HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

10 December 2008

VIRAFERONPEG 50 µg/ 0.5 ml powder and solvent for injectable solution
Pack of 1 (CIP: 355 189.3)
Pack of 4 (CIP: 355 191.8)
VIRAFERONPEG prefilled 50 µg pen
Pack of 1 (CIP: 359 419.3)
Pack of 4 (CIP: 359 420.1)
VIRAFERONPEG prefilled 80 µg pen
Pack of 1 (CIP: 359 423.0)
Pack of 4 (CIP: 359 424.7)
VIRAFERONPEG prefilled 100 µg pen
Pack of 1 (CIP: 359 428.2)
Pack of 4 (CIP: 359 429.9)
VIRAFERONPEG prefilled 120 µg pen
Pack of 1 (CIP: 359 433.6)
Pack of 4 (CIP: 359 434.2)
VIRAFERONPEG prefilled 150 µg pen
Pack of 1 (CIP: 359 437.1)
Pack of 4 (CIP: 359 438.8)

Applicant: SCHERING PLOUGH

Peg-interferon alpha-2b

ATC Code: L03AB10

List I
Medicine requiring initial prescription for six months by specialists and/or specialised units (gastroenterology, hepatology, internal medicine or infectiology). Unrestricted renewal.

Date of initial MA (single therapy): May 29, 2000
Date of last amendment to MA: July 10, 2008

Reason for request: Inclusion on the list of medicines reimbursed by National insurance and approved for use by hospitals in the indication extension ***"in patients suffering from chronic hepatitis C, when refractory to prior treatment with alpha-interferon (PEGylated or unPEGylated) and ribavirin in dual therapy or with alpha-interferon alone"***.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Peg-interferon alpha-2b

1.2. Background

This is an application for an extension of the indication to patients:
- not responding to single or dual therapy
- suffering a relapse with dual therapy (patients relapsing with single therapy were already included in the prior indication).

1.3. Indication

"ViraferonPeg is indicated in the treatment of adult patients suffering from chronic hepatitis C with elevated transaminases, without hepatic decompensation, and with positive serum HCV RNA or positive HCV antibodies, including patients thus far untreated with concomitant stable HIV.
The best way to use ViraferonPeg in this indication is combined with ribavirin.
This combination is indicated in patients thus far untreated, including patients with concomitant stable HIV and **patients refractory to prior treatment with alpha-interferon (PEGylated or unPEGylated) and ribavirin in dual therapy or with alpha-interferon alone**.
Interferon as a single therapy, including ViraferonPeg, is indicated mainly for patients showing intolerance or a contraindication to ribavirin."

See also Summary of Product Characteristics (SPC) of ribavirin when ViraferonPeg is used in combination with ribavirin.

1.4. Dosage

"Treatment should be initiated and monitored exclusively by physicians with experience in the treatment of hepatitis C patients.
ViraferonPeg must be administered as a weekly subcutaneous injection. The dose administered depends on whether it is used in combination with ribavirin or as a single therapy.

Combined treatment
ViraferonPeg 1.5 micrograms/kg/week with ribavirin capsules.
The required dose of 1.5 µg/kg ViraferonPeg to be used in combination with ribavirin can be administered according to the patient's weight with the appropriate dose of ViraferonPeg pen/vial (see SPC table).
The ribavirin capsules are administered orally twice daily at mealtimes (morning and evening).

ViraferonPeg single therapy
In single therapy, the dosage of ViraferonPeg is 0.5 or 1.0 microgram/kg/week. The lowest available dose in the vials or pens is 50 µg/0.5 ml; therefore, for patients who are prescribed the dosage of 0.5 µg/kg/week, injection volumes must be adjusted: see SPC.

Duration of treatment:
For patients giving a virologic response at week 12, treatment must be continued for at least 3 more months (giving a total duration of 6 months). The decision to extend treatment to 1

year will be based on other prognostic factors (e.g. genotype, age > 40, male, septal fibrosis)."

