HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

14 December 2011

VICTRELIS 200 mg, hard capsules
B/336 (CIP code: 419 467-9)

Applicant: MSD FRANCE

boceprevir
ATC code: J05AE12 (protease inhibitor)

List I

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

Date of Marketing Authorisation (centralised European procedure): 18/07/2011

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

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
boceprevir

1.2. Background
This product is a hepatitis C genotype 1 NS3/4A protease inhibitor.

1.3. 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 (see sections 4.4 and 5.1 of SPC).”

1.4. Dosage
"Treatment with VICTRELIS should be initiated and monitored by a physician experienced in the management of chronic hepatitis C.

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 dosage of VICTRELIS is 800 mg administered orally three times daily (TID) with food (a meal or light snack). The maximum daily dose of VICTRELIS is 2,400 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 100 IU/ml at TW 12; then discontinue 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 cirrhotic patients and null responders

Recommended treatment duration is 48 weeks: 4 weeks of bitherapy with peginterferon alfa + ribavirin + 44 weeks of triple therapy 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 undesirable events 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)."

[…]

"Dose reduction

Dose reduction of VICTRELIS is not recommended.

If a patient presents with a serious undesirable effect potentially related to peginterferon alfa and/or ribavirin, the peginterferon alfa and/or ribavirin dose should be reduced. Refer to the Summary of Product Characteristics for peginterferon alfa and ribavirin for additional information about how to reduce and/or discontinue the peginterferon alfa and/or ribavirin dose. VICTRELIS must not be administered in the absence of peginterferon alfa and ribavirin.

Special populations

Renal impairment
No dose adjustment of VICTRELIS is required in patients with any degree of renal impairment (see section 5.2).

Hepatic impairment
No dose adjustment of VICTRELIS is required for patients with mild, moderate or severe hepatic impairment. VICTRELIS has not been studied in patients with decompensated cirrhosis (see section 5.2).

Paediatric population
The safety and efficacy of VICTRELIS in children aged below 18 years have not yet been established. No data are available.

Elderly
Clinical studies of VICTRELIS did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other clinical experience has not identified differences in responses between the elderly and younger patients (see section 5.2)."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification

J	Antiinfectives for systemic use
J05	Antivirals for systemic use
J05A	Direct acting antivirals
J05AE	Protease inhibitors
J05AE12	Boceprevir

2.2. Medicines in the same therapeutic category

Comparator medicines

There is another protease inhibitor indicated in the treatment of chronic hepatitis C genotype 1 infection available with a marketing authorisation dated 19/09/2011: INCIVO (telaprevir).

2.3. Medicines with a similar therapeutic aim

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

The actual benefit of these proprietary medicinal products is substantial.

- ribavirin:

COPEGUS, film-coated tablets 200 mg and 400 mg

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

and its generics

- peginterferon alpha:

PEGASYS (peginterferon alfa 2a) 135 µg, 180 µg, solution for injection in pre-filled syringe

VIRAFERONPEG (peginterferon alfa 2b) 50 µg, 80 µg, 100 µg, 120 µg, 150 µg, powder and solvent for solution for injection in pre-filled pen and 50 µg, powder and solvent for solution for injection in a vial

- interferon alpha:

ROFERON-A (interferon alpha 2a) 3, 4, 5, 6 and 9 million IU, solution for injection in pre-filled syringe

INTRONA (interferon alpha 2b) 10 and 18 million IU, solution for injection and 18, 30 and 60 million IU, solution for injection, multi-dose pen

3. ANALYSIS OF AVAILABLE DATA

The file submitted includes 3 phase III studies, evaluating boceprevir in combination with peginterferon alfa and ribavirin versus peginterferon alfa and ribavirin in previously untreated adults and relapse patients or those who have partially responded to a previous treatment, in the absence of liver decompensation:
- 2 pivotal studies carried out with peginterferon alfa 2b (SPRINT2 and RESPOND2) and
- one study carried out with peginterferon alfa-2a (P05685).

The Committee has highlighted that boceprevir has not been evaluated on null responders to previous treatment.
Furthermore, data presented does not concern certain populations, such as transplant patients, patients co-infected with HIV or the hepatitis B virus and children.

3.1. Efficacy

3.1.1 Previously untreated adult patients

SPRINT2 Study (P05216)[1]

A randomised, double-blind study versus placebo with the primary objective of evaluating the efficacy of two therapeutic regimens of boceprevir combined with peginterferon alfa-2b and ribavirin (BPR and BPR-RGT) versus peginterferon alfa-2b and ribavirin (PR) in adults with chronic hepatitis C genotype 1 infection and not previously treated with interferon alfa.

Main inclusion criteria:
- adults ≥ 18 years with chronic hepatitis C genotype 1 infection with a HCV-RNA viral load ≥ 10 000 IU/ml,
- availability of a liver biopsy,
- for patients with fibrosis or cirrhosis: availability of an ultrasound scan result with no hepatocellular carcinoma suspected.

Main non-inclusion criteria:
- patients co-infected with HIV or hepatitis B virus,
- previously received treatment for hepatitis C,
- decompensated liver disease.

Treatment: patients were randomised (1:1:1) into 3 groups.
Randomisation was stratified according to HCV genotype (1a or 1b) and the RNA-HCV viral load (≤ 400 000 IU/ml versus > 400 000 IU/ml).

