HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

10 March 2010

PEGASYS 135 micrograms, solution for injection in prefilled syringe
Box of 1 (CIP: 359 958-1)
Box of 4 (CIP: 359 959-8)

PEGASYS 180 micrograms, solution for injection in prefilled syringe
Box of 1 (CIP: 359 960-6)
Box of 4 (CIP: 359 961-2)

Applicant: ROCHE

peginterferon alfa-2a

ATC code: L03AB11

List I.
Medicinal product requiring close monitoring during treatment.
Medicinal product subject to six-month prescription initially, reserved for specialists and/or departments specialising in gastroenterology, hepatology, internal medicine or infectious diseases.
Unrestricted renewal.

Medicine dispensed in both pharmacies and hospitals.
Included on the French "retrocession" [dispensing of drugs to outpatients by hospital pharmacies] list.

Date of Marketing Authorisation and of most recent revision of Marketing Authorisation: 20 June 2002, 21 August 2009

Reason for request: Inclusion on the list of medicines reimbursed by National Health Insurance and approved for hospital use in the extension of indication (revision of marketing authorisation on 28/11/08):
"Treatment of patients with chronic hepatitis C who have failed previous treatment with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin."

Medical, Economic and Public Health Assessment Division.

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Peginterferon alfa-2a

1.2. Indications

"Chronic hepatitis B

PEGASYS is indicated for the treatment of HBeAg-positive or HBeAg-negative chronic hepatitis B in adult patients with compensated liver disease and evidence of viral replication, increased ALT and histologically verified liver inflammation and/or fibrosis.

Chronic hepatitis C

PEGASYS is indicated for the treatment of chronic hepatitis C in adult patients who are positive for serum HCV-RNA, including patients with compensated cirrhosis and/or co-infected with clinically stable HIV (see section 4.4).

The optimal way to use PEGASYS in patients with chronic hepatitis C is in combination with ribavirin. The combination of Pegasys and ribavirin is indicated in naive patients and patients **who have failed previous treatment with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin.**

Monotherapy is indicated mainly in case of intolerance or contraindication to ribavirin".

1.3. Dosage

"Treatment should be initiated only by a physician experienced in the treatment of patients with hepatitis B or C.
Please also refer to the ribavirin Summary of Product Characteristics (SPC) when PEGASYS is to be used in combination with ribavirin.

Dose to be administered and duration of treatment

Chronic hepatitis B:

The recommended dose for PEGASYS for both HBeAg-positive and HBeAg-negative chronic hepatitis B is 180 micrograms once weekly for 48 weeks by subcutaneous administration in the abdomen or thigh.

Chronic hepatitis C - treatment-naive patients:
The recommended dose for PEGASYS is 180 micrograms once weekly by subcutaneous administration in the abdomen or thigh given in combination with oral ribavirin or as monotherapy.
The dose of ribavirin to be used in combination with PEGASYS is given in Table 1.
The ribavirin dose should be administered with food.

Duration of treatment
The duration of combination therapy with ribavirin for chronic hepatitis C depends on viral genotype. Patients infected with HCV genotype 1 who have detectable HCV RNA at week 4 regardless of pre-treatment viral load should receive 48 weeks of therapy.
Treatment for 24 weeks may be considered in patients infected with
- genotype 1 with low viral load (LVL) (≤ 800,000 IU/ml) at baseline or
- genotype 4

who become HCV RNA negative at week 4 and remain HCV RNA negative at week 24. However, an overall 24 weeks duration may be associated with a higher risk of relapse than a 48 weeks treatment duration (see section 5.1). In these patients, tolerability to combination therapy and additional prognostic factors such as degree of fibrosis should be taken into account when deciding on treatment duration. Shortening the treatment duration in patients with genotype 1 and high viral load (HVL) (> 800,000 IU/ml) at baseline who become HCV RNA negative at week 4