REMINDER
Duration of treatment – Patients thus far untreated (ViraferonPeg in combined treatment):
Predictability of sustained virologic response: Genotype 1 patients who produced no virologic response at week 12 of treatment are unlikely to produce a sustained virologic response.
• Genotype 1: For patients producing a virologic response at week 12, treatment must be continued 9 more months (giving a total duration of 48 weeks).
In the subgroup of genotype 1 patients with a low viral load (< 600,000 IU/ml) with an undetectable HCV RNA level at week 4 of treatment and remaining undetectable at week 24, treatment can be stopped after these 24 weeks of treatment or be prolonged for a further 24 weeks (giving a total treatment duration of 48 weeks).
However, treatment lasting 24 weeks can carry a greater risk of relapse than treatment over 48 weeks (see section 5.1).
• Genotype 2 or 3: It is advisable for all patients to be treated for 24 weeks, except for patients with both HCV and HIV, who should be treated for 48 weeks.
• Genotype 4: In general, genotype 4 patients are considered harder to treat and the study's limited data (n=66) is compatible with a treatment duration identical to the one recommended for genotype 1.

HIV-HCV coinfection:
The treatment duration recommended for patients with both HIV and HCV is 48 weeks, regardless of genotype.

Duration of treatment - Patients thus far untreated (ViraferonPeg single therapy):
For patients giving a virologic response at week 12, treatment must be continued for at least 3 more months (giving a total duration of 6 months). The decision to extend treatment to 1 year will be based on other prognostic factors (e.g. genotype, age > 40, male, septal fibrosis)."

Duration of treatment: Repeat treatment (Indication extension)

Predictability of sustained virologic response: all patients, regardless of genotype, with a serum HCV RNA level below the detection limits at week 12 should be treated for 48 weeks. Patients retreated and who produced no virologic response at week 12 are unlikely to become responsive after 48 weeks' treatment

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC classification (2008)

L : antineoplastic and immunomodulating agents
L03 : immunostimulants
L03AB : interferons
L03AB10 : peg-interferon alpha-2b

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

VIRAFERONPEG is the only PEGylated alpha-interferon to have been granted this indication extension.

3 ANALYSIS OF AVAILABLE DATA

The clinical data includes one phase III non-comparative clinical study (Study P02370) on patients unresponsive to or relapsing after initial treatment consisting of:
- non-PEGylated dual therapy (unPEGylated alpha-interferon and ribavirin) or
- PEGylated dual therapy (PEGylated alpha-interferon and ribavirin).

Three other clinical studies published (Moucari, Jacobson and Krawitt studies), involving patients refractory to initial treatment consisting of:
- non-PEGylated dual therapy (unPEGylated alpha-interferon and ribavirin) or
- single therapy

The committee notes that the 2002 consensus conference on the treatment of chronic hepatitis C recommends using a dual PEGylated therapy (PEGylated alpha-interferon and ribavirin) in patients thus far untreated.

3.1. Efficacy in patients refractory to initial treatment

3.1.1. Study P02370

Objective: to evaluate the efficacy of ViraferonPeg + Rebetol in adult patients with moderate to severe liver fibrosis refractory (relapsing or unresponsive) to unPEGylated dual therapy (unPEGylated alpha-interferon + ribavirin) or PEGylated dual therapy (PEGylated alpha-interferon + ribavirin).

Method: non-comparative phase III study.

Inclusion criteria:
- adult patients aged 18 to 65
- suffering from chronic hepatitis C with moderate to severe liver fibrosis or cirrhosis (METAVIR score F2, F3, F4)
- patients refractory to previous treatment comprising PEGylated or unPEGylated alpha-interferon + ribavirin.

Patients refractory to prior treatment was defined:
- either as complete absence of response, i.e. positive plasma or serum HCV RNA level at the end of a period of at least 12 weeks' treatment,
- or a relapse, i.e. a negative HCV RNA level after at least 12 weeks' treatment followed by a relapse (positive HCV RNA) during the post-treatment follow-up period.

Treatment: ViraferonPeg (1.5 µg/ kg, once a week) in combination with Rebetol (dosage according to patient's weight).

Dosage of REBETOL

Patient's weight (kg)	Daily dose (mg)
40 – 65	800
> 65 – 85	1,000
> 85 – 105	1,200
> 105 – 125	1,400

At week 12, patients with a negative HCV RNA or a decrease in viral load of more than 2 logs continued their treatment 48 weeks. As of week 18, unresponsive patients could be included in maintenance protocols (positive HCV RNA or decrease of less than 2 logs at week 12) that are not submitted with this application.

Primary endpoint: sustained virologic response 24 weeks after the 48-week treatment (undetectable HCV RNA).