In each of the groups, during an initial phase, dual peg therapy over 4 weeks, combining peginterferon alfa-2b at a dose of 1.5 µg/kg/week subcutaneously and ribavirin at a dose between 600-1400 mg/day taken twice orally, was administered. Then the patients were treated according to one of the following three regimens:

1. Group PR (N=363):
initial dual peg therapy for 4 weeks, followed by 44 weeks of the combination of:
- peginterferon alfa-2b: 1.5 µg/kg/week, subcutaneously
- ribavirin: 600-1400 mg/day, taken twice orally
- placebo

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

2. Group BPR (N=366):
initial peg dual therapy for 4 weeks, followed by 44 weeks of the combination of:
- boceprevir: 800 mg (4 capsules) three times/day, orally
- peginterferon alfa-2b: 1.5 µg/kg/week, subcutaneously
- ribavirin: 600-1400 mg/day, taken twice orally

3. Group BPR-RGT (Response-Guided Therapy) (N=368):
initial dual peg treatment for 4 weeks followed by 24 weeks of the combination of:
- boceprevir : 800 mg (4 hard capsules) three times/day orally
- peginterferon alfa-2b: 1.5 µg/kg/week subcutaneously
- ribavirin: 600-1400 mg/day taken twice orally

then continuation, or not, of dual therapy (peginterferon and ribavirin) based on reduction in viral load at TW 8 and TW 24:
  - quick responders[2]: stop treatment at TW 28, or a total treatment duration of 28 weeks
  - slow responders[3]: dual therapy (peginterferon and ribavirin) and placebo for 20 additional weeks, or a total treatment duration of 48 weeks.

In cases of detectable levels of plasma RNA-HCV at TW 24, treatment was stopped.
The management of anaemia (by the reduction in doses of ribavirin and/or the administration of erythropoietin) was left to the discretion of the clinical trial investigators.

Primary efficacy endpoint: achieving a sustained virological response (SVR), defined as an undetectable RNA-HCV viral load at the 24th week of follow-up after finishing treatment, in the FAS (Full Analysis Set) population, including all randomised patients who received at least one treatment (peginterferon alfa-2b, ribavirin or boceprevir/placebo).
Primary analysis is based on a comparison between the BPR versus PR groups then the BPR-RGT versus PR groups.

Secondary endpoints, especially:
- sustained virological response (SVR) in the mITT population including all randomised patients who received at least one dose of boceprevir or placebo. This secondary endpoint was added following an amendment to the protocol.
- proportion of patients with a sustained virological response (SVR) among the patients with an undetectable viral load at TW 4 and TW 8.

Results:
A total of 1,099 patients were randomised: 938 patients were Caucasian and 159 Afro-American. Among the randomised patients, 1,097 received at least one dose of any treatment (FAS population) and 1,048 received at least one dose of boceprevir or placebo (mITT population).
The mean age of patients was 49.1 years (18-76 years) and 60% of patients were male. Half of patients were infected with HCV genotype 1a and 36% with HCV genotype 1b. The majority of patients (85%) had an extremely high initial viral load (> 800,000 IU/ml). The percentage of patients with a METAVIR[4] F0/1/2 fibrosis score was 86%. Cirrhosis (METAVIR F4 score) was present in 5% (53/1097) of patients.

[2] Patients with an undetectable level of RNA-HCV at TW 8 and also undetectable at TW 24
[3] Patients with detectable levels of RNA-HCV at TW 8 or during all weeks of a previous treatment, but then undetectable at TW 24
[4] The METAVIR score evaluates the severity of hepatitis. The stage of fibrosis is graded from F0 (absence of fibrosis) to F4 (cirrhosis).

- Primary efficacy endpoint:

The percentage of patients achieving a sustained virological load at the 24th week of follow-up was 37.8% in the PR group, 66.1% in the BPR group and 63.3% in the BPR-RGT group, or an absolute increase of 28.4% between the BPR and PR groups (p<0.0001) and an absolute increase of 25.6% between the BPR-RGT and PR groups (p<0.0001) in the FAS population. Comparable results were seen in the mITT analysis.

- Other endpoints:

A SVR was more commonly observed when the reduction in viral load in the initial dual therapy phase (TW 4) was ≥ 1 $\log_{10}$ compared with a < 1 $\log_{10}$ reduction, and with boceprevir combined with dual therapy compared with dual therapy alone (see table 2).

An undetectable viral load at TW 4 was observed by 8% (30/363) of patients in the PR group, by 5% in the BPR (20/366) and BPR-RGT group (19/368). Among these patients who achieved an undetectable viral load at TW 4, the percentage of sustained virological response was 97% in the PR group, 90% in the BPR group and 89% in the BPR-RGT group (see table 2).

Table 2: SVR at 24th week of follow-up, according to viral load at TW 4 or TW 8: SPRINT2 study

SVR at 24th week of follow-up	PR Group (N=363)	BPR Group (N=366)	BPR-RGT Group(N=368)
Reduction in viral load at TW 4			
< 1 $\log_{10}$	3/83 (4%)	36/95 (38%)	27/97 (28%)
≥ 1 $\log_{10}$	133/260 (51%)	200/254 (79%)	203/252 (81%)
Viral load undetectable at			
TW 4	29/30 (97%)	18/20 (90%)	17/19 (89%)
TW 8	51/60 (85%)	184/204 (90%)	184/208 (88%)

The percentage of relapses[5] was 22.2% (39/176) in the PR group, 9.1% (24/265) in the BPR group and 9.3% (24/257) in the BPR-RGT group.