and remain HCV RNA negative at week 24 should be considered with even more caution since the limited data available suggest that this may significantly negatively impact the sustained virological response.
Patients infected with HCV genotype 2 or 3 who have detectable HCV RNA at week 4, regardless of pre-treatment viral load should receive 24 weeks of therapy. Treatment for only 16 weeks may be considered in selected patients infected with genotype 2 or 3 with LVL (≤ 800,000 IU/ml) at baseline who become HCV negative by week 4 of treatment and remain HCV negative by week 16. Overall 16 weeks of treatment may be associated with a lower chance of response and is associated with a higher risk of relapse than a 24 week treatment duration (see section 5.1). In these patients, tolerability to combination therapy and the presence of additional clinical or prognostic factors such as degree of fibrosis should be taken into account when considering deviations from standard 24 weeks treatment. Shortening the treatment duration in patients infected with genotype 2 or 3 with HVL (> 800,000 IU/ml) at baseline who become HCV negative by week 4 should be considered with more caution as this may significantly negatively impact the sustained virological response (see Table 1).
Available data for patients with genotype 5 or 6 are limited; therefore, combination treatment with1,000/1,200 mg of ribavirin for 48 weeks is recommended.

Table 1: Dosing Recommendations for Combination Therapy for HCV patients

Genotype	PEGASYS Dose	Ribavirin Dose	Duration
Genotype 1 LVL with RVR*	180 micrograms	< 75 kg = 1000 mg ≥ 75 kg = 1200 mg	24 weeks or 48 weeks
Genotype 1 HVL with RVR*	180 micrograms	< 75 kg = 1000 mg ≥ 75 kg = 1200 mg	48 weeks
Genotype 4 with RVR*	180 micrograms	< 75 kg = 1000 mg ≥ 75 kg = 1200 mg	24 weeks or 48 weeks
Genotype 1 or 4 without RVR*	180 micrograms	< 75 kg = 1000 mg ≥ 75 kg = 1200 mg	48 weeks
Genotype 2 or 3 without RVR**	180 micrograms	800 mg	24 weeks
Genotype 2 or 3 LVL with RVR**	180 micrograms	800 mg [(a)]	16 weeks [(a)] or 24 weeks
Genotype 2 or 3 HVL with RVR**	180 micrograms	800 mg	24 weeks

*RVR = rapid viral response (HCV RNA undetectable) at week 4 and HCV RNA undetectable at week 24
**RVR = rapid viral response (HCV RNA negative) by week 4
LVL: ≤ 800,000 IU/ml; HVL: > 800,000 IU/ml
[(a)] It is presently not clear whether a higher dose of ribavirin (e.g.: 1000/1200 mg/day based on body weight) results in higher SVR rates than does the 800 mg/day, when treatment is shortened to 16 weeks.

The ultimate clinical impact of a shortened initial treatment of 16 weeks instead of 24 weeks is unknown, taking into account the need for retreating non-responding and relapsing patients.

The recommended duration of PEGASYS monotherapy is 48 weeks.

Chronic hepatitis C - treatment-experienced patients:
The recommended dose of PEGASYS in combination with ribavirin is 180 mcg once weekly by subcutaneous administration. For patients < 75 kg and ≥ 75 kg, 1000 mg daily and 1200 mg daily of ribavirin, respectively, should be administered.
Patients who have detectable virus at week 12 should stop therapy.
The recommended total duration of therapy is 48 weeks. If patients with virus genotype 1, not responding to prior treatment with PEG-IFN and ribavirin are considered for treatment, the recommended total duration of therapy is 72 weeks (see section 5.1).

HIV-HCV co-infection
The recommended dosage for PEGASYS, alone or in combination with 800 milligrams of ribavirin, is 180 micrograms once weekly subcutaneously for 48 weeks, regardless of genotype. The safety and efficacy of combination therapy with ribavirin doses greater than 800 milligrams daily is

currently being studied. A duration of therapy less than 48 weeks has not been adequately studied.

Predictability of response and non-response - treatment-naive patients
Early virological response by week 12, defined as a 2 log viral load decrease or undetectable levels of HCV RNA has been shown to be predictive for sustained response (see Table 2).

Table 2: Predictive Value of Week 12 Virological Response at the Recommended Dosing Regimen while on Pegasys Combination Therapy

Genotype	Negative			Positive		
	No response by week 12	No sustained response	Predictive Value	Response by week 12	Sustained response	Predictive Value
Genotype 1 (N = 569)	102	97	95% (97/102)	467	271	58% (271/467)
Genotype 2 and 3 (N = 96)	3	3	100% (3/3)	93	81	87% (81/93)

The negative predictive value for sustained response in patients treated with PEGASYS in monotherapy was 98%.
A similar negative predictive value has been observed in HIV-HCV co-infected patients treated with PEGASYS monotherapy or in combination with ribavirin (100% (130/130) or 98% (83/85)), respectively. Positive predictive values of 45% (50/110) and 70% (59/84) were observed for genotype 1 and genotype 2/3 HIV-HCV co-infected patients receiving combination therapy.