Baseline patient characteristics:
Prior treatment:
- unPEGylated interferon + ribavirin: 77% of patients
(dual therapy not recommended for first-line treatment since 2002)
- PEGylated interferon alph-2a + ribavirin: 16% of patients
- PEGylated interferon alpha-2b + ribavirin: 7% of patients

Genotype: 80% of genotype 1
METAVIR score: F4 (cirrhosis): 40%

Results (intermediate analysis):
Population: In all, 1,336 patients were evaluated out of 2,293.

All patients included, a sustained virologic response (undetectable HCV RNA) was observed in 22.6% of cases (303/1,336) regardless of prior treatment [99% CI: 19.7; 25.6], 24 weeks after the end of treatment:

Sustained virologic response 24 weeks after the 48-week treatment according to prior treatment:

	Patients refractory to treatment with interferon alpha/Ribavirin		Patients refractory to treatment with PEG-interferon alpha/Ribavirin	
	SVR % (n)	99% CI	SVR % (n)	99% CI
All patients	**25 (255/1,030)**	**[21;28]**	**16 (48/299)**	**[11;22]**
Previous response				
Relapse	**45 (95/213)**	**[36;53]**	**36 (40/112)**	**[24;47]**
Genotype 1/4	34 (52/154)	[24;44]	29 (24/83)	[16;42]
Genotype 2/3	73 (41/56)	[58;89]	16/29	-
Unresponsive	**17 (117/673)**	**[14;21]**	**4 (7/172)**	**[0;8]**
Genotype 1/4	13 (75/592)	[9;16]	4 (6/160)	[0;8]
Genotype 2/3	51 (40/78)	[37;66]	1/10	-
Genotype				
1	17 (138/825)	[13;20]	12 (28/243)	[6;17]
2/3	62 (103/166)	[52;72]	44 (17/39)	[23;64]
4	31 (10/32)	[10;52]	3/15	-
METAVIR fibrosis score				
F2	33 (92/289)	[25;39]	23 (15/66)	[9;36]
F3	27 (86/323)	[20;33]	17 (16/92)	[7;28]
F4	19 (77/416)	[14;23]	12 (17/141)	[5;19]
Baseline viral load				
High viral load (> 600,000 IU/ml)	21 (128/622)	[16;25]	9 (17/192)	[4;14]
Low viral load (< 600,000 IU/ml)	31 (127/406)	[25;37]	29 (30/105)	[17;40]

Breakdown of relapsing and unresponsive patients (documented)

	Alpha-interferon/ribavirin	PEG-interferon alpha/ribavirin
Relapsing patients	213	112
Unresponsive patients	673	172
Total	886	284

In the relapse subgroup, there was a sustained virologic response for:
- 45% (95/213) in the group of patients refractory to alpha-interferon / ribavirin
- 36% (40/112) in the group of patients refractory to PEG-interferon alpha / ribavirin

In the unresponsive subgroup, there was a sustained virologic response for:
- 17% (117/673) in the group of patients previously treated with alpha-Interferon / ribavirin
- 4% (7/172) in the group of patients previously treated with PEG-interferon alpha / ribavirin

The virologic response achieved after a repeat treatment was less common:
- in unresponsive patients than in relapsing patients
- in patients unresponsive to prior treatment with PEGylated interferon/ribavirin than in patients unresponsive to an unPEGylated interferon/ribavirin.
- in genotype 1 patients, in patients with advanced stage fibrosis and in patients with a high initial viral load regardless of previous treatment (PEGylated or unPEGylated alpha-interferon).

Furthermore, for all patient genotypes with detectable plasma HCV RNA levels at week 12 of treatment, the sustained virologic response was very low.
In patients who, at week 12, produced a > 2log10 decrease in viral load without a negative viral load, the sustained virologic response concerned only 6% (18/308) and 0% (0/449) of those who did not produce a > 2log10 decrease in viral load.
However, for patients with undetectable plasma HCV RNA levels at week 12 of treatment, there was a sustained virologic response for 56% (281/501).

Hence, patients retreated and who produced no virologic response at week 12 (i.e. patients who had detectable plasma HCV RNA levels) are unlikely to become responsive after 48 weeks' treatment.

3.1.2. Moucari et al J. study[1] (2006)

Objective: to evaluate the efficacy and safety of ViraferonPeg + Rebetol in adult patients refractory (relapsing or unresponsive[2]) to prior dual unPEGylated therapy.