Sub-group analyses were carried out, focussing on parameters that could potentially impact on the sustained virological response, namely the genotype, the initial viral load as well as the stage of fibrosis.
A sustained virological response was more common in genotype 1b patients, with a low initial viral load (≤ 400 000 IU/ml) and in patients with less fibrosis (F0-2 versus F3/4).
It should be noted, however, that the number of patients with a low initial viral load (8% of patients included) and a METAVIR F3/4 score was very low (9%) in this study.

Determination of treatment duration:
Although the SPRINT2 study was not designed to compare the treatment durations between the BPR and BPR-RGT groups in the fast responder and slow responder patient sub-groups, available data for these sub-groups were investigated to validate the therapeutic regimens.
Among the patients who received comparable treatment up to TW 28:

- in the sub-group of fast responder[2] patients (N=323/734):

Among the 734 patients in the BPR and BPR-RGT groups, 44% (323/734) had an undetectable viral load at TW 8 and TW 24 (fast responders), or 161/366 in the BPR group and 162/368 patients in the BPR-RGT group.
The percentages of fast responder patients who achieved a sustained virological response was comparable between the BPR (treated over 48 weeks) and BPR-RGT (treated over 28 weeks) groups: 96% in each of the groups (BPR: 155/161 and BPR-RGT: 156/162), or a difference of 0% $_{95\%}$ CI [-4.1; 4.1]. The percentage of relapses was 1.3% (2/157) in the BPR group and 3.1% (5/161) in the BPR-RGT group.

[5] proportion of patients with undetectable RNA-HCV at the end of treatment but detectable at the end of the follow-up period

- in the sub-group of slow responders[3] (N=141/734):

A difference of -9.2% $_{95\%}$ CI [-24.4; 6.3] between the percentage of sustained virological response was observed between the BPR-RGT group (treated over 48 weeks of which 24 weeks were triple therapy) and the BPR group (treated over 48 weeks of which 44 weeks were triple therapy): 66% (45/68) versus 75% (55/73).
The percentage of relapses was 13.5% (7/52) in the BPR-RGT group and 14.1% (9/64) in the BPR group.

In summary, with the exception of cirrhosis patients, for the fast responders, the validated treatment duration in the marketing authorisation corresponds to that evaluated in the BPR-RGT group, namely dual therapy for 4 weeks followed by 24 weeks of triple therapy, or a total treatment duration of 28 weeks.
Conversely, for the slow responders, a different treatment duration to that studied in the SPRINT2 study was validated. Triple therapy (following on from 4 weeks of peg dual therapy) is recommended over 32 weeks, followed by 12 weeks of peg dual therapy. This therapeutic regimen was evaluated for patients previously treated with interferon alfa and ribavirin in the RESPOND2 study described below.

Data for cirrhosis patients is very limited (5% of patients included); the therapeutic regimen conservatively validated by the marketing authorisation is for 48 weeks of treatment: 4 weeks of peg dual therapy, followed by 44 weeks of triple therapy.

3.1.2 Adults in relapse or partial responders to a previous treatment

RESPOND2 study (P05101)[6]

A randomised, double-blind study versus placebo with the primary objective of evaluating the efficacy of two therapeutic regimens of boceprevir combined with peginterferon alfa-2b and ribavirin (BPR and BPR-RGT) versus peginterferon alfa-2b and ribavirin (PR) in relapsing adult patients with chronic hepatitis C genotype 1 infection or partial responders to dual therapy (peginterferon alfa and ribavirin).

Main inclusion criteria:
- adults ≥ 18 years with chronic hepatitis C genotype 1 infection with no sustained virological response:
  - relapse patients: a relapse was defined as an undetectable viral load at the end of the previous treatment then detectable during the follow-up period
  - partial responder patients: a partial response was defined as a decrease in viral load ≥ 2 $\log_{10}$ after 12 weeks of treatment with standard peg dual therapy
- availability of a liver biopsy,
- for patients with fibrosis or cirrhosis: availability of an ultrasound scan result with no hepatocellular carcinoma suspected.

Main non-inclusion criteria:
- null responders, defined as those with a reduction in viral load < 2 $\log_{10}$ after 12 weeks of previous standard peg dual therapy treatment
- patients co-infected with HIV or the hepatitis B virus,
- decompensated liver disease.

Treatment: patients were randomised (1:2:2) into 3 groups.
Randomisation was stratified according to HCV genotype (1a or 1b) and previous response (relapsers or partial responders).

In each of the groups, during an initial phase, peg dual therapy over 4 weeks, combining peginterferon alfa-2b at a dose of 1.5 µg/kg/weeks subcutaneously and ribavirin at a dose

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

between 600-1400 mg/day taken twice orally was administered. Then patients were treated according to one of the following three regimens:

1. PR Group (N=80):
initial peg dual therapy for 4 weeks, followed by 44 weeks of the combination of:
- peginterferon alfa-2b: 1.5 µg/kg/week subcutaneously
- ribavirin: 600-1400 mg/day taken twice orally
- placebo

2. BPR Group (N=161):
initial dual therapy for 4 weeks, followed by 44 weeks of the combination of:
- boceprevir: 800 mg (4 capsules) three times/day taken orally
- peginterferon alfa-2b: 1.5 µg/kg/week subcutaneously
- ribavirin: 600-1400 mg/day taken twice orally

3. BPR-RGT Group (Response-Guided Therapy) (N=162):
initial peg dual therapy for 4 weeks, followed by 32 weeks of the combination of:
- boceprevir: 800 mg (4 capsules) three times/day taken orally
- peginterferon alfa-2b: 1.5 µg/kg/week subcutaneously
- ribavirin: 600-1400 mg/day taken twice orally

then continuation, or not, of dual therapy (peginterferon and ribavirin) based on the reduction in viral load at TW 8 and TW 12:
  - quick responders[7]: stop treatment at TW 36, or a total treatment duration of 36 weeks
  - slow responders[8]: dual therapy (peginterferon and ribavirin) and placebo for 12 additional weeks, or a total treatment duration of 48 weeks.

In cases of detectable levels of plasma RNA-HCV at TW 12, treatment was stopped.
The management of anaemia (by the reduction in doses of ribavirin and/or the administration of erythropoietin) was left to the discretion of the clinical trial investigators.

Primary efficacy endpoint: achieving a sustained virological response (SVR), defined as an undetectable RNA-HCV viral load at the 24th week of follow-up after finishing treatment, in the FAS (Full Analysis Set) population including all randomised patients who received at least one treatment (peginterferon alfa-2b, ribavirin or boceprevir/placebo).
The primary analysis is based on a comparison between the BPR versus PR groups then the BPR-RGT versus PR groups.

Secondary endpoints, especially:
- a sustained virological response (SVR) in the mITT population, including all randomised patients who received at least one dose of boceprevir or placebo. This secondary endpoint was added following an amendment to the protocol.
- the proportion of patients with a sustained virological response (SVR) among the patients with an undetectable viral load at TW 4 and TW 8.

Results:
A total of 404 patients were randomised: 403 received at least one dose of any treatment (FAS population) and 394 received at least one dose of boceprevir or placebo (mITT population).
Overall, the baseline characteristics of the patients were comparable with the exception of the initial viral load: more patients in the BPR-RGT group had a higher initial viral load (> 800,000 IU/ml): BPR: 88% versus BPR-RGT: 91%; p=0.004.

[7] Patients with an undetectable RNA-HCV level from TW 8 to TW 12
[8] Patients with a detectable RNA-HCV level between TW 8 and TW 12

The mean age of patients was 52.7 years (26-74 years) and 67% of patients were male. Nearly half of patients (47%) were infected with HCV genotype 1a and 44% with HCV genotype 1b.
The percentage of patients with a fibrosis METAVIR[4] F0/1/2 score was 74%. Cirrhosis (METAVIR F4 score) was present in 12% (49/403) of patients.
Approximately two thirds (64%) of patients included were relapsers and one third (36%) were partial responders.

- Primary efficacy endpoint:

The percentage of patients achieving a sustained virological load at the 24th week of follow-up was 21.3% in the PR group, 66.5% in the BPR group and 58.6% in the BPR-RGT group, or an absolute increase of 45.2% between the BPR and PR groups ($p<0.0001$) and an absolute increase of 37.4 between the BPR-RGT and PR groups ($p<0.0001$) in the FAS population. Comparable results were seen in the mITT analysis.

- Other endpoints:

A SVR was more commonly observed when the reduction in viral load in the initial dual therapy phase (TW 4) was ≥ 1 $\log_{10}$ compared with a < 1 $\log_{10}$ reduction and with boceprevir combined with dual therapy compared with dual therapy alone (see table 3).

An undetectable viral load at TW 8 was observed by 9% (7/80) of patients in the PR group, by 52% (84/161) in the BPR group and by 46% (74/162) in the BPR-RGT group. The percentage of patients who achieved a sustained virological response among those with an undetectable viral load at TW 8 was between 86.5% and 100%, depending on the group (see table 3).

SVR was shown to be higher for the sub-group of relapse patients compared with that obtained by partial responder patients (see table 3):
- in the relapser sub-group: a sustained virological response was achieved by 31% in the PR group, by 75% in the BPR group and by 69% in the BPR-RGT group;
- in the partial responders sub-group: sustained virological response was achieved by 7% in the PR group, by 52% in the BPR group and by 40% in the BPR-RGT group.

Table 3: SVR at 24th week of follow-up depending on viral load at TW 4 or TW 8 and depending on previous treatment response: RESPOND2 study

SVR at 24th week of follow-up	PR Group (N=80)	BPR Group (N=161)	Group BPR-RGT (N=162)
Reduction in viral load at TW 4			
< 1 $\log_{10}$	0/12 (0%)	15/44 (34%)	15/46 (33%)
≥ 1 $\log_{10}$	17/67 (25%)	90/114 (79%)	80/110 (73%)
Viral load undetectable at			
TW 8	7/7 (100%)	74/84 (88%)	64/74 (86.5%)
Response to previous treatment			
Relapsers	16/51 (31%)	77/103 (75%)	73/105 (70%)
Partial responders	2/29 (7%)	30/58 (52%)	23/57 (40%)

The percentage of relapses was 32% (8/25) in the PR group, 12% (14/121) in the BPR group and 15% (17/111) in the BPR-RGT group.

