whose viral load has decreased by at least 2 log IU/ml without negativation during the course of treatment;
- Null-responders: patients whose viral load has decreased by less than 2 log IU/ml during the course of at least 12 weeks of treatment.

---
wild-type phenotype regained predominance during the follow-up period in 105 (83%) patients.

9.1.2 CUPIC cohort

The CUPIC cohort included patients treated with a protease inhibitor (telaprevir or boceprevir) within the framework of their temporary authorisation for use by a cohort (cirrhosis patients [stage F4] whose prior dual therapy treatment had failed). The main aim of the ANRS prospective study conducted with the CUPIC cohort was to evaluate the SVR percentage. A cohort of 900 patients was needed to obtain an accuracy of 3% for estimating the SVR.

A total of 674 patients with chronic hepatitis C at the compensated cirrhosis stage, and who had not obtained any virologic response with a standard treatment, were included to receive 48 weeks of treatment.

The results presented were obtained from an interim analysis performed after 60 weeks of follow-up (12 weeks after treatment discontinuation) in March 2013. Only 511 patients completed the follow-up 12 weeks after treatment discontinuation. Of these, 299 were treated with telaprevir according to the following regimen: triple therapy (telaprevir, peginterferon, and ribavirin) for 12 weeks followed by dual therapy (peginterferon and ribavirin) for 36 weeks. These patients had a mean age of 57 years and 34% had at least one exclusion criterion from the REALIZE study. The majority of the patients had a CPT stage A score\(^{30}\) (95%) and/or a MELD score\(^{31}\) of less than 10 (82%). The HCV was genotype 1a in 34% of these patients, genotype 1b in 56%, and another genotype in 10%. Before being treated with telaprevir, patients were predominantly non-responders (45% partial responders and 10% null-responders) and relapsers\(^{32}\) (39%); the other patients had virological escape to an earlier treatment (2%) or an indeterminate response profile. RNA-HCV was undetectable (SVR at 12 weeks) in 52% (155/299) of patients, with a higher percentage response among relapsers (76%) than among partial responders (40%) or null-responders (19%).

9.1.3 OPTIMIZE study

The OPTIMIZE study is an open-label phase III study that showed the non-inferiority of two daily intakes in comparison with three daily intakes of telaprevir in terms of sustained virologic response 12 weeks after the end of treatment. The non-inferiority of the dosage regimen of two daily doses was extrapolated to patients who were non-responders to a previous treatment with peginterferon and ribavirin.

09.2 Adverse Effects

According to the SPC, the most common (≥ 1/100) adverse effects of telaprevir are: blood disorders (anaemia, thrombocytopenia, lymphopenia), skin disorders (skin rash, pruritus) and gastrointestinal disorders (nausea, anorectal disorders).

Under triple therapy with peginterferon, ribavirin, and telaprevir, these effects are added to those occurring with dual therapy combining peginterferon and ribavirin, the most common of which are:

---

\(^{30}\) The CPT (Child-Turcotte-Pugh) score consists of five parameters (blood bilirubin and albumin levels, prothrombin index, and presence or otherwise of ascites or encephalopathy) indicating the severity of the liver disease. The higher the score, the more severe the liver disease. Conventionally, compensated cirrhosis is CPT A (score of 5-6 points) and decompensated cirrhosis is CPT B (7-9 points) or C (10-15 points).

\(^{31}\) The MELD (Model for End-Stage Liver Disease) score is calculated from 3 parameters (total serum bilirubin, serum creatinine, and INR) in order to assess the seriousness of the liver disease. Developed initially to predict the survival rate three months after surgery in patients who have had a transjugular intrahepatic shunt, it serves to determine the order of priority for liver transplantation. The MELD score is a continuous score varying from 6 to 40 points. The higher the score, the more severe the liver disease. Liver transplantation is indicated in patients whose score is above 15.

\(^{32}\) Relapser patients are those who have obtained negativation of the HCV RNA during treatment and whose viral load has reappeared after discontinuation of treatment.
fatigue, flu-like symptoms, gastrointestinal disorders, blood disorders (anaemia, neutropenia), skin disorders and psychiatric disorders (irritability, insomnia, mood disorders, and depression).

Certain specific risks are highlighted in the SPC:
- Rash and severe cutaneous reactions: during the course of controlled phase II and III clinical trials, skin eruptions (all grades together) were reported in 55% of patients treated with telaprevir in combination with peginterferon and ribavirin dual therapy and in 33% of patients who received only the dual therapy. Severe, potentially life-threatening and fatal cutaneous reactions were also reported under treatment with telaprevir in combination, including cases of DRESS (Drug Rash with Eosinophilia and Systemic Symptoms), Stevens-Johnson syndrome, and Lyell's syndrome.
- Anaemia: during the course of controlled phase II and III clinical trials, anaemia (all grades together) was reported in 32% of patients treated with telaprevir in combination with dual therapy and in 15% of patients who received only the dual therapy.
- Anorectal signs and symptoms: in the clinical trials, the majority of these events (haemorrhoids, anorectal discomfort, anal pruritus, and anal burning sensation) were of mild to moderate intensity.

The identified or potential risks followed up under the Risk Management Plan (RMP) associated with the Marketing Authorisation are the following: skin disorders, anaemia, lymphopenia, thrombocytopenia, elevated creatinine levels, hypothyroidism, hyperuricaemia, retinopathy, anorectal disorders, QT interval prolongation, and development of resistance.

9.2.1 New safety data obtained from post-Marketing Authorisation studies

EXTEND study
Of the 408 included patients, 6 presented a serious hepatic adverse event (4 hepatocellular carcinomas, 1 hepatic encephalopathy, and 1 ascites) during the course of the follow-up period. These patients already presented hepatic involvement at baseline in the initial phase II and III studies.

Early Access Program
Of the 1587 patients who had received 12 weeks of triple therapy (telaprevir, peginterferon, and ribavirin) followed by 4 weeks of dual therapy (peginterferon and ribavirin), 1014 patients (64% reported at least one adverse event of grade $\geq 2$, the most common of which were: anaemia (44%), skin rash (13%), thrombocytopenia (8%), pruritus (6%), and asthenia (6%). Triple therapy had to be discontinued due to adverse effects for 193 patients (12%). Anaemia was reported in 59% of patients, including 31% of them with grade $\geq 3$, and this led to a reduction in the ribavirin dose in 68% of cases, EPO treatment in 36% of cases, and transfusion in 17% of cases. Skin rash of grade $\geq 3$ was reported in 4% of patients. Cirrhotic patients (stage F4) had more adverse effects than the others (67% versus 60%), including more cases of anaemia and thrombocytopenia. Seven deaths during dual therapy were notified (multiple organ failure following infection, pneumonia, septic shock, ischaemic colitis, or haemorrhage), 6 of them in cirrhotic patients and 1 in a diabetic patient.

CUPIC cohort
Safety data were analysed on 1 May 2012 for patients reaching the 16th treatment week owing to the frequency of adverse effects. On this date, 497 patients had received at least the first 16 weeks of treatment, including 292 of telaprevir (in combination with peginterferon + ribavirin dual therapy for 12 weeks, followed by peginterferon + ribavirin dual therapy). Of these, 23% discontinued treatment early, including 15% due to serious adverse effects. In total, 45% of patients had a serious adverse effect such as anaemia of grade $\geq 3$ (12%), infection of grade $\geq 3$ (7%), skin rash of grade 3 (5%), neutropenia of grade $\geq 3$ (3%), thrombocytopenia of grade 4 (3%), or liver

---

decompensation (2%). Management of the anaemia led to a reduction in the ribavirin dose in 13% of patients, EPO treatment in 54%, and a transfusion in 16%. There were five reported deaths. These data show a less satisfactory safety profile for telaprevir-based triple therapy in cirrhotic patients, with a risk of adverse effects that increases with the level of hepatic involvement. Following publication of the data obtained with this cohort, the SPC is being amended to include information about patients with advanced hepatic involvement in section 4.4 Special warnings and precautions for use in order to recommend closer surveillance of these patients and not to use telaprevir-based triple therapy in cirrhotic patients with blood albumin < 33 g/l and/or thrombocytopenia < 90,000/mm³.

9.2.2 New pharmacovigilance data

Temporary authorisation for use by a named person and temporary authorisation for use by a cohort
Pharmacovigilance reports recorded during the temporary authorisation for use period relating to patients in the CUPIC cohort are not presented in this part. At least one adverse effect was observed in 26 of the 47 patients who received telaprevir in the framework of the temporary authorisation for use by a named person. In total, 57 adverse effects, including 23 serious effects, were notified. As regards the risks identified during the course of the clinical studies, 9 cases of anaemia, 6 of them serious, and 5 cases of toxicoderma, 2 of them serious, were reported. One death, possibly telaprevir-related, was notified (pneumococcal infection).

Of the 558 patients who received telaprevir under the temporary authorisation for use by a cohort, 417 (75%) had at least one adverse effect. In total, 871 adverse effects, including 361 serious effects, were notified. As regards the risks identified during the course of the clinical studies, 150 cases of anaemia, 90 of them serious, and 163 cases of toxicoderma, 27 of them serious, were reported, including a case of AGEP (acute generalised exanthematous pustulosis) and 2 cases of DRESS. Six deaths, possibly telaprevir-related, were notified (3 as a result of septic shock or sepsis, 2 following cardiac events, and 1 following a case of hepatic encephalopathy).

National pharmacovigilance system
ANSM [French National Agency for Medicines and Health Products Safety] has put in place a national pharmacovigilance system for telaprevir. In November 2013, the CTV [French Pharmacovigilance Technical Committee] produced an initial report based on the available pharmacovigilance data gathered within the framework of this system (corresponding to all cases of adverse effects notified to 19/09/2012, including data from the CUPIC study, temporary authorisations for use, and PSURs, as well as cases notified up to the National Pharmacovigilance Database to 19/09/2013). This report confirmed the considerable frequency of skin disorders, in particular severe cutaneous reactions which accounted for 25% of all serious effects notified, including 14 possible cases of DRESS, one case of AGEP, and 2 of erythema multiforme. The incidence of DRESS, estimated on the basis of data from this system (3.9/1000), is similar to that observed in clinical studies (4/1000). Haematological disorders constitute the second largest category of reported adverse effects in terms of frequency. These are predominantly cases of anaemia, the most severe of which are usually managed by the administration of EPO. This report also pointed out the risk of pancreatitis (10 notified cases). In light of this report, the CTV decided to maintain the national pharmacovigilance system. It also recommended updating information brochures on the haematological adverse effects and their management within the framework of antiviral tri-therapies and has asked for pancreatitis to be added to the adverse effects in the SPC for telaprevir.

PSUR

34 Meeting of the Pharmacovigilance Technical Committee – CT012013083. Minutes of the meeting. Consulted on 12 March 2014. http://ansm.sante.fr/var/ansm_site/storage/original/application/6ac3b5756a632e85c75b75f05c608400.pdf.
The last periodic pharmacovigilance report (PSUR) to be provided by the company covers the period from 20/09/2012 to 19/03/2013. During this period, two cases of Lyell’s syndrome were reported, one of them fatal. Given the clinical importance of this adverse effect, the following information has been added to the SPC:

- Section 4.4 Special warnings and precautions for use:
  “Severe skin reactions
Severe, potentially life-threatening and fatal skin reactions have been reported with INCIVO combination treatment. Toxic epidermal necrolysis (TEN), including fatal outcome, has been observed in post-marketing experience (see section 4.8). Fatal cases have been reported in patients with progressive rash and systemic symptoms who continued to receive INCIVO combination treatment after a serious skin reaction was identified.”

- Section 4.8 Undesirable effects: the adverse effects “toxic epidermal necrolysis (TEN)” and “erythema multiforme” were added to the adverse effects of rare frequency (≥ 1/10,000 to < 1/1000).

9.2.3 Further information

In April 2013, a letter was sent out to healthcare professionals to inform them of the two cases of Lyell’s syndrome and the recommendations for managing severe skin reactions when treating with INCIVO.35 The main recommendations are as follows:

- Patients should be informed about the need to contact their doctor immediately in the event of the appearance of a skin rash or worsening of an existing skin rash.

- In cases of severe skin rash (covering more than 50% of the body surface or associated with vesicles, bullae, ulcerations other than Stevens-Johnson syndrome): immediate and permanent discontinuation of INCIVO. Referral to a dermatologist is recommended. The appearance or aggravation of systemic symptoms should be monitored until disappearance of the skin rash. Peginterferon alfa and ribavirin may be continued.

If the rash is not observed to improve within 7 days following INCIVO discontinuation, consideration should be given to suspending or successively or simultaneously discontinuing ribavirin and/or peginterferon alfa. Peginterferon alfa and ribavirin may need to be suspended or discontinued sooner depending on the clinical condition.

- In the event of severe skin reactions, including skin rash associated with systemic symptoms, severe progressive skin rash, suspicion or diagnosis of generalised bullous eruption, DRESS, Stevens-Johnson syndrome, AGEP, erythema multiforme: permanent and immediate discontinuation of INCIVO, peginterferon alfa, and ribavirin; consult a dermatologist.

---

09.3 Usage/prescription data

9.3.1 GERS data

According to GERS [Group for the Development and Implementation of Statistics] data, 1,234,800 tablets of INCIVO 375 mg were dispensed (i.e. 29,400 bottles of 42 tablets) in the period from 1 July 2012 to 30 June 2013 (moving annual total June 2013).

9.3.2 Data from the PDS-HCV observatory

The PDS-HCV [PDS-HCV] observatory, established by Cegedim, enabled a survey to be conducted based on prescription data collected from gastroenterologists, infectious diseases specialists, and hospital internists relating to the management of patients with genotype 1 chronic hepatitis C.

For the period from 4 March to 7 April 2013, the data on 370 patients were collected from 81 doctors. The patients had a mean age of 50.7 years; 48% had a METAVIR score ≥ 3; all patients treated with triple therapy including a protease inhibitor, including 101 with boceprevir and 249 with telaprevir; more than half (57%) were treatment-naïve; the remainder were relapsers (21%) or non-responders, 14% of whom were partial responders and 8% null-responders. As regards telaprevir, the mean treatment duration was 11 weeks; anaemia was reported in 26% of patients and skin rash in 16% of patients treated with a triple therapy that included telaprevir. Early discontinuation of triple therapy was notified in the case of 25 patients (9 treated with boceprevir and 16 with telaprevir). These treatment discontinuations were mostly due to adverse effects (68%) or were the patient’s decision (28%).

09.4 Summary and discussion

The controlled clinical studies showed that treatment of genotype 1 chronic hepatitis C with triple therapy (telaprevir, peginterferon, and ribavirin) allows a sustained virologic response to be obtained 24 weeks after discontinuation of treatment in about 75% of treatment-naïve patients and in 65% of previously-treated patients.

The new efficacy data available tend to confirm the improvement in the SVR observed during controlled studies and its maintenance over time, but also the limitations of triple therapy including telaprevir (viral escape in the most affected patients, emergence of resistance, poor safety). The EXTEND study has thus helped identify viral resistance in 77% of patients in whom triple therapy including telaprevir had failed, and the CUPIC study showed the proportion of virological response in previously treated cirrhotic patients (about 50% of SVR 12 weeks after treatment discontinuation) with a substantial number of early treatment discontinuations.

The safety profile and especially the cutaneous and haematological toxicity were also confirmed by new real-life clinical data.

Overall, despite a superior efficacy to that of dual therapy with peginterferon and ribavirin, triple therapy including telaprevir has major limitations and in particular a limited efficacy in patients with a high therapeutic need, risk of resistance, numerous adverse effects, numerous drug interactions, and complex dosage regimen (six tablets daily taken at fixed times with a fat-rich meal).
09.5 Planned studies

9.5.1 HEPATHER cohort

A prospective observational study including patients from the HEPATHER cohort is currently being conducted by ANRS. The main aim of this study was to evaluate the benefits and risks associated with different approaches to the management of hepatitis B and C and to identify their individual, virological, environmental, and social determinants. As part of this study, 25,000 hepatitis C patients were to be included and followed up for 8 years by 32 French centres. An ANRS report is expected in 2015 and the study is due to end in 2022.

9.5.2 HEPAVIH cohort

Another prospective observational study is currently being conducted by ANRS based on the HEPAVIH cohort. Its main objective is to describe the natural history of HIV-HCV co-infection in terms of morbidity and mortality, to investigate its determinants, and to understand the interactions between these two viruses and their treatments.

010 THERAPEUTIC USE

French guidelines on the management of hepatitis C are in process of being updated by AFEF and ANRS, taking into account the progress in the management of this infection with the arrival of new treatments.36

The treatments recommended in the treatment of genotype 1 HCV before sofosbuvir came onto the market are summarised below:

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1</td>
<td>Naïve patients: PEG-IFN, RBV ± boceprevir or telaprevir for 24 to 48 weeks</td>
<td>AFEF 2011, EASL 2013</td>
</tr>
<tr>
<td></td>
<td>Failure of prior treatment: PEG-IFN, RBV ± boceprevir or telaprevir for 48 weeks</td>
<td></td>
</tr>
<tr>
<td>HIV co-infected patients</td>
<td>GT1: PEG-IFN, RBV and boceprevir or telaprevir</td>
<td>SPILF, AFEF, SFLS, SNFMI, 2013</td>
</tr>
<tr>
<td></td>
<td>Other genotypes: PEG-IFN + RBV for 48 weeks irrespective of the genotype</td>
<td>Consensus 2005, HCV/HBV – HIV co-infections</td>
</tr>
<tr>
<td>Decompensated cirrhosis.</td>
<td>Treatment strongly recommended, in the absence of any contraindications, for patients with compensated cirrhosis, in order to avoid complications from chronic HCV infection which occur exclusively in this group in the short and medium term. However, sustained virologic response (SVR) with PEG-IFN + RBV is weaker in patients with advanced fibrosis or cirrhosis than in patients with moderate fibrosis. Although superior to dual therapy, the SVR with triple therapy in genotype 1 patients is also negatively affected by the stage of fibrosis.</td>
<td>EASL 2013</td>
</tr>
<tr>
<td>Liver transplantation</td>
<td>There are no data on the use of protease inhibitor-based tritherapies in the treatment of patients on a waiting list, with very advanced liver disease. The two protease inhibitors (boceprevir and telaprevir) present a haematological toxicity and an increased risk of serious infections, so that the adverse effects profile in this group of patients may be especially difficult.</td>
<td>Consensus conference 2002 EASL 2013</td>
</tr>
</tbody>
</table>

While awaiting the French guidelines for the management of hepatitis C patients, due in 2015, AFEF has put forward expert opinions37 on the choice of treatments for hepatitis C. The AFEF and


HAS - Medical, Economic and Public Health Assessment Division 19/22
the DHUMEAX\textsuperscript{38} report no longer recommend the use of VICTRELIS (boceprevir) or INCIVO (telaprevir) in the treatment of chronic hepatitis C due to genotype 1 HCV.

\textbf{Role of INCIVO and VICTRELIS protease inhibitors in treatment strategy}

In light of the safety profile, the risk of development of resistance, but above all the arrival of new treatments with a better profile in terms of efficacy, safety, resistance, and drug interactions, together with a shorter duration of treatment, the role of INCIVO and VICTRELIS first-generation protease inhibitors in therapeutic strategy is therefore becoming very limited.


\textsuperscript{38} Report on the management of persons infected with the hepatitis B virus or hepatitis C virus. Consulted on 5 May 2014 (proposed publication date: 19 May 2014).
In view of all the above information, and following the debate and vote, the Committee’s opinion is as follows:

011.1 Actual Benefit

- Hepatitis C is a serious condition owing to the fact that it frequently turns chronic, which in the long term can lead to cirrhosis, liver failure, and hepatocellular carcinoma. Of the six genotypes of the hepatitis C virus, genotype 1 is predominant.
- These proprietary medicinal products come within the framework of a triple therapy treatment (in combination with peginterferon alfa and ribavirin) for chronic hepatitis C caused by the genotype 1 HCV virus, whose role in the treatment strategy has become limited with the arrival of new treatments with a better efficacy, safety, resistance, and drug interaction profile, as well as a shorter treatment duration in this indication.
- It is intended as curative treatment.
- The efficacy/adverse effects ratio is modest, in particular on account of its toxicoderma.
- There are treatment alternatives.

Consequently, the Transparency Committee considers that the actual benefit of INCIVO remains substantial in the Marketing Authorisation indication.

The Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indication and at the dosages in the Marketing Authorisation.

- Proposed reimbursement rate: 65%

011.2 Improvement in actual benefit (IAB)

In the treatment of chronic hepatitis C due to HCV genotype 1 in patients with compensated liver disease, INCIVO in combination with peginterferon alpha and ribavirin dual therapy provides a minor improvement in actual benefit (level IV) in comparison with this dual therapy.

011.3 Target population

INCIVO is indicated for the treatment of genotype 1 chronic hepatitis C due to the HCV virus in adult patients with compensated liver disease. However, the arrival of new treatments with a better efficacy, safety, resistance, and drug interaction profile, as well as a shorter treatment duration in this indication, limits considerably this proprietary medicinal product’s role in the treatment strategy.

For information, according to data from the EGB [a representative sample of individuals covered by French national health insurance] extrapolated to the French population:
- the number of persons who have had reimbursement for at least one box of INCIVO between 31 October 2012 and 01 November 2013 was estimated at 2475 (95% CI = 1463 to 3486);
- the number of persons who have had reimbursement for at least one box of VICTRELIS between 31 October 2012 and 01 November 2013 was estimated at 1937 (95% CI = 1042 to 2831);
- the number of persons who have had reimbursement for at least one box of INCIVO or VICTRELIS between 31 October 2012 and 01 November 2013 was estimated at 4411 (95% CI = 3061 to 5762);

Table 1: Number of patients who have had at least one reimbursement for INCIVO or VICTRELIS between 31/10/2012 and 01/11/2013 according to EGB data extrapolated to the French population

<table>
<thead>
<tr>
<th>Product</th>
<th>Number</th>
<th>Number extrapolated to the French population</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower limit</td>
</tr>
<tr>
<td>INCIVO</td>
<td>23</td>
<td>2475</td>
<td>1463</td>
</tr>
<tr>
<td>VICTRELIS</td>
<td>18</td>
<td>1937</td>
<td>1042</td>
</tr>
<tr>
<td>TOTAL</td>
<td>41</td>
<td>4411</td>
<td>3061</td>
</tr>
</tbody>
</table>

012 TRANSPARENCY COMMITTEE RECOMMENDATIONS

- **Packaging**
  Since the Transparency Committee’s previous opinion of 14 December 2011, the pack of 4 bottles of 42 tablets is no longer marketed (withdrawn from the market declared in July 2012).
  The packaging in bottles of 42 tablets remains appropriate for the prescribing conditions in terms of indication, dosage and treatment duration.

- **Other recommendations**
  The Transparency Committee wishes to re-assess this medicinal product in the short term in the light of changing clinical data and the changing approach to the management of chronic hepatitis C.