Predictability of response and non-response - treatment-experienced patients
In non-responder patients re-treated for 48 or 72 weeks, viral suppression at week 12 (undetectable HCV RNA defined as <50 IU/ml) has been shown to be predictive for sustained virological response. The probabilities of not achieving a sustained virological response with 48 or 72 weeks of treatment if viral suppression was not achieved at week 12 were 96% (363 of 380) and 96% (324 of 339). The probabilities of achieving a sustained virological response with 48 or 72 weeks of treatment if viral suppression was achieved at week 12 were 35% (20 of 57) and 57% (57 of 100).

Dose adjustment for adverse reactions
General
Where dose adjustment is required for moderate to severe adverse reactions (clinical and/or laboratory) initial dose reduction to 135 micrograms is generally adequate. However, in some cases, dose reduction to 90 micrograms or 45 micrograms is necessary. Dose increases to or towards the original dose may be considered when the adverse reaction abates (see Special warnings and precautions for use and Undesirable effects)".

See SPC for special populations

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2005)

L : antineoplastic and immunomodulating agents
L03 : immunostimulants
L03A : immunostimulants
L03AB : interferons
L03AB11 : peginterferon alfa-2a

2.2. Medicines in the same therapeutic category

Comparator medicines (in the extension of indication)

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

2.3. Medicines with a similar therapeutic aim

Not applicable

3 ANALYSIS OF AVAILABLE DATA

The clinical dossier contains four studies, the details of which are summarised in Table 1.

Table 1 Summary of the studies submitted.

Study	Objectives	Number and type of patients
Pivotal study: efficacy/safety in non-responders		
REPEAT *Pivotal study*	Treatment of patients with HCV infection who did not respond to a previous treatment with PEG-IFN alfa-2b + ribavirin (VIRAFERONPEG) administered for at least 12 weeks	N= 950 HCV+ patients not responding to PEG-IFN alfa-2b + ribavirin
Supporting study: efficacy/safety in non-responders		
HALT-C	Treatment of patients with advanced HCV infection who did not respond to a previous treatment with interferon (pegylated or non-pegylated) as monotherapy or in combination with ribavirin	N=1,050 with advanced fibrosis HCV+ and non responders
Supporting study: efficacy among relapsing patients		
WV16143	Treatment of patients with HCV infection following relapse: efficacy of peginterferon alfa-2a + ribavirin.	N=64 patients who relapsed following previous treatment for 24 weeks with peginterferon alfa-2a
Supporting studies: efficacy/tolerance		
Study M 78014	Comparison of the efficacy and safety of peginterferon + RBV at 48 weeks and 72 weeks.	N=225 treatment-naive patients with genotype 1 HCV
Study M 78019	Comparison of the efficacy and safety of peginterferon + RBV at 48 weeks and 72 weeks.	N= 162 treatment-naive patients with HCV who had not achieved virological response at 4 weeks

Only the data relating to the extension of indication (REPEAT and HALT-C studies) will be taken into account when assessing efficacy and safety. Bitherapy (peginterferon alfa-2a (PEGASYS) and ribavirin (COPEGUS)) administered to treatment-naive patients and relapsing patients was taken into consideration in previous assessments. The efficacy data from study WV16143 will be presented for information.

3.1. Efficacy among patients with chronic hepatitis C who did not respond to a previous treatment

3.1.1 Study MV17150 – REPEAT[1]

Purpose

The purpose of this open-label study was to assess the efficacy and safety of treatment with peginterferon alfa-2a (PEGASYS) plus ribavirin in patients who did not respond to peginterferon alfa-2b (VIRAFERONPEG) plus ribavirin. Non-response was defined by a positive HCV RNA serum reading at the end of 12 weeks treatment with peginterferon alfa-2b (≥ 1µg/kg/week) plus ribavirin (≥ 800 mg/day).

The various treatment regimens assessed were:

- Treatment with an induction dose (peginterferon alfa-2a at twice the normal dose: 360µg/week for 12 weeks) followed by the normal dose of 180 µg/week *versus* treatment with the normal dose of 180 µg/week throughout the entire course of treatment,

[1] Jensen D. et al. Re-treatment of patients with chronic hepatitis C who do not respond to peginterferon-alfa2b: A randomized trial. Ann Intern Med. 2009;150:528-540.