Sub-group analyses were carried out, focussing on the parameters that could potentially impact on the sustained virological response, namely the genotype, the initial viral load as well as the stage of fibrosis.
A sustained virological response was more common in genotype 1b patients with a low initial viral load (≤ 400,000 IU/ml) and in patients with less fibrosis (F0-2 versus F3/4).
It should be noted, however, that the percentage of patients with an initial viral load ≤ 400,000 IU/ml (5%) was very low and that the number of patients with a F3 or F4 score per treatment group was low (n<30).

- Determination of treatment duration:
Although the RESPOND2 study was not designed to compare treatment durations between the BPR and BPR-RGT groups in the fast responder and slow responder patient sub-groups, available data for these sub-groups were investigated to validate the therapeutic regimens.

Among the patients who received comparable treatments up to TW 36:

- in the sub-group of fast responder patients[9] (N=144/323):

Among the 323 patients in the BPR and BPR-RGT groups, 45% (144/323) had an undetectable viral load a TW 8 and TW 12 (fast responders), or 73/161 in the BPR group and 71/162 patients in the BPR-RGT group.
The percentage of patients that had a sustained virological response was 89% (63/71) in the BPR-RGT group (treated over 36 weeks) and 97% (71/73) in the BPR group (treated over 48 weeks), or a difference of -8.5% $_{95\%}$ CI [-16.8; -0.3]. Relapses were more common in the BPR-RGT group (10.1% or 7/69) than in the BPR group (0% or 0/71).

- in the sub-group of slow responders[10] (N=75/323):

The percentage of patients that had a sustained virological response was 80% (28/35) in the BPR-RGT group (treated over 48 weeks, of which 32 weeks were triple therapy) and 72.5% (29/40) in the BPR group (treated over 48 weeks of which 44 weeks were triple therapy), or a difference of 7.5% $_{95\%}$ CI [-11.7; 26.7]. The percentage of relapses was comparable for the two groups: BPR-RGT (17.6% or 6/34) and BPR (19.4% or 7/36).

From this data, for fast responders, a different treatment duration to that studied in this sub-group in the RESPOND2 trial was validated by the marketing authorisation: additional peg dual therapy over 12 weeks is thus recommended following the 32 weeks of triple therapy (following 4 weeks of peg dual therapy). This therapeutic regimen corresponds to that evaluated in the slow responder sub-group of patients from the BPR-RGT group.
For slow responder patients, the treatment duration validated by the marketing authorisation corresponds to that evaluated for this sub-group in the BPR-RGT group.

In summary, for all non-cirrhosis patients who have had a failed previous treatment independently from the non-detection of RNA-HCV at TW 8 and TW 12, the therapeutic regimen validated by the marketing authorisation includes 4 weeks of peg dual therapy followed by 32 weeks of triple therapy and a further 12 weeks of dual therapy.

An unbiased evaluation of the level of effect was not possible for the sub-groups of cirrhosis patients, for whom data is limited (12% of patients included), and for patients who re-qualified retrospectively from being null responders[11] based on their virological response at the end of the initial peg dual therapy phase compared with at inclusion. Thus, the therapeutic regimen validated conservatively by the marketing authorisation comprised 48 weeks of treatment: 4 weeks of peg dual therapy followed by 44 weeks of triple therapy for cirrhosis patients and null responders.

Study P05685 (in combination with IFN-PEG alpha-2a)
A randomised, double-blind study, versus peg dual therapy with the primary objective of comparing the efficacy of boceprevir combined with peginterferon alfa-2a and ribavirin (BPR) versus peg interferon alfa-2a and ribavirin (PR) in adult relapsers with chronic hepatitis C genotype 1 or partial responders to peginterferon alfa and ribavirin dual therapy.

The inclusion and non inclusion criteria were comparable to the RESPOND2 study described above.

[9] undetectable viral load between TW 8 and TW 12. For previously untreated patients, the viral load should be undetectable at TW 8 and TW 24 to be a fast responder.
[10] detectable viral load between TW 8 and TW 24
[11] Non response to a previous treatment was a non-inclusion criteria for the RESPOND2 study

Treatment: patients were randomised (1:2) into 2 groups.
Randomisation was stratified according to the HCV genotype (1a or 1b) and previous response (relapsers or partial responders).

In each of the groups, during an initial phase, peg dual therapy for 4 weeks combining peginterferon alfa-2a at a dose of 180 µg/kg/week subcutaneously and ribavirin at a dose of between 1000-1200 mg/day taken twice orally was administered. Then patients were treated according to one of the following two regimens:

1. PR Group (N=67):
initial dual therapy for 4 weeks followed by 44 weeks of the combination of:
- peginterferon alfa-2a: 180 µg/kg/week, subcutaneously
- ribavirin: 1000-1200 mg/day taken twice orally
- placebo

2. BPR Group (N=134):
initial dual therapy for 4 weeks followed by 44 weeks of the combination of:
- boceprevir: 800 mg (4 capsules) three times/day taken orally
- peginterferon alfa-2a: 180 µg/kg/week subcutaneously
- ribavirin: 1000-1200 mg/day taken twice orally

This therapeutic regimen is not that which is found in the marketing authorisation for boceprevir for non-cirrhosis patients who have had a previous failed treatment.

In cases of a detectable plasma RNA-HCV at TW 12, treatments were stopped.
The management of anaemia (by the reduction in doses of ribavirin and/or the administration outside of the scope of the marketing authorisation for erythropoietin) was left to the discretion of the clinical trial investigators.

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

Results:
A total of 202 patients were randomised: 201 received at least one dose of any treatment (FAS population) and 197 received at least one dose of boceprevir or placebo (mITT population). Patient characteristics were comparable to those patients in the RESPOND2 study.

The percentage of sustained virological response at 24th week of follow-up (primary efficacy endpoint) was 20.9% (14/67) in the PR group and 64.2% (86/134) in the BPR group, $p<0.0001$ (FAS population). Comparable results were observed in the RESPOND2 study (21.3% versus 66.5%).

3.2. Adverse effects

Safety data was from the SPRINT2, RESPOND2 and P05685 studies.

The adverse effects reported with a frequency ≥ 10% for the combination of boceprevir with peginterferon and ribavirin were of the same type (fatigue, anaemia, nausea and headaches) as those usually seen with peginterferon and ribavirin treatment with the exception of dysgeusia.

Specific adverse events
Anaemia
Anaemia was more commonly observed in patients treated with the combination of boceprevir, peginterferon alfa-2b and ribavirin than those treated with peginterferon alfa-2b and ribavirin (49% versus 29%).

The management of anaemia was more commonly required in groups using boceprevir than in the dual therapy group (peginterferon and ribavirin):
- reduction in dose of ribavirin (when the haemoglobin concentration was between 8.5 and 10 g/dl): 26% versus 13%;
- administration of erythropoietin[12]: 43% versus 24% (in the majority of cases started during the first 12 weeks of treatment);
- transfusions: 3% versus <1%.

Neutropaenia
Grade 3-4 neutropaenia (neutrophils < 0.75 x 10^9/l) was observed in 29% of patients treated with the combination of boceprevir, peginterferon alfa-2b and ribavirin and in 17% of patients treated with peginterferon alfa-2b and ribavirin.
Grade 4 neutropaenia was more common in patients treated with boceprevir, peginterferon alfa-2b and ribavirin than those treated with peginterferon alfa-2b and ribavirin (7% versus 4%).

➢ Previously untreated adult patients

SPRINT2 Study *(*P05216)
Stopping treatment due to adverse events was reported by 16% of patients in the PR group, 16% in the BPR group and 12% in the BPR-RGT group. The adverse events which led to a stoppage in treatment included: anaemia (1% versus 2% versus 2%), fatigue (4% versus 3% versus 2%) and psychiatric disorders (4% versus 4% versus 2%).
Serious adverse events were observed by 9% of patients in the PR group, 12% in the BPR group and by 11% in the BPR-RGT group.

➢ Adults in relapse or partial responders to previous treatment

RESPOND2 Study (P05101)
Stopping treatment due to adverse events was reported by 3% of patients in the PR group, 12% in the BPR group and by 8% in the BPR-RGT group. The adverse events which led to a stoppage in treatment included: anaemia (0% versus 3% versus 0%), nausea (0% versus 1% versus 1%), asthaenia (0% versus 2% versus 0%), fatigue (0% versus 2% versus 0%) and psychiatric disorders (0% versus 2% versus 3%).
Serious adverse events were observed by 5% of patients in the PR group, 15% in the BPR group and by 10% in the BPR-RGT group.

Study P05685 (in combination with IFN-PEG alpha-2a)
Stopping treatment due to adverse events was reported by 4% of patients in the PR group and by 17% in the BPR group. The adverse events which led to a stoppage in treatment included: asthaenia, fatigue and neutropaenia.
Serious adverse events were observed by 10% of patients in the PR group and by 13% in the BPR group.
Compared with the combination of boceprevir, peginterferon alfa-2b and ribavirin, the administration of boceprevir with peginterferon alfa-2a and ribavirin was more commonly associated with neutropaenia (including grade 4 neutropaenia) and infections.

3.3. Pending data (especially sought by the Marketing Authorisation)
A post-hoc analysis aimed at describing the benefit of boceprevir depending on the polymorphism of the IL28B gene (predictive response factor) on the sustained virological response was carried out on a restrictive number of participants (62-66% of randomised patients), which means it is difficult to draw any conclusions from this investigation. Due to this, within the scope of the granting of the marketing authorisation, the pharmaceutical company is planning on carrying out a study to evaluate the benefit of triple versus dual therapy as a function of the polymorphism of the IL28B gene (study P07755).

[12] temporary treatment protocol validated by AFSSAPS for NEORECORMON (epoetin beta) http://www.afssaps.fr/var/afssaps_site/storage/original/application/3bcab882bd0404a837c9c6917cda30be.pdf

The pharmaceutical company is also planning on providing the results from the P06086 study (in progress), which aims to evaluate two anaemia management strategies (reduction in dose of ribavirin alone versus the use of erythropoietin). These results, which are expected in April 2012, will help in defining the best way of managing anaemia and in documenting the benefit of its impact on the efficacy and safety of treatment with boceprevir.

Within the scope of the RMP (risk management plan), an observational study (P08518), which aims to describe the use of hepatitis C genotype 1 treatments (protease inhibitors, peginterferon and ribavirin) and the management of specific adverse events (especially anaemia), will be carried out in Europe.

The open-label study, P05514, carried out on relapse patients and non responders to dual therapy in the clinical study control groups is still in progress.

Data from a long-term follow-up study (P05063) will allow the sustainability of virological response and long-term safety to be determined.

3.4. Conclusion

In the treatment of chronic hepatitis C genotype 1 infection, the efficacy and 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 Treatment) 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%, $p<0.0001$ or 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 at 24 weeks after stopping treatment was less significant for treatment-naive 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, depending on the different patient profiles (previously treated, failed treatment, fast or slow responders, patients with or without cirrhosis) is 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 (AE) 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 headaches) as those usually seen with peginterferon/ribavirin treatment, with the exception of dysgeusia.

However, the addition of boceprevir to peginterferon/ribavirin increases the risk of anaemia (49% versus 29%), grade 3-4 neutropaenia (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 patients treated with boceprevir, than those who had been previously treated or untreated.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

The severity of hepatitis C is linked to the fact that it frequently becomes chronic, which can lead to long-term cirrhosis, hepatocellular impairment and hepatocellular carcinoma. Among the 6 genotypes of the hepatitis C virus, genotype 1 is the most predominant.

This medicinal product is intended as a triple therapy (in combination with peginterferon alfa and ribavirin) for first-line or second-line treatment.

It is intended for curative treatment.

The efficacy/safety ratio is moderate, especially given its high haematological toxicity.

Public health benefit:
Hepatitis C represents a moderate public heath burden. In the indication (treatment of hepatitis C patients infected with HCV genotype 1, with compensated liver disease), the burden is more specifically represented by the population of patients who have been previously treated; however, it remains moderate.
A reduction in morbidity and mortality due to chronic hepatitis C is a public health need that is an established priority (GTNDO*, National Hepatitis B and C Plan, 2009-2012).
Data from clinical trials showed a substantial impact from treatment with boceprevir on the rate of sustained virological response, especially for patients who had already had treatment. Modelling results show that protease inhibitors have an impact on the morbidity and mortality of treated patients (evolution towards chronic stage of the disease, liver fibrosis, liver cancer and death). This impact is substantial for those who have already been treated, but low for treatment-naive patients.
The impact of the treatment on quality of life and organisation of care is not documented.
Transferability of results is questionable, especially due to the complexity of the therapeutic regimen, the fact that routine IL-28 genotype testing still does not take place before starting treatment and in the absence of data for patients co-infected with HIV.
Treatment with boceprevir, combined with peginterferon alfa and ribavirin, thus appears to provide a partial additional response to the identified public health need.
Consequently, in the light of current knowledge, VICTRELIS is expected to offer a moderate public health benefit in this indication.

*GTNDO: Groupe technique national de définition des objectifs [National technical group for setting of public-health objectives] (Directorate-General for Health -2003)

There is a treatment alternative available validated by a marketing authorisation: INCIVO (telaprevir).

Consequently, the actual benefit of VICTRELIS is substantial.

4.2. Improvement in actual benefit (IAB)

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 treatment alternatives available,
- the possible reduction in 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 level of evidence from data in support of the determination in therapeutic regimens, especially for non-responders who were excluded from the RESPOND2 study, not being ideal,

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.

4.3. Therapeutic use

The consensus conference on the Treatment of hepatitis C in February 2002[13] was not updated; the therapeutic use of VICTRELIS in the management of patients infected with HCV genotype 1 is based on the SPRINT2 and RESPOND2 pivotal studies.

The purpose of the treatment is to eradicate the virus, with the aim of preventing complications linked to the infection.
The decision to treat should take into account all criteria, including biochemical, virological and biological factors, especially the stage of fibrosis.
The reference treatment for chronic infection by the hepatitis C virus comprises dual therapy with peginterferon and ribavirin over 6 to 12 months. In cases of intolerance or if ribavirin is contraindicated, peginterferon is used as a monotherapy. For the patient population infected with HCV genotype 1, this dual therapy, as a first-line treatment, results in a failed treatment for more than 50% of patients. The response rate is lower still for a second course for patients who have had a failed previous treatment.

In studies carried out on mono-infected patients and those who have not had a transplant, as a first-line treatment or due to failure of the combination of peginterferon/ribavirin in the absence of liver decompensation, an absolute increase in terms of a sustained virological response was in the order of 25% to 40% with the addition of boceprevir to the peginterferon/ribavirin dual therapy, compared with dual therapy alone.
The therapeutic regimen recommended in the marketing authorisation, which comprises 48 weeks of treatment, including an initial peg dual therapy phase over 4 weeks, followed by 32 weeks of triple therapy, then a further 12 weeks of dual therapy, with the exception of:
- adults who do not have cirrhosis and were previously untreated and who achieved a fast response (characterised by an undetectable viral load at the 8th and 24th treatment weeks) for whom the total treatment duration is reduced during treatment to 28 weeks, of which 24 weeks are of triple therapy;
- cirrhosis patients and null responders[14] for whom the recommended regimen comprises 4 weeks of peg dual therapy, followed by 44 weeks of triple therapy (a minimum of 32 weeks of triple therapy, depending on the safety and tolerance to treatment).

The efficacy of treatment is monitored by repeated viral load measurements. In the absence of virological efficacy at the 12th (viral load ≥ 100 IU/ml) or 24th treatment week (detectable viral load), triple therapy should be stopped (boceprevir, peginterferon and ribavirin).
How to best manage anaemia, which was more commonly observed with the addition of boceprevir to peg dual therapy, is yet to be determined.

A better understanding of response prediction factors, notably a fast virological response and IL28B genotype, will allow patients who did not see a significant benefit in the addition of a protease inhibitor to dual therapy to be identified.
The decision to treat should also take into consideration the possibility of inclusion in clinical trials evaluating new substances, especially for cirrhosis patients not responding to previous treatments.

[13] Consensus conference "the treatment of hepatitis C. February 2002. Available at: http://www.infectiologie.com/site/medias/_documents/consensus/Vhc-2002.pdf
[14] Non-responding patients were excluded from the RESPOND2 study

A study comparing two protease inhibitors (boceprevir and telaprevir) is not available, given clinical concomitant developments.
Furthermore, no clinical data is available regarding the re-treatment of patients who have had failed treatment including a HCV NS3-4A protease inhibitor.

Therapeutic use of VICTRELIS
In the treatment of chronic hepatitis C genotype 1 infection, in cases of compensated liver disease, given the levels of virological efficacy which vary depending on the sub-populations evaluated and its safety profile, boceprevir, and also telaprevir, combined with peginterferon and ribavirin,
- would be a new therapeutic method appropriate for some patient profiles, previously untreated,
- should become the reference treatment for patients who have had a failed dual therapy treatment.

4.4. Target population

The target population is represented by patients with chronic hepatitis C genotype 1 infection, previously untreated and with one failed previous treatment, in the absence of liver decompensation.

Epidemiology data concerning hepatitis C is mainly based on an investigation into its prevalence, carried out by the Institut de veille sanitaire (French Health Monitoring Institute) in 2004.[15]

The prevalence of being seropositive for the HCV antibody was estimated, in France, to be approximately 0.84% (95% CI: 0.65-1.10) or 367,055 people (269,361 - 464,750).
For these people with the HCV antibody, the prevalence of chronic infection (RNA positive) was estimated at 65% (95% CI: 50-78), which corresponds to an overall prevalence in the population of 0.53% (95% CI: 0.40-0.70) or 232,196 people (167,869 - 296,523) aged from 18 to 80 years.
Only 59.1% of these people are diagnosed, or 137,228 patients (99,210 - 175,245), of whom 23,000 people can be deducted as they are carriers of the HIV virus and co-infected with HCV.[16] VICTRELIS does not have marketing authorisation for patients co-infected with HIV, or 114,228 patients (76,210-152,245).
Some of these patients will not be able to receive treatment due to a contraindication (e.g. liver decompensation). The population can therefore be estimated as approximately 10%[17], or 113,026 (68,589 - 137,020) people likely to benefit from treatment.

Approximately 60% of cases of hepatitis C in France are genotype 1.[18]
Consequently, the population likely to receive treatment would be in the order of 67,816 patients (41,153 to 82,212).

In addition to previously diagnosed cases, new cases of hepatitis C must be taken into account that will be diagnosed during the year. This figure is estimated at 5,000 new cases per year in France[19] or approximately 3,000 new cases of genotype 1.
For infected patients being treated for the first time for hepatitis C in reference centres in 2007, antiviral treatment was given to 26% of patients, was foreseen for 19% of patients and not foreseen for 55% of patients.[20]

[15] Meffre C, Le Strat Y, Delarocque-Astagneau E, Antona D, Desenclos JC. Prévalence des hépatites B et C en France en 2004 - Institut de veille sanitaire, InVS, Saint-Maurice, March 2007
http://www.invs.sante.fr/publications/2006/prevalence_b_c/vhb_france_2004.pdf
[16] National Hepatitis B and C Plan 2009-2012 http://www.sante.gouv.fr/IMG/pdf/Plan_national_Hepatites.pdf
[17] National monitoring of hepatitis C from national voluntary reference centres 2001-2006. Institut de veille sanitaire 9(French Health Monitoring institute) - April 2008. http://www.invs.sante.fr/surveillance/hepatite_c/poleref_volontaire/stades_cliniques.pdf
[18] National monitoring of hepatitis C from Epidemiology data reference centres 2001-2007 INVS
[19] Roudot-Thoraval F. Évolution des caractéristiques épidémiologiques de l'hépatite C. Gastroenterol Clin Biol 2002 ;26 :B138-B143
[20] The starting of antiviral treatment (a) for viraemic patients newly treated for hepatitis C at reference centres – Data 2004-2007

Furthermore, in 2006, approximately 72,500 people with hepatitis C had an ALD (chronic condition) n°6 "active chronic liver diseases and cirrhoses".[15]

Finally, the number of previously untreated patients or those who have had a failed previous treatment likely to benefit from the addition of a protease inhibitor to standard peg dual treatment should be able to be estimated.

4.5. Transparency Committee recommendations

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

The Committee would like to re-evaluate this proprietary medicinal product after one year based on updated clinical data.

4.5.1 Packaging: Appropriate for the prescription conditions.

4.5.2 Reimbursement rate: 65%

Given the data available, the complexity of therapeutic regimens for the management of hepatitis C patients, the possibility of carrying out IL-28 genotype testing, which is not yet systematic, the potential discovery of new substances and the expected additional data on:

- the characteristics of patients being managed for hepatitis C
- the conditions of use (therapeutic strategies implemented, genotype testing before treatment and treatments undertaken, etc.).

treatment, based on data on patients with hepatitis B and C, started by ANRS (HEPATER study), which will be implemented in 2012, could be foreseen.