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TRANSPARENCY COMMITTEE

Opinion
14/05/2014

VICTRELIS 200 mg, hard capsule
B/336 hard capsules (CIP: 34009 419 467 9 0)

Applicant: MSD FRANCE

INN	boceprevir
ATC Code (2013)	J05AE12 (protease inhibitor)
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**
Lists concerned	**National Health Insurance (French Social Security Code L.162-17)** **Hospital use (French Public Health Code L.5123-2)**
Indication concerned	**"VICTRELIS is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease who are previously untreated or who have failed previous therapy."**

Actual Benefit	**Substantial**
Improvement in Actual Benefit	**In the treatment of chronic hepatitis C due to genotype 1 HCV in patients with compensated liver disease, VICTRELIS 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 role	**In light of the safety profile, the risk of development of resistance, but especially 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 use 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

Marketing Authorisation	Date initiated (centralised procedure): 18 July 2011 The Marketing Authorisation is combined with a Risk Management Plan
Prescribing and dispensing conditions/ special status	List I Hospital prescription restricted to specialists in gastroenterology and hepatology, internal medicine, and infectious diseases Medicinal product authorised for dispensing by hospital pharmacies to outpatients (on 'retrocession' list)

ATC Classification	2014	
	J	Antiinfectives for systemic use
	J05	Antivirals for systemic use
	J05A	Direct acting antivirals
	J05AE	Protease inhibitors
	J05AE12	boceprevir

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, "in view of:

- the level of virological efficacy achieved through triple therapy, especially for patients who have had a failed dual therapy and for whom there are no available treatment alternatives,
- the possible reduction in the total treatment duration from 48 weeks (dual therapy) to 28 weeks (triple therapy) for certain previously untreated patients (patients without cirrhosis achieving a fast response during treatment)

but considering,

- the increased toxicity, especially anaemia commonly requiring a reduction in the dose of ribavirin and/or the administration of erythropoietin,
- the sub-optimal level of evidence from data in support of the determination in therapeutic regimens, especially for null-responders who were excluded from the RESPOND2 study,

The Committee considers that, compared with dual therapy alone, the addition of boceprevir to dual therapy with peginterferon/ribavirin provides:

- a level IV IAB (minor) for previously untreated adults,
- a level III IAB (moderate) for adults who had a failed previous treatment,

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

In this opinion, the Transparency Committee explained that: "Given the data available, the complexity of the therapeutic regimens for the management of hepatitis C patients, the possibility of carrying out IL28 genotype testing, which is not yet systematic and the potential discovery of new substances, additional data are expected on:

- the characteristics of patients being managed for hepatitis C
- the conditions of use (therapeutic strategies adopted, genotype tests prior to treatment, tests undertaken, etc.).

Use of the database on patients with hepatitis B and C, started by ANRS [National AIDS Research Agency] (HEPATER study), which will be implemented in 2012, could be foreseen."
In conclusion, the Transparency Committee indicated that it would like to re-assess the proprietary medicinal product VICTRELIS within one year, in light of updated clinical data.

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 and in order to re-assess the improvement in actual benefit of VICTRELIS in treatment-naïve patients.

03 DEFINITIONS

In accordance with the international terminology used, non-responders 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 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

"VICTRELIS is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease who are previously untreated or who have failed previous therapy."

05 DOSAGE

VICTRELIS must be administered in combination with peginterferon alfa and ribavirin. The Summary of Product Characteristics of peginterferon alfa and ribavirin (PR) must be consulted prior to initiation of therapy with VICTRELIS.

The recommended dose of VICTRELIS is 800 mg administered orally three times daily (TID) with food (a meal or light snack). Maximum daily dose of VICTRELIS is 2400 mg. Administration without food could be associated with a net loss of efficacy due to sub-optimal exposure.

"Patients without cirrhosis who are previously untreated or who have failed previous therapy
The following dosing recommendations differ for some subgroups from the dosing studied in the Phase 3 trials (see section 5.1).

Table 1: Duration of therapy using Response-Guided Therapy (RGT) guidelines in patients without cirrhosis who are previously untreated or who have failed previous therapy to interferon and ribavirin therapy

	ASSESSMENT* (HCV-RNA Results†)		**ACTION**
	At Treatment Week 8	**At Treatment Week 24**	
Previously untreated patients	Undetectable	Undetectable	*Treatment duration = 28 weeks* 1. Administer peginterferon alfa and ribavirin for 4 weeks, and then 2. Continue with all three medicines (peginterferon alfa and ribavirin [PR] + VICTRELIS) and finish through Treatment Week 28 (TW 28).
	Detectable	Undetectable	*Treatment duration = 48 weeks*‡ 1. Administer peginterferon alfa and ribavirin for 4 weeks, and then 2. Continue with all three medicines (PR + VICTRELIS) and finish through TW 36, and then 3. Administer peginterferon alfa and ribavirin and finish through TW 48.
Patients who have failed previous therapy	Undetectable	Undetectable	*Treatment duration = 48 weeks* 1. Administer peginterferon alfa and ribavirin for 4 weeks, and then 2. Continue with all three medicines (PR + VICTRELIS) and finish through TW 36, and then 3. Administer peginterferon alfa and ribavirin and finish through TW 48.
	Detectable	Undetectable	

***Stopping rule:**
- If the patient has hepatitis C virus ribonucleic acid (HCV-RNA) results greater than or equal to 1000 IU/ml at TW 8, then discontinue the triple therapy.
- If the patient has HCV-RNA results greater than or equal to 100 IU/ml at TW 12, then three-medicine regimen.
- If the patient has confirmed, detectable HCV-RNA at TW 24, then discontinue three-medicine regimen.