- Extension of the duration of treatment to 72 weeks *versus* the normal duration of 48 weeks. Combining these four options resulted in four groups being created.

Population

- **Inclusion criteria**: Adult patients (≥ 18 years), with chronic hepatitis C confirmed by serological and histological tests, quantifiable HCV RNA (> 600 IU/ml), compensated liver disease and non-responders to a previous treatment with peginterferon alfa-2b/ribavirin given for at least 12 weeks.

- **Main non-inclusion criteria**: patients who stopped treatment with peginterferon alfa-2b/ribavirin because of adverse haematological effects; patients with a history of severe depression or other psychiatric disorders; patients who had had another antiviral or immunomodulating systemic treatment within the six months prior to inclusion. Patients co-infected with HAV, HBV or HIV were also ineligible.

Treatments

The patients (N=950) were randomised to four groups:

- Group A: PEGASYS 360 micrograms/week for 12 weeks, followed by 180 micrograms/week for a further 60 weeks
- Group B: PEGASYS 360 micrograms/week for 12 weeks, followed by 180 micrograms/week for a further 36 weeks
- Group C: PEGASYS 180 micrograms/week for 72 weeks
- Group D: PEGASYS 180 micrograms/week for 48 weeks

All patients received ribavirin (1,000 or 1,200 mg/day depending on their weight) in addition to PEGASYS. All the groups had a 24-week follow-up after the end of treatment.

Primary efficacy endpoint

Sustained virological response (HCV RNA undetectable) at the 24 weeks after the end of 48 or 72 weeks treatment.

Efficacy results

The analysis was performed on the intention-to-treat (ITT) population, which consisted of patients who had been randomised and had received at least one treatment dose. Eight of the 950 patients taking part were randomised but did not receive treatment (five because they refused treatment and three as a result of protocol violation).

- the median age of the patients was 49 years [min-max 18-74],
- 91% of the patients had genotype 1 virus,
- 79% to 86% of the patients had a viral load greater than 800,000 IU/ml,
- 25 to 30% of the patients were cirrhotic,
- the most common source of infection was drug injection..

The median length of prior treatment with peginterferon alfa-2b/ribavirin was 190 to 201 days depending on the group (average 225 days), and the median doses of peginterferon alfa-2b and ribavirin were 1.5 µg/kg and 1,000 mg respectively.

- **Efficacy according to the therapeutic dose of IFN (with or without induction dose) and duration of treatment (48 weeks versus 72 weeks)**

The sustained virological response (SVR) obtained in each treatment group is presented in Table 2.

Table 2: Sustained virological response observed in each group (ITT analysis)

	Group A 360/180 µg* 72 weeks (N=317)	Group B 360/180 µg* 48 weeks (N=156)	Group C 180 µg* 72 weeks (N=156)	Group D 180 µg* 48 weeks (N=313)	Odds Ratio (95% CI)	p
A vs. D	16%	-	-	9%	2.00 [1.21-3.31]	0.006
A vs. B	16%	7%	-	-	2.77 [1.36-5.67]	0.004
C vs. D	-	-	14%	9%	1.80 [0.97-3.32]	0.060
B vs. C	-	7%	14%	-	0.49 [0.23-1.03]	0.049
A vs. C	16%	-	14%	-	1.11 [0.64-1.93]	0.714
B vs. D	-	7%	-	9%	0.79 [0.38-1.64]	0.530

* dose of peginterferon alfa-2a, in combination with ribavirin (1,000 or 1,200 mg/day, depending on weight)

- Pegylated interferon administered at a double dose (360 µg/week) for three months followed by the normal dose (groups A and B) was not associated with a better virological response compared to the standard treatment regimen (180 µg/week throughout the entire duration of the treatment) (groups C or D).
- Extending the duration of treatment from 48 to 72 hours was associated with a better sustained virological response (according to a logistic regression analysis).

- **Efficacy analysis in sub-groups (genotype, viral load and cirrhotic status)**

A sub-group analysis was performed on the basis of the three main parameters which might affect SVR, i.e. genotype, baseline viral load and disease stage (cirrhosis). Patients with genotype 1, a high baseline viral load and/or cirrhosis were less likely to achieve virological response following re-treatment *(Table 3)*. However, it should be noted that this study included very few patients with HCV infection of a genotype non 1 and very few patients with a low baseline viral load.