Method: non-comparative clinical study
154 patients were included in the study.
- 101 patients were unresponsive to prior treatment
- 53 patients relapsed after prior treatment

47.4% of patients had a Metavir score of F3-F4
71.4% of patients were genotype 1

Treatment: PEGylated interferon alpha-2b (1.5 µg/kg/week) + Rebetol (≤ 75kg: 1,000 mg and > 75 kg: 1,200 mg) for 48 weeks.

[1] Moucari et al. J. High predictive value of early viral kinetics in retreatment with peginterferon and ribavirin of chronic hepatitis C patients non-responders to standard combination therapy. Journal of hepatology 46 (2007). 596-604.

[2] The lack of response was defined as detectable HCV RNA levels at the end of a period of at least 12 weeks.

Primary endpoint: sustained virologic response (negative HCV RNA 24 weeks after the end of treatment).

Results:
A sustained virologic response was achieved in 28.6% (44/154) of the general population:
- 12.9% in the unresponsive patient group
- 58.5% in the relapse patient group.

3.1.3 Jacobson Study[3] (February 2000)

Objective: to evaluate the efficacy of ViraferonPeg (at 2 different doses) + Rebetol in adult patients refractory (relapsing or unresponsive[4]) to prior dual unPEGylated therapy or single therapy.

Method: open-label comparative phase III study
321 patients were included in the study:
- 219 unresponsive patients treated previously with dual therapy and 47 treated with single therapy
- 55 patients relapsing after dual therapy

89% of patients were genotype 1
39% of patients had a Metavir score of F3-F4

Treatment: 2 treatment groups: PEGinterferon alpha-2b 1.5 µg/week + ribavirin 800 mg/day in 2 doses (160 patients) (MA dosage) (N=160)
- PEG-interferon alpha-2b 1.0 µg/week + ribavirin 1,000 or 1,200 mg/day in 2 doses (N=161) for 48 weeks.

Primary endpoint: sustained virologic response (negative HCV RNA 24 weeks after the end of treatment).

Results:
In the treatment group corresponding to the MA dosage, a virologic response was achieved in 18% of patients: 10% of unresponsive patients and 50% of relapse patients.

3.1.4 Krawitt study[5] (2000/2001)

Objective: to evaluate the efficacy of ViraferonPeg + Rebetol in adult patients refractory (relapsing or unresponsive[4]) to prior dual unPEGylated therapy or single therapy.

Method: non-comparative phase III study
182 patients were included in the study:
- 116 unresponsive patients
- 66 relapse patients

87% of patients were genotype 1
17% of patients had a Metavir score of F4
Treatment: PEG-interferon alpha-2b 100 µg/week (weight < 75 kg) and 150 µg/week (weight > 75 kg) in combination with 1,000 mg ribavirin for 48 weeks

Primary endpoint: sustained virologic response (negative HCV RNA 24 weeks after the end of treatment).

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[3] Jacobson and al. A randomized trial of pegylated interferon alfa-2b plus ribavirin in retreatment of chronic hepatitis C. American Journal of Gastroenterology 2005 ; 100:2453-2462.

[4] The lack of response was defined as detectable HCV RNA levels at the end of a period of at least 24 weeks.

[5] Krawitt and al. Peginterferon alfa-2b and ribavirin for treatment-refractory chronic hepatitis C. Journal of Hepatology 43 (2005) 243-249.

Results:
A sustained virologic response was achieved in 32% (95% CI: 27-40%)
of patients (59/182)
- 20% of unresponsive patients
- 55% of relapse patients

3.2 Long-term efficacy data (updated SPC extract)
“A vast long-term clinical study enrolled 567 patients previously treated with ViraferonPeg (with or without ribavirin) in a clinical study.
The aim of this study was to evaluate how well the sustained virologic response was maintained and to estimate the impact of ongoing negative viraemia on clinical results.
A long-term follow-up of at least 5 years after treatment was available for 327 patients and just 3 of the 366 with a sustained response suffered a relapse during the study.

The probability of sustained virologic response maintained after 5 years was estimated, using the Kaplan-Meier method, as 99% for all of the patients (95% CI: 98-100 %).
The sustained virologic response after chronic hepatitis C treatment with ViraferonPeg (with or without ribavirin) enables negative viraemia to be maintained in the long term, the resolution of the liver infection and the chronic hepatitis C to be clinically 'cured’. However, this does not exclude the progression of the liver disease (including progression into hepatocellular carcinoma) in patients with cirrhosis.”

3.3 Adverse effects
(SPC extract/Reminder)
“The adverse effects related to the treatment most commonly reported in clinical studies with ViraferonPeg in combination with ribavirin, observed in over half of patients, were headaches, injection site reactions and fatigue.

Other major adverse effects reported among over 25% of patients included myalgia, fever, asthenia, alopecia, nausea, anorexia, weight loss, depression, irritability and insomnia.
Fatigue, alopecia, itching, nausea, anorexia, weight loss, irritability and insomnia occur among a much lower rate of patients treated with single ViraferonPeg therapy compared to those treated with dual therapy.

The severity of the adverse effects most commonly reported was mostly mild to moderate and the adverse effects were managed without having to modify doses or cease treatment.

In one clinical trial, 1.2% of patients treated with ViraferonPeg or interferon alpha-2b in combination with ribavirin reported life-threatening psychiatric effects during the treatment. These effects included suicidal thoughts and attempted suicide.”

<u>Refractory patients retreated</u>
The safety profile was comparable to that observed among patients thus far untreated.
The frequency of serious adverse effects was similar to that observed among patients thus far untreated.

3.4 Conclusion
There was a sustained virologic response observed 24 weeks after stopping the retreatment for approximately 20% of the entire population of retreated patients refractory to prior treatment with PEGylated or unPEGylated alpha-interferon + ribavirin.

The response was significantly less common:
- in unresponsive patients than in relapsing patients
- in patients unresponsive to prior treatment with PEGylated interferon/ribavirin than in patients unresponsive to an unPEGylated interferon/ribavirin (4% - 17%).
- in genotype 1 patients, in patients with advanced stage fibrosis and in patients with a high initial viral load regardless of previous treatment (PEGylated or unPEGylated alpha-interferon).

In unresponsive patients, particularly in genotype 1 patients given dual first-line PEGylated therapy, a very low percentage of sustained virologic response was observed: 4% (6/160).

Furthermore, in patients retreated who, at 12 weeks, had detectable plasma HCV RNA levels and a > 2 log10 decrease in viral load, a very low percentage of sustained virologic response was observed: 6% (18/308).

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

The severity of hepatitis C is related to the common switch to a chronic state, which can cause long-term complications: cirrhosis, hepatic insufficiency and hepatocellular carcinoma.

The products are intended for curative treatment.

These products are used in dual therapy (in combination with ribavirin). In the event of intolerance or a contraindication to ribavirin, these products are used in single therapy.

The efficacy/adverse effects ratio of these products in this indication extension is moderate.

There is no alternative treatment:
- for patients relapsing after dual PEGylated or unPEGylated therapy + ribavirin
- for patients unresponsive to a prior dual therapy (PEGylated or unPEGylated) and single alpha-interferon therapy.

Public health benefit:

Hepatitis C is a moderate public health burden.
This burden remains moderate in the population corresponding to the indication (patients refractory to prior dual alpha-interferon/ribavirin therapy or single alpha-interferon therapy), despite a lower number of patients, due to the level of severity of the disease in this subpopulation.

The decrease in morbidity and mortality attributable to chronic hepatitis C corresponds to a public health need established as a priority by the French Public Health objectives group (GTNDO).
The clinical trial data for refractory patients previously treated (relapsing or unresponsive) showed the impact of the treatment on the sustained virologic response rate (at 24 weeks), primarily for relapse patients. Based on this intermediary endpoint, it is difficult to judge the impact of the VIRAFERONPEG-REBETOL combination in terms of morbidity and mortality (progression towards chronic state, liver fibrosis, liver cancer, etc.) in patients refractory to treatment.
Giving VIRAFERONPEG-REBETOL to patients refractory to previous treatment therefore does not appear to provide any additional solution as far as the identified public health need is concerned.

Consequently, given the current knowledge of the subject, the dual VIRAFERONPEG-REBETOL therapy is not expected to benefit public health in this indication extension to patients refractory to prior treatment.

The actual benefit of these products is substantial.

4.2. Improvement in actual benefit

No improvement in actual benefit.

4.3. Therapeutic use

The recommendations of the consensus conference on the treatment of chronic hepatitis C in February 2002 have not been updated.

The treatment currently indicated for patients refractory to initial treatment with PEGylated or unPEGylated alpha-interferon + ribavirin or with alpha-interferon alone is VIRAFERONPEG combined with REBETOL where there is no intolerance or contraindication to ribavirin.

The efficacy of the repeat treatment, in terms of sustained virologic response, differs mainly according to:
- the reason why the patient is refractory to the initial treatment
- the composition of the initial treatment
- the genotype
- the fibrosis score

In patients relapsing after initial treatment with PEGylated or unPEGylated dual therapy or single therapy (patients identified as having an undetectable serum HCV RNA level at the end of the initial treatment and a positive level during the post-treatment period) VIRAFERONPEG and REBETOL are indicated in combination.

In unresponsive patients a sustained virologic response was mainly observed in patients not responding to an initial treatment consisting of unPEGylated dual therapy or single therapy. Inversely, the probability of achieving a sustained virologic response is very low in patients not responding to initial treatment consisting of PEGylated dual therapy with the recommended dose and treatment duration.

Furthermore, in relapse and unresponsive patients, regardless of genotype, the decision to continue treatment is based on undetectable serum HCV RNA levels at week 12 of treatment.

4.4. Target population

The prevalence of positivity for serum HCV antibodies has been estimated in France (INVS 2004 data[6]) as about 0.84% (95% CI: 0.65 - 1.10), i.e. 367,055 people (269,361 – 464,750).
In people with HCV antibodies, the prevalence of the chronic infection (positive RNA) has been estimated as 65% (95% CI: 50 - 78), corresponding to an overall prevalence in the population of 0.53% (95% CI: 0.40 – 0.70), i.e. 221,386 people (158,909-283,862).

[6] Meffre C, Le Strat Y, Delarocque-Astagneau E, Antona D, Desenclos JC. Prévalence des hépatites B et C en France en 2004 – Health Monitoring Institute, InVS, Saint-Maurice, March 2007.
http://www.invs.sante.fr/publications/2006/prevalence_b_c/vhb_france_2004.pdf

Only 59.1%, i.e. 130,839 people, are diagnosed, (93,915 - 167,762). A portion of these patients will not be treatable due to a contraindication to the treatment (e.g. hepatic decompensation); this portion is estimated at about 10%[7] (2006 data in reference centres – stages of cirrhosis and decompensated cirrhosis).
Therefore, the target population eligible for treatment is thought to be about 85,000 to 151,000.
In addition to cases already diagnosed, new cases of hepatitis C to be diagnosed during the year must also be taken into account. This figure is estimated as 5,000 new cases per year in France[8], about a quarter of which are estimated[9] to be able to benefit from treatment, i.e. 1,250 patients.
Among those diagnosed with chronic hepatitis C, it is important to differentiate between patients already treated and those thus far untreated.

In the group of people already treated, it would be useful to be able to estimate the number of people that could benefit from repeat treatment (indication extension):

- one recent European study[10] based on IMS data estimates that 16% of those with HCV in France (prevalence of seropositivity of antibodies), i.e. 62,000 patients, have already been given treatment.
- according to the observational studies ADEQUATION and HECOS[11], about 30 to 40% of patients treated are unresponsive to and relapse after treatment (i.e. 28,200 to 67,200 patients).

As the patients relapsing after single therapy were already included in the previous indication, the target population corresponding to the indication extension can be estimated as 28,200 to 67,200 patients at most.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services for the indication extension and at the dosage stated in the marketing authorisation.

Packaging: the packaging is appropriate for prescription requirements

Reimbursement rate: 65 %

[7] Surveillance nationale de l'hépatite C à partir des pôles de référence volontaires 2001-2006. Health Monitoring Institute – April 2008. http://www.invs.sante.fr/surveillance/hepatite_c/poleref_volontaire/stades_cliniques.pdf
[8] Roudot-Thoraval F. Évolution des caractéristiques épidémiologiques de l'hépatite C. Gastroenterol Clin Biol 2002 ;26 :B138-B143
[9] Introduction of antiviral treatment (a) in RNA positive patients recently managed by reference centres 2004-2006. http://www.invs.sante.fr/surveillance/hepatite_c/poleref_volontaire/anti_viral.pdf
[10] Lettmeier B, Mühlberger N, Schwarzer R, Sroczynski G, Wright D, Zeuzem S, Siebert U. Market uptake of new antiviral drugs for the treatment of hepatitis C. J Hepatol. 2008 Oct;49(4):528-36
[11] See appendix to Transparency Committee opinion of September 17, 2008 for VERAFERONPEG: Opinion of PHB group on studies submitted by Schering Plough concerning VIRAFERONPEG.