†In clinical trials, HCV-RNA in plasma was measured with the Roche COBAS Taqman 2.0 assay with a limit of detection of 9.3 IU/ml and a limit of quantification of 25 IU/ml.

‡This regimen has only been tested in subjects who have failed previous therapy who were late responders (see section 5.1)

All cirrhosis patients and null-responders

Recommended treatment duration is 48 weeks: 4 weeks of bitherapy with peginterferon alfa + ribavirin + VICTRELIS and then 44 weeks of tritherapy with peginterferon alfa + ribavirin + VICTRELIS. (Refer to the stopping rule in Table 1 for all patients.)

The duration of the tritherapy after the first 4 weeks of bitherapy should not be less than 32 weeks. Given the incremental risk of adverse effects with VICTRELIS (anaemia notably), in case the patient cannot tolerate the treatment, consideration could be given to pursue with 12 weeks of bitherapy for the final 12 weeks of treatment instead of tritherapy (see sections 4.8 and 5.1)."

06 THERAPEUTIC NEED[1,2,3,4,5,6]

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[7] 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),[8] 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 virtually constant in these patients, and that treatment for HCV may be proposed in this context.

[1] Consensus conference. Treatment of hepatitis C. 27 and 28 February 2002. http://www.infectiologie.com/site/medias/_documents/consensus/Vhc-2002.pdf.

[2] Meffre C. Prévalence des hépatites B et C en France en 2004. Saint-Maurice: Institut de Veille Sanitaire [Health Monitoring Institute] 2007. http://www.invs.sante.fr/publications/2006/prevalence_b_c/vhb_france_2004.pdf.

[3] Position paper by AFEF [French Association for the Study of the Liver] on tritherapies [Peg-IFN + ribavirin + protease inhibitor] in the management of patients with chronic hepatitis C. http://www.afef.asso.fr/.

[4] Position paper by SPILF [French Society for Infectious Diseases], AFEF [French Association for the Study of the Liver], SFLS [French Society for the Fight Against AIDS], and SNFMI [French National Society for Internal Medicine] on "The use of first-generation HCV protease inhibitors in patients co-infected with HIV and genotype 1 HCV", March 2013. http://vih.org/sites/default/files/RecomandationsIPantiVHC%20coinfection%20VIHVHC220313.pdf.

[5] CMIT [College of Professors of Infectious and Tropical Diseases] Hépatites virales C. IN E.PILLY: Vivactis Plus Ed; 2012: pp376-379.

[6] EASL Clinical practice Guidelines: Management of chronic hepatitis B virus infection. Journal of Hepatology 2012. http://dx.doi.org/10.1016/j.jhep.2012.02.010.

[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 virological 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). Currently, there is no treatment strategy that does not involve interferon.
Until 2011, pegylated alfa interferon/ribavirin dual therapy (PEG-IFN/RBV) for 24 to 48 weeks was the reference treatment for hepatitis C. This treatment entails 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. In 10 to 30% of cases, intolerance leads to treatment being discontinued within the first 6 months. The main and almost invariable adverse effect of ribavirin is a fall in the haemoglobin level (by about 13% in the first two months) due to haemolysis.

In patients infected with genotype 1 HCV, the discovery of direct acting substances (HCV protease inhibitors: boceprevir and telaprevir)[9,10] has changed the management strategy since 2011. In this population, triple therapy (peginterferon + ribavirin + protease inhibitor) constitutes a therapeutic approach suited to certain profiles of previously untreated patients (in particular those not having factors predictive of a good response to peginterferon + ribavirin dual therapy) and represents the reference treatment in certain patients whose peginterferon + ribavirin dual therapy had 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 patients without cirrhosis, either previously untreated or relapsers obtaining fast 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 with 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 players 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).

[9] Opinion of the Transparency Committee of 14 December 2011 relating to VICTRELIS (boceprevir). Available at www.has-sante.fr/.
[10] Opinion of the Transparency Committee of 14 December 2011 relating to INCIVO (telaprevir). Available at WWW.HAS-SANTE.FR/.

07 CLINICALLY RELEVANT COMPARATORS

07.1 Medicinal products

Currently, treatment of hepatitis C, irrespective of the genotype in question, is based on the use of the pegylated interferon + ribavirin (PEG-IFN/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-IFN/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.

Name (INN) ***Company***	**Indication**	**Date of opinion/AB/IAB**
SOVALDI (sofosbuvir) *Gilead*	"SOVALDI is indicated in combination with other medicinal products for the treatment of chronic hepatitis C in adults"	Under assessment
INCIVO (telaprevir) Janssen	"INCIVO, in combination with peginterferon alfa and ribavirin, is indicated for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease (including cirrhosis): - who are treatment-naïve - who have previously been treated with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin, including relapsers, partial responders, and null-responders."	Transparency Committee opinion of 14/12/2011 AB: Substantial IAB: "The Transparency Committee considers that the addition of telaprevir to 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."
PEGASYS (pegylated interferon alfa 2a) *Roche*	"PEGASYS is indicated for the treatment of chronic hepatitis C in adults who are positive with serum HCV-RNA, including patients with compensated cirrhosis and/or co-infected with HIV (stable HIV infection)"	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 (level III) in terms of efficacy in comparison with 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."

VIRAFERON PEG (pegylated interferon alfa-2a) *MSD*	"VIRAFERONPEG is indicated for the treatment of adult patients with chronic hepatitis C who are positive for HCV-RNA, including patients with compensated cirrhosis and/or co-infected with clinically stable HIV."	Transparency Committee opinion of 10/10/2001 AB: Substantial IAB: As dual therapy "For all patients: VIRAFERONPEG/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." "In genotype 1 patients with a small viral load, VIRAFERONPEG/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" Transparency Committee opinion of 20/10/2010 AB: Substantial IAB: "No improvement in actual benefit (IAB 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 or 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 under 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**
  - 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
  - or on the waiting list for a liver or kidney transplant
  - or having undergone a liver transplant and presenting recurrence of the HCV infection.

◗ Conclusion

The clinically relevant comparators of boceprevir (VICTRELIS) 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: telaprevir (INCIVO) 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/9dc54d141586170d08b13eafff20f05a.pdf.

08 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 lies in the fact that it can frequently become chronic, which can entail long-term cirrhosis, hepatocellular insufficiency, and hepatocellular carcinoma. Of the six genotypes of hepatitis C virus, genotype 1 is the predominant one. These proprietary medicinal products fall into the category of first- or second-line triple 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 increased haematological toxicity. 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 treatment-experienced patients and remains moderate. The decrease in morbidity and mortality attributable to chronic hepatitis C is a public health need that is 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 the substantial impact of boceprevir treatment on the rate of sustained virological response, particularly in treatment-experienced patients. The modelling results show that the antiproteases have an impact on the morbidity and mortality of the treated patients (progression towards chronicity, liver fibrosis, liver cancer, death). This impact is substantial in treatment-experienced patients and small in treatment-naïve patients. The impact on quality of life and the organisation of care is not documented. Transferability is debatable, particularly because of the complexity of the therapeutic regimen, the possibility of carrying out IL28 genotype testing, which is not yet systematic, and the absence of data on patients co-infected with HIV. Treatment with boceprevir, in combination with peginterferon alfa and ribavirin, does seem therefore 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 VICTRELIS in this indication. There is one treatment alternative validated by the Marketing Authorisation: INCIVO (telaprevir). Consequently, the actual benefit of VICTRELIS is substantial.
Improvement in Actual Benefit	Taking into account: - the degree of virological efficacy achieved with triple therapy, particularly in patients who have had a failed dual therapy and who did not have any therapeutic alternative available to them, - the possible reduction in the total treatment duration of 48 weeks (dual therapy) to 28 weeks (triple therapy) in some previously untreated patients (non-cirrhotic patients achieving a fast response during treatment) but considering, - the increased toxicity, in particular the anaemia that more frequently necessitates a reduction in the dose of ribavirin and/or the administration of erythropoietin, - the sub-optimal level of evidence from data in support of the determination of treatment regimens, particularly in null-responders who were excluded from the RESPOND2 study, The Transparency Committee considers that, compared with peginterferon/ribavirin dual therapy alone, the addition of boceprevir to this dual therapy provides: - 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 as yet not systematic IL28 genotype testing, the potential discovery of new substances, additional data are expected on: - the characteristics of patients under care for hepatitis C - the conditions of use (therapeutic strategies adopted, genotype testing prior to 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.

09 ANALYSIS OF AVAILABLE DATA

In the context of this re-assessment of the improvement in actual benefit of the proprietary medicinal product VICTRELIS, the company has presented:

- a Phase IIB clinical study and a Phase III clinical study;
- two open-label follow-up studies in patients who had participated in the clinical studies;
- three pharmacoepidemiology studies;
- a summary of pharmacovigilance data;
- usage and prescription data.

The double-blind, randomised, Phase III comparative studies that led to Marketing Authorisation being granted for VICTRELIS (SPRINT2,[13] RESPOND2,[14] and P05685 studies) were presented in the previous Transparency Committee opinion dated 14 December 2011.

Reminder of the Transparency Committee's conclusions concerning these studies:[9]

"In the treatment of chronic hepatitis C genotype 1 infection, the efficacy safety of boceprevir combined with peginterferon alfa and ribavirin was evaluated versus peginterferon alfa combined with ribavirin in randomised, double-blind studies on previously untreated adults and relapsers or partial responders to peginterferon combined with ribavirin, in the absence of liver decompensation. Null-responders to previous treatments were excluded from the RESPOND2 study.

The addition of boceprevir (800 mg 3 times/day) to peginterferon alfa-2b/ribavirin (BPR and BPR-Response-Guided Therapy) leads to an increase in the percentage of sustained virological response (undetectable viral load at 24th week of follow-up) compared with the combination of peginterferon alfa-2b/ribavirin (PR):

- for previously untreated adults: BPR: 66% versus PR: 38%, $p < 0.0001$ and BPR-RGT: 63% versus PR: 38%, $p < 0.0001$, i.e. an absolute increase of 25% to 28% (SPRINT2 study);
- for adult relapsers or partial responders to previous treatment: BPR: 67% versus PR: 21%, $p < 0.0001$ and BPR-RGT: 59% versus PR: 21%, $p < 0.0001$, or an absolute increase of 37% to 45% (RESPOND2 study).

The improvement in sustained virological response (SVR) observed 24 weeks after stopping treatment was less significant for treatment-naïve patients than for patients with a failed previous treatment and the SVR at 24 weeks after stopping treatment was less frequent for partial responder patients than for relapse patients.

Data from a long-term follow-up study will allow the sustainability of virological response and viral resistance at 3 years to be determined.

Data allowing the duration of treatment to be defined, according to the different patient profiles (previously treated, failed treatment, fast or slow responders, patients with or without cirrhosis) are not particularly conclusive. The total recommended treatment duration is 48 weeks, with the exception of adults who do not have cirrhosis and were previously untreated and who achieved a fast response, for whom the total treatment duration is 28 weeks.

In terms of safety, the addition of boceprevir to peginterferon/ribavirin is associated with an increase in serious adverse events (AEs) and stopping treatment due to an AE, especially for previously treated patients.

The most commonly reported AEs in the groups combining boceprevir/peginterferon/ribavirin were of the same nature (fatigue, anaemia, nausea, and headache) as those usually seen with peginterferon/ribavirin treatment, with the exception of dysgeusia.

[13] Poordad F, McCone J, et al. Boceprevir for Untreated Chronic HCV Genotype 1 Infection. NEJM 2011; 364(13): 1195-206

[14] Bacon BR, Gordon SC, et al. Boceprevir for Untreated Chronic HCV Genotype 1 Infection. NEJM 2011; 364(13): 1207-17

However, the addition of boceprevir to peginterferon/ribavirin increased the risk of anaemia (49% versus 29%), grade 3-4 neutropenia (29% versus 17%), and gastrointestinal AEs compared with peginterferon alfa-2b and ribavirin dual therapy.
Reductions in doses of ribavirin and/or the use of erythropoietin (43% in the groups treated with boceprevir versus 24% in the group treated solely with peginterferon alfa-2b and ribavirin) and/or transfusions (3% versus < 1%) were more common in adults treated with boceprevir than those who had been previously treated or untreated.

09.1 Efficacy

The new data presented by the company were obtained from clinical studies, open-label follow-up studies, and observational studies:

- Study P05411:[15] Phase IIB double-blind, randomised, controlled study which evaluated the efficacy of boceprevir in HCV treatment-naïve patients co-infected with HIV and genotype 1 HCV;
- Study P06086 or EPO:[16] Phase III randomised, open-label, controlled study which evaluated the impact of two strategies for the management of anaemia on the efficacy of the triple therapy combining boceprevir, peginterferon, and ribavirin;
- Study P05514 or PROVIDE study: follow-up study which evaluated the efficacy and safety of boceprevir in patients included in the control group of previous clinical studies in which dual therapy had failed;
- Study P05063: long-term follow-up study to evaluate the maintenance of the virological response in subjects who had achieved a sustained virological response (SVR) or changes in HCV-variants in the subjects who had not achieved a SVR during the course of an earlier clinical study;
- CUPIC cohort (ANRS CO20):[17,18] prospective French cohort monitored by the Agence Nationale de Recherche sur le Sida (ANRS) [French National AIDS Research Agency], 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).

9.1.1 Study P05411:

Study P05411 is a Phase IIB randomised, double-blind, controlled study, whose primary aim was to evaluate the efficacy of a triple therapy combining boceprevir, peginterferon, and ribavirin versus a dual therapy (peginterferon and ribavirin) in patients co-infected with HIV and genotype 1 HCV, naïve of treatment for chronic hepatitis C. The treatment duration was 48 weeks.

A total of 98 patients were included: 64 in the triple therapy group and 34 in the dual therapy group. The median age of the patients was 44 years and 3% (3/98) of them had cirrhosis. The HCV was genotype 1a for 65% of patients. Of the 54 patients in the triple therapy group found to be of genotype IL28B: 30 had genotype CT and 16 genotype CC.

[15] Sulkowski M. et al. Boceprevir versus placebo with pegylated interferon alfa-2b and ribavirin for treatment of hepatitis C virus genotype 1 in patients with HIV: a randomised, double-blind, controlled phase 2 trial. Lancet Infect Dis 2013 + appendix.
[16] Poordad F, Lawitz E, Reddy KR, et al. Protocol 6086 Investigators. Effects of ribavirin dose reduction vs erythropoietin for boceprevir-related anemia in patients with chronic hepatitis C virus genotype 1 infection--a randomized trial. Gastroenterology. 2013 Nov; 145(5): 1035- 1044. e5. doi: 10.1053/j.gastro.2013.07.051. Epub 2013 Aug 4.
[17] 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.
[18] Hezode C, Fontaine H, Dorival C, et al; CUPIC Study Group. Effectiveness of telaprevir or boceprevir in treatment-experienced patients with HCV genotype 1 infection and cirrhosis. Gastroenterology. 2014 Jul; 147(1): 132-142.e4.

The percentage of patients achieving a SVR at 24 weeks after stopping treatment was 63% (40/64) in the triple therapy group versus 29% (10/34) in the dual therapy group.

9.1.2 EPO study[16]

The EPO study is a Phase III randomised, open-label, controlled study whose principal aim is to evaluate the impact on efficacy of two anaemia management strategies (reducing the dose of ribavirin versus using erythropoietin) in patients treated with a boceprevir/peginterferon/ribavirin triple therapy.

At inclusion, patients were treatment-naïve and had a haemoglobin level ≤ 15 g/dl. A total of 688 patients (434 women and 254 men) were treated by triple therapy. Of these, 500 patients had anaemia (haemoglobin level ≤ 10 g/dl) during treatment and were randomised into one of the two anaemia management groups (ribavirin dose reduction in steps of 200 or 400 mg/day or addition of 40,000 units/week of EPO by the subcutaneous route). Additional measures, including a reduction in the ribavirin dose or using EPO, were taken when the haemoglobin level continued to drop to a value ≤ 8.5 g/dl. The median age of patients was 51 years (19-73 years) and 9% of them had cirrhosis. The HCV was genotype 1a in 54% of these patients, genotype 1b in 33%, and an unknown subgenotype in 13%.

The results presented are from a FAS analysis conducted in 500 patients who had anaemia under triple therapy: 249 who had a reduction in the dose of ribavirin and 251 who were given EPO. In the case of 77 patients, management of the anaemia required five or more steps of ribavirin dose reduction. For the majority of subjects (54), the lowest dose of ribavirin received during at least 14 days was ≥ 600 mg/day. A limited number of subjects (12) were given a dose of ribavirin ≤ 200 mg/day for at least 14 days.
The percentage of patients obtaining an SVR at 24 weeks was comparable with both anaemia management strategies: 72% (178/249) in patients who had their ribavirin dose reduced versus 71% (178/251) in patients who were given EPO.

9.1.3 PROVIDE study

The PROVIDE study is an open-label follow-up study with just one treatment group receiving triple therapy, conducted among patients from the control groups of previous Phase II and III clinical studies who failed to achieve a SVR with biotherapy. The main aim of this study was to evaluate the efficacy of triple therapy that included boceprevir in patients who have had failed previous pegylated interferon + ribavirin dual therapy, in particular patients with a null response to this dual therapy.

A total of 168 patients were included: 29 (17%) relapsers,[19] 137 null-responders[20] including 85 (51%) partial responders, [19] and 52 (31%) non-responders[19] as well as 2 other patients who had a failed treatment. The median age of the patients was 52 years (25-73 years) and 17 (10%) of them had cirrhosis. Of the cirrhotic patients, 12 (14%) were partial responders, 2 (7%) were relapsers, and 3 (6%) were null-responders. The HCV was genotype 1a in 61% of patients, genotype 1b in 38%, and of unknown genotype in 1%. HCV variants resistant to boceprevir were present in 8% of patients.

In the ITT analysis (including patients who had received at least one dose of one of the components of the triple therapy), the percentage of patients who achieved a SVR was

[19] Relapsers are patients whose HCV-RNA was negativated during treatment and whose viral load reappeared after discontinuation of treatment.
[20] Non-responders 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 obtaining negativation during the course of treatment;
- Non-responders: patients whose viral load decreased by less than 2 log IU/ml during a treatment period of at least 12 weeks.

63% (106/168) for the patients as a whole; this percentage was 93% (27/29) for relapsers, 67% (57/82) for partial responders, and 38% (20/52) for null-responders. Relapse was observed in 11% (13/119) of patients. HCV variants resistant to boceprevir were identified in 68% of patients who failed to achieve a SVR.

9.1.4 Study P05063

The P05063 study is a long-term 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 boceprevir treatment (cohort A);
- changes in HCV variants in patients without a SVR who have developed resistance after boceprevir treatment (cohort B).

The results presented are taken from an interim analysis carried out on 21 December 2012. On this date, 1148 patients were included, all of whom had received boceprevir:

- cohort A (n = 696): the median duration of follow-up was 3.4 years (0.5-4.1 years). Four patients had a late relapse during the follow-up period.
- cohort B (n = 452): the median duration of follow-up was 3.3 years (0.0-4.1 years). Of the 341 patients shown to have resistant variants of HCV at the time of treatment failure, 228 (73%) patients no longer had detectable resistant variants at the end of the follow-up period. The median time taken for resistant variants to become undetectable was 1.1 years.

9.1.5 CUPIC cohort[17,17]

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 the SVR estimation.

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

The results presented are from an interim analysis performed after 60 weeks of follow-up (12 weeks after stopping treatment) in March 2013. Only 511 patients completed the follow-up 12 weeks after stopping treatment. Of these, 212 were treated with boceprevir according to the following regimen: dual therapy (peginterferon and ribavirin) for 4 weeks followed by triple therapy (boceprevir, peginterferon, and ribavirin) for 44 weeks. These patients had a mean age of 57 years and 30% had at least one exclusion criterion from the RESPOND2 study. The majority of them had a CPT stage A score[21] (93%) and/or a MELD score[22] of less than 10 (83%). The HCV was genotype 1a in 41% of these patients, genotype 1b in 49%, and another genotype in 10%. Before being treated with boceprevir, patients were predominantly non-responders (44% partial responders and 5% null-responders) and relapsers[23] (43%); the other patients had virological escape to an earlier treatment (5%) or an indeterminate response profile (3%). HCV-RNA was

[21] The CPT score (Child-Turcotte-Pugh) 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).

[22] The MELD (Model for End-Stage Liver Disease) score is calculated from three 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.

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

undetectable (SVR at 12 weeks) in 43% (91/212) of patients, with a higher percentage response among relapsers (54%) than among partial responders (38%). None of the null-responders had achieved a SVR 12 weeks after stopping treatment.

09.2 Adverse effects

According to the SPC, the most common (≥ 1/100) adverse effects of triple therapy with peginterferon, ribavirin, and boceprevir are, in particular: blood disorders (anaemia, neutropenia, leukopenia, thrombocytopenia), gastrointestinal disorders (nausea, dysgeusia, decreased appetite), fatigue, headache and psychiatric disorders (irritability, insomnia, mood disorder, and depression).

Certain specific risks are highlighted in the SPC:

- Anaemia and neutropenia: the addition of boceprevir to dual therapy with peginterferon and ribavirin increases the risk of anaemia and neutropenia. Complete blood counts (with white blood cell differential counts) should be obtained at pretreatment, and at weeks 2, 4, 8, and 12 of treatment, and should be monitored closely at other times, as clinically appropriate.
  If the haemoglobin < 10 g/dl, it may be necessary to treat the anaemia. Reducing the dose of ribavirin is the preferred approach in managing treatment-induced anaemia. Should it be necessary to stop ribavirin permanently, then the peginterferon alfa and the VICTRELIS will also need to be stopped.
  Certain neutropenias may necessitate reducing the dose of peginterferon alfa or stopping the treatment. Should it be necessary to stop peginterferon permanently, then ribavirin and boceprevir will also need to be stopped. It is recommended that infections should be assessed and treated as promptly as possible.
- Hypersensitivity: serious or acute hypersensitivity reactions (urticaria, angioedema) have been observed during treatment with boceprevir, peginterferon alfa, and ribavirin. If such a reaction occurs, the treatment should be suspended and appropriate medical therapy immediately instituted.

The identified or potential risks followed up under the Risk Management Plan (RMP) associated with the Marketing Authorisation for boceprevir are the following: anaemia, neutropenia, thrombocytopenia, drug interactions (CYP3A4/5, ritonavir-boosted HIV protease inhibitors), dysgeusia, thyroid neoplasm, prolongation of the QT interval, development of resistance, and medication errors. In 2013, hypersensitivity reactions and severe skin reactions were also added to the identified or potential risks in the RMP.

9.2.1 New safety data obtained from post-Marketing Authorisation studies

Study P05411

Of the 64 patients treated by triple therapy (boceprevir, peginterferon, ribavirin), 11 presented with a serious adverse event, 6 of which were considered to be treatment-related (2 cases of anaemia, 1 of depression, 1 pulmonary embolism, 1 syncope, and 1 case of palpable lymph nodes). Triple therapy had to be stopped due to adverse effects in 13 patients (20%). Anaemia was observed in 49% of patients, including 3% with grade ≥ 3, and this led to a reduction in dose of ribavirin combined with EPO in 54% of cases, treatment with EPO alone in 19% of cases, and a reduction in the dose of ribavirin alone in 4% of cases.

EPO study

Of the 500 patients who had anaemia during triple therapy, 249 had their dose of ribavirin reduced and 251 received EPO. The percentages of treatments stopped due to anaemia and to transfusion were similar in both groups: 2% (5/249) of treatments stopped and 4% (10/249) of cases of transfusion in the patients whose ribavirin dose was reduced versus 2% (6/251) of treatments stopped and 2% (5/251) transfusions in the patients receiving EPO.
The use of erythropoiesis-stimulating agents was associated with an increased risk of thromboembolic events, including pulmonary embolism, acute myocardial infarction, stroke, and deep vein thrombosis.

The results of this study led to the following information being added to the SPC: “Reducing the dose of ribavirin is the preferred approach in managing treatment-induced anaemia. […] Should it be necessary to stop ribavirin permanently, then the peginterferon alfa and the VICTRELIS will also need to be stopped.”

Study P08518 or PASS study

The PASS study is an observational study conducted within the framework of the RMP with the aim of evaluating the use of boceprevir and managing its haematological adverse effects. The data were collected from 100 doctors in 4 European countries (22 in France, 27 in Germany, 34 in Spain, and 17 in the United Kingdom) with the aid of a questionnaire and an electronic form. The presented results are taken from an interim analysis carried out on 4 June 2013 based on data obtained for 262 patients, 111 of whom had received triple therapy that included boceprevir. The patients treated with boceprevir had a mean age of 51.7 years; 47% had a METAVIR score ≥ 3. The mean duration of treatment with boceprevir was 11.3 weeks, and premature treatment discontinuation was reported in 20 patients (18%). These treatment discontinuations predominantly came as a result of the doctor’s decision (25%), the viral load (20%), adverse effects (20%), or the patient’s choice (20%). Anaemia was reported in 42% of patients, grade ≥ 3 neutropenia in 17% of patients, and grade ≥ 3 thrombocytopenia in 5% of patients. Management of anaemia during triple therapy including a protease inhibitor led to the ribavirin dose being reduced in 53% of cases, EPO treatment in 66% of cases, and transfusion in 19% of cases.

CUPIC cohort[24]

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 205 of boceprevir (peginterferon + ribavirin dual therapy for 4 weeks followed by boceprevir + peginterferon + ribavirin triple therapy for 12 weeks). Of these, 26% stopped treatment early, including 7% due to a serious adverse effect. In total, 33% of patients had a serious adverse effect such as grade ≥ 3 anaemia (4%), grade ≥ 3 neutropenia (4%), grade ≥ 3 infection (2%), grade 4 thrombocytopenia (2%), or liver decompensation (3%). Management of the anaemia led to a reduction in the ribavirin dose in 11% of patients, EPO treatment in 46%, and transfusion in 6%. One death was reported. These data show the safety profile of the triple therapy containing boceprevir to be inferior in cirrhotic patients in the context of real-life use.

Following publication of the data obtained with this cohort, a change will be proposed in the SPC 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 to avoid using telaprevir-based triple therapy in cirrhotic patients with blood albumin < 33 g/l and/or thrombocytopenia < 90,000/mm^3.

9.2.2 New pharmacovigilance data

National pharmacovigilance system[25]

ANSM [French National Agency for Medicines and Health Products Safety] has put in place a national pharmacovigilance system for boceprevir. 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 PSURs covering the period from 13/05/2011 to 12/05/2013, as well as cases notified to the National Pharmacovigilance Database up to 04/10/2013). This report confirmed the major risk of haematological adverse effects with boceprevir (anaemia, neutropenia, thrombocytopenia) and that management of anaemia varied from one prescriber to another, with frequent recourse to EPO,

[24] Hézode C, Fontaine H, Dorival C et al. CUPIC Study Group. Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme (ANRS CO20-CUPIC) - NCT01514890. 2013 Sep; 59(3): 434-41. Epub 2013 May 10.

[25] Meeting of the Pharmacovigilance Technical Committee – CT012013083. Minutes of the meeting. Consulted 12 March 2014. http://ansm.sante.fr/var/ansm_site/storage/original/application/6ac3b5756a632e85c75b75f05c608400.pdf.

although reducing the ribavirin dose should be the preferred option. This report also drew attention to a risk of sometimes severe infectious complications, psychiatric effects, and skin disorders, including two cases of DRESS (Drug Rash with Eosinophilia and Systemic Symptoms), one confirmed and one suspected. At the time of this report it was stressed that the risk of pancytopenia and agranulocytosis was to be added to the SPC and to the package leaflet, based on the assessment of the latest PSUR. In light of this report, the CTV decided to maintain the national pharmacovigilance system. It also recommended updating information brochures concerning the haematological adverse affects and their management, anaemia in particular.

PSUR

Since the previous Transparency Committee opinion, analysis of the Periodic Safety Update Reports on pharmacovigilance has led, in particular, to the following changes being made in the SPC:

- Section 4.3 Contraindications: *"simvastatin", "lovastatin", "alfuzosine", "silodosine"* have been added to the list of medicinal products whose co-administration with boceprevir is contraindicated on account of their being metabolised by CYP3A4/5 and with which high plasma concentrations are associated with serious and/or life-threatening events.
- Section 4.4 Special warnings and precautions for use:
  "Pancytopenia
  Cases of pancytopenia have been reported in patients receiving VICTRELIS in combination with peginterferon alfa and ribavirin. Complete blood counts (with white blood cell differential counts) should be obtained at pretreatment, and at treatment weeks 2, 4, 8, and 12, and should be monitored closely at other time points, as clinically appropriate.
  Hypersensitivity
  Serious, acute hypersensitivity reactions (e.g., urticaria, angioedema) have been observed during combination therapy with VICTRELIS, peginterferon alfa, and ribavirin. If such reaction occurs, combination therapy should be discontinued and appropriate medical therapy immediately instituted."
- Section 4.8 Undesirable effects: *"agranulocytosis"* has been added to the common adverse effects (≥ 1/100 to < 1/10*)* and the adverse effects *"angioedema", "DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms)",* and *"Stevens-Johnson syndrome"* to the adverse effects of indeterminate frequency.

9.2.3 Further information

In February 2012, a letter was sent to all health professionals to inform them about the risk of drug interactions between VICTRELIS and ritonavir-boosted HIV protease inhibitors.[26]
The main points were as follows:

- Based on the results of a pharmacokinetic study, section 4.5 Interactions with other drugs and other forms of interactions has been updated as follows:
  "It is not recommended to co-administer darunavir/ritonavir and VICTRELIS." and *"Co-administration of atazanavir/ritonavir with boceprevir resulted in lower exposure of atazanavir which may be associated with lower efficacy and loss of HIV control. This co-administration might be considered on a case by case basis if deemed necessary, in patients with suppressed HIV viral loads and with HIV viral strain without any suspected resistance to the HIV regimen. Increased clinical and laboratory monitoring for HIV suppression is warranted."*
- These pharmacokinetic interactions could have clinical implications in patients infected with both HCV and HIV by reducing the efficacy of these treatments when they are co-administered.

[26] Communication to healthcare professionals on drug interactions between VICTRELIS (boceprevir) and ritonavir-boosted HIV protease inhibitors. February 2012. Consulted on 13 March 2014. file:///U:/08_Infectiologie/01_Virologie/VHC/VICTRELIS/Lettre%20info_022012.pdf

09.3 Usage/prescription data

Of the data available, only the French data collected after 2012 will be given in detail.

9.3.1 GERS data

According to GERS [Group for the Development and Implementation of Statistics] data, 4,285,344 capsules of VICTRELIS 200 mg were dispensed (i.e. 12,754 bottles of 336 hard capsules) 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 boceprevir, the mean treatment duration was 27 weeks; anaemia was reported in 41% of patients and skin rash in 5% of patients treated with a triple therapy that included boceprevir. 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 choice (28%).

09.4 Summary and discussion

The controlled clinical studies showed that treatment of genotype 1 chronic hepatitis C with triple therapy (boceprevir, peginterferon, and ribavirin) allows a sustained virological response to be obtained 24 weeks after stopping treatment in about 65 to 70% of treatment-naïve or experienced patients.

The latest available efficacy data tend to confirm the improvement in the SVR observed during controlled studies and its maintenance over time, but also the limitations of triple therapy that include boceprevir (viral escape in the worst affected patients, emergence of resistance, poor safety). Thus, according to the studies, viral resistance was identified in about 50 to 70% of patients who have had a failed triple therapy that included boceprevir, and the CUPIC study showed a low proportion of virological response in experienced cirrhotic patients (about 45% of SVR 12 weeks after stopping treatment) with a substantial number of prematurely stopped treatments.

The safety profile and especially the 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 boceprevir 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 (12 hard capsules daily taken at fixed times with a light 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 particular aim of this study is 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 discovery of new treatments.[27]

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

Population	Recommendation	References
Genotype 1	Naïve patients: PEG-IFN, RBV ± boceprevir or telaprevir for 24 to 48 weeks	AFEF 2011, EASL 2013
	Failure of prior treatment: PEG-IFN, RBV ± boceprevir or telaprevir for 48 weeks	
HIV co-infected patients	GT1: PEG-IFN, RBV and boceprevir or telaprevir	SPILF, AFEF, SFLS, SNFMI, 2013
	Other genotypes: PEG-IFN + RBV for 48 weeks irrespective of the genotype	Consensus 2005, HCV/HBV – HIV co−infection
Decompensated cirrhosis	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 virological 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.	EASL 2013
Liver transplantation	There are no data on the use of protease inhibitor-based triple therapies 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, such that the adverse effects profile in this group of patients may be especially difficult.	Consensus conference 2002 EASL 2013

While awaiting the French guidelines for the management of hepatitis C patients, due in 2015, AFEF has put forward expert opinions[28] on the choice of treatments for hepatitis C. The AFEF and the DHUMEAUX[29] report no longer recommend the use of VICTRELIS (boceprevir) or INCIVO (telaprevir) in the treatment of chronic hepatitis C due to genotype 1 HCV.

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 discovery 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.

[27] AFEF: http://www.afef.asso.fr/rc/org/afef/nws/News/2013/20130702-140724-645/src/nws_fullText/fr/Texte%20AFEF%20ANRS%20Rapport%20hépatites%20virales.pdf.

[28] AFEF expert opinion on the treatment of hepatitis C in France, March 2014. Available at http://www.afef.asso.fr/ (consulted on 21 March 2014).

[29] 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).

011 TRANSPARENCY COMMITTEE CONCLUSIONS

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.

◗ This proprietary medicinal product comes 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 discovery 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, particularly because of the haematological toxicity.

◗ There are treatment alternatives.

Consequently, the Transparency Committee considers that the actual benefit of VICTRELIS 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 genotype 1 HCV in patients with compensated liver disease, VICTRELIS 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.

011.3 Target population

VICTRELIS 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 discovery 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.

By way of 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 is 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 is 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 is 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

Product	Number	Number extrapolated to the French population	95% CI	
			Lower limit	Upper limit
INCIVO	23	2475	1463	3486
VICTRELIS	18	1937	1042	2831
TOTAL	41	4411	3061	5762

012 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Packaging

The packaging is appropriate for the prescribing conditions in terms of indication, dosage and treatment duration.

◗ Other recommendations

The Transparency Committee would like 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.