Table 3: Sustained viral load (SVR): efficacy analysis in sub-groups (genotype, viral load and cirrhotic status)

	Group A 360/180 µg* 72 weeks (N=317)		**Group B 360/180 µg* 48 weeks (N=156)**		**Group C 180 µg* 72 weeks (N=156)**		**Group D 180 µg* 48 weeks (N=313)**	
	N	**SVR**	**N**	**SVR**	**N**	**SVR**	**N**	**SVR**
Patients who received at least one dose of treatment	317	52 (16%)	156	11 (7%)	156	22(14%)	313	27 (9%)
Genotype 1	288	42 (15%)	142	10 (7%)	142	18 (13%)	284	21 (7%)
Genotype non 1	29	10	14	1	14	4	29	6
VL<= 800,000 IU/ml	61	22 (36%)	22	2	25	5	62	9 (15%)
VL> 800,000 IU/ml	244	29 (12%)	130	9 (7%)	128	17 (13%)	233	16 (7%)
Cirrhotic	79	3 (4%)	45	2 (4%)	46	3 (7%)	88	4 (5%)
Not cirrhotic	237	49 (21%)	110	8 (7%)	109	19 (17%)	223	23 (10%)

* dose of peginterferon alfa-2a in combination with ribavirin (1,000 or 1,200 mg/day, depending on weight)

- **Predictability of response and non-response**

Viral suppression at week 12 (undetectable HCV RNA defined as < 50 IU/ml)[2] was identified as a predictive factor for sustained virological response. Fifty seven % of patients with undetectable HCV RNA at week 12 achieved sustained virological response after 72 weeks (57/100), while the corresponding figure after 48 weeks of treatment was 35% (20/57).
In contrast, the SVR rate after 72 weeks and 48 weeks of treatment for patients who had detectable HCV RNA plasma levels at week 12 was only 4% (15/339 and 17/380 respectively).

Consequently, re-treated patients who have not achieved an early virological response (i.e. patients with detectable HCV RNA plasma levels at week 12) are unlikely to respond irrespective of treatment duration.

[2] It should be noted that the proportion of patients with undetectable HCV RNA at 12 weeks was 24% in group A, 14% in group B, 16% in group C and 11% in group D.

3.1.2 Study HALT-C[3] and study WV16143[4] (supporting studies)

The HALT-C study was carried out in patients with chronic hepatitis C and advanced fibrosis or cirrhosis non respondersto a previous treatment with interferon alfa or pegylated interferon alfa alone or in combination with ribavirin. The patients were treated with PEGASYS 180 micrograms per week in combination with ribavirin 1,000/1,200 mg daily.
Patients who achieved an undetectable HCV RNA level after 20 weeks of treatment continued on PEGASYS/ribavirin for 48 weeks in total and were then monitored for 24 weeks after the end of treatment.
The sustained virological response achieved varied according to the previous treatment received by the patients (Table 4). Overall, SVR was observed in 18% of patients who had failed previous interferon-based treatment. The SVR rate was 35% in patients who had undetectable HCV RNA at week 12.

Table 4: **Sustained virological response (SVR) in the HALT-C study according to the previous treatment administered to non-responding patients[5].**

Previous treatment	PEGASYS 180 µg & ribavirin - SVR 1,000/1,200 mg 48 weeks
Interferon	**27% (70/255)**
Pegylated interferon	**34% (13/38)**
Interferon and ribavirin	**13% (90/692)**
Pegylated interferon and ribavirin	**11% (7/61)**

In study WV16143, carried out on patients who had relapsed (n=64) following treatment with pegylated bitherapy (peginterferon alfa-2a 180µg/week combined with RBV 800, 1,000 or 1,200 mg/day) for 24 weeks, the new treatment with pegylated bitherapy administered for 48 weeks led to a sustained virological response in 55% of patients. This SVR rate was 72% in patients who had undetectable HCV RNA at week 12.

3.2. Tolerance in patients who had not responded to previous treatment (according to the SPC)

Overall, the safety profile of PEGASYS in combination with ribavirin in patients who had not responded to previous treatment was similar to that of treatment-naive patients. In the clinical study carried out in patients who had not responded to previous treatment with pegylated interferon alfa-2b/ribavirin, who were treated for either 48 weeks or 72 weeks, the proportion of patients stopping treatment with PEGASYS and ribavirin because of adverse effects or abnormal laboratory findings was 6% - 7% in the groups treated for 48 weeks and 12% - 13% in the groups treated for 72 weeks. Among patients with cirrhosis or who were likely to become cirrhotic, the proportion of patients stopping treatment with PEGASYS/ribavirin was higher in the groups treated for 72 weeks (13% and 15%) than in the groups treated for 48 weeks (6% and 6%). Patients who stopped a previous treatment with pegylated interferon alfa-2b/ribavirin because of haematological toxicity were excluded from recruitment for this study.

In the clinical study carried out in non-responding patients with severe fibrosis or cirrhosis (Ishak score 3 to 6) and a low baseline platelet count of 50,000/mm^3, the haematological abnormalities

[3] Shiffman ML, Di Bisceglie AM, Lindsay KL, Morishima C, Wright EC, Everson GT, et al. Peginterferon alfa-2a and ribavirin in patients with chronic hepatitis C who failed prior treatment. Gastroenterology 2004; 126: 1015-1023.

[4] Berg C, Goncales Jr FL, Bernstein DE et al. Re-treatment of chronic hepatitis C patients after relapse: efficacy of peginterferon-alpha-2a (40 kDa) and ribavirin. J Viral Hepat 2006; 13: 435-440.

[5] Everson G, Hoefs J, Seeff L et al. Impact of disease severity on outcome of antiviral therapy for chronic hepatitis C: lessons from the HALT-C trial. Hepatology 2006; 44: 1675-1684.

observed in the first 20 weeks of the study included anaemia (26% of patients had a haemoglobin level of < 10 g/dl), neutropenia (30% had an absolute neutrophil count of < 750/mm^3) and thrombopenia (13% had a platelet count of < 50,000/mm^3).

3.3. Conclusion

The extension of indication to include treatment of patients suffering from chronic hepatitis C who have not responded to previous antiviral treatment is based on the results of the REPEAT study performed on 950 patients (91% with genotype 1) who had not responded to bitherapy with peginterferon alfa-2b/ribavirin (VIRAFERONPEG/REBETOL).

At the dosage recommended in the marketing authorisation (PEGASYS 180 µg & ribavirin 1000/1200 mg), the rate of sustained virological response (HCV RNA undetectable at week 24 after the end of treatment) was 9% in the group of patients treated for 48 weeks and 14% in the group treated for 72 weeks.

The exploratory analysis of predictive factors of treatment response showed that:

- doubling the dose of pegylated interferon (360 µg/week) for 3 months followed by the usual dose of 180 µg/week is not associated with a better sustained virological response compared to the usual regimen of 180 µg/week throughout the entire duration of treatment.
- treatment administered for 72 weeks was associated with a better sustained virological response compared to the standard duration of 48 weeks (14% vs. 9%).
- patients undergoing re-treatment who have not achieved an early virological response (i.e. patients with detectable HCV RNA plasma levels at week 12) are unlikely to become responsive irrespective of treatment duration.

Overall, the safety profile of PEGASYS in combination with ribavirin in patients who had not responded to previous treatment with pegylated or unpegylated bitherapy and ribavirin was similar to that of treatment-naive patients. However, patients who stopped a previous treatment with pegylated interferon alfa-2b/ribavirin because of haematological toxicity were not included in this study.

The Committee finds it regrettable that little data is available for non-responsive patients with genotype 2 or 3, that no data is available for patients previously treated with bitherapy involving PEGASYS and ribavirin, given the current trend in prescription habits in France, with PEGASYS coming to replace VIRAFERONPEG, and that no comparative data versus bitherapy with VIRAFERONPEG/ribavirin is available.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Hepatitis C is such a severe condition because it often becomes chronic, which can lead to long-term complications: cirrhosis, hepatocellular insufficiency, and hepatocellular carcinoma.

For patients who have failed previous treatment, PEGASYS is a first-line curative treatment used in bitherapy with ribavarin or as monotherapy where ribavirin is not tolerated or is contraindicated.

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

There is a treatment alternative: the combination of VIRAFERONPEG/REBETOL.

Public health benefit:
Hepatitis C represents a moderate public health burden. This burden remains moderate in the population affected by the indication (patients who have failed a previous treatment with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin, despite a smaller number of patients but because of the severity of the condition in this sub-population.

The reduction in morbidity and mortality attributable to forms of chronic hepatitis C meets a public health need that is part of an established priority (GTNDO[6]).

Data from clinical trials carried out on previously treated patients who had not responded to bitherapy with pegylated alfa-2b/ribavirin (VIRAFERONPEG/REBETOL) have shown the impact of the treatment on the sustained virological response, especially among patients who were treated for 72 weeks.
Administering Pegasys in combination with ribavirin to patients who have failed previous treatment therefore seems to be able to offer an additional response to the identified public health need.
Consequently, in the current state of knowledge, bitherapy involving Pegasys/ribavirin is expected to have a low public health benefit in this extension of indication to patients who have failed previous treatment.

The actual medical benefit of these medicinal products is substantial.

4.2. Improvement in actual benefit (IAB)

No improvement in actual benefit (IAB V) in the management of patients suffering from chronic hepatitis C in whom previous treatment with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin has failed.

4.3. Therapeutic use

The therapeutic strategy for the management of patients infected with HCV has not been changed since the consensus-setting conference on the treatment of hepatitis C held in February 2002[7].

The consensus-setting conference merely recommended re-treatment with pegylated interferon and ribavirin for patients who had relapsed after monotherapy with interferon. This indication (treatment of relapsed patients) was included in the marketing authorisation for PEGASYS.

As these recommendations have not been updated, the therapeutic use of PEGASYS in the management of non-responding patients is based on the pivotal REPEAT study relating to this extension of indication.

[6] Groupe Technique National de Définition des Objectifs [National Technical Objective Definition Group]
[7] Consensus-setting conference on the treatment of hepatitis C. February 2002. Available in French at: http://www.infectiologie.com/site/medias/_documents/consensus/Vhc-2002.pdf

The treatment currently indicated for patients who have failed initial treatment with interferon alfa (pegylated or non-pegylated) and ribavirin or interferon alfa as monotherapy is either PEGASYS/COPEGUS or VIRAFERONPEG/REBETOL, provided that ribavirin is tolerated and is not contraindicated.

The level of efficacy of the new treatment, in terms of sustained virological response, varies according to the following factors in particular:
- the type of failure of the initial treatment
- the composition of the initial treatment
- the genotype
- the fibrosis score

Indeed, patients who did not respond to standard bitherapy are unlikely to benefit from pegylated bitherapy, especially if they have severe fibrosis, and the benefit for patients who did not respond to pegylated bitherapy appears dubious unless the initial treatment had to be reduced or stopped prematurely because of abnormal laboratory findings and/or clinical adverse effects, or if the doses given at that time were insufficient.

The decision as to whether to continue treatment is based on undetectability of HCV RNA serum levels at week 12 of treatment. Treatment must be stopped and another strategy selected if virological efficacy is not obtained by week 12 (reduction of less than 2 logs in the viral load, or detectable HCV RNA).

4.4. Target population

The prevalence of anti-HCV antibody seropositivity in France has been estimated (INVS data collected in 2004[8]) at around 0.84% (95% CI: 0.65-1.10), or 367,055 individuals (269,361-464,750).
It has been estimated that 65% of individuals with anti-HCV antibodies have chronic infection (RNA positive) (95% CI: 50-78), which would give an overall prevalence in the population of 0.53% (95% CI: 0.40-0.70), or 232,196 individuals (167,869 - 296,523).

Only 59.1% of these individuals have been diagnosed, i.e. 137,228 patients (99,210-175,245)[2]. Some of them will not be suitable for treatment because of treatment contraindication (such as hepatic decompensation). The population can be estimated at around 10%[9] (2006 data from reference centres - stages of cirrhosis and decompensated cirrhosis).
Consequently, the population eligible for treatment would comprise around 89,000 to 158,000 individuals.
In addition to the cases that have already been diagnosed, new cases of hepatitis C that will be diagnosed in the course of the year need to be taken into account. This figure is estimated at 5,000 new cases a year in France[10], with the proportion of individuals likely to benefit from treatment estimated[11] at around 25%, or 1250 patients.

Among individuals who have been diagnosed with chronic hepatitis C, it is necessary to distinguish between those who have had treatment and those who have not.

[8] 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, mars 2007. http://www.invs.sante.fr/publications/2006/prevalence_b_c/vhb_france_2004.pdf
[9] Surveillance nationale de l'hépatite C à partir des pôles de référence volontaires 2001-2006. Institut de veille sanitaire – Avril 2008. http://www.invs.sante.fr/surveillance/hepatite_c/poleref_volontaire/stades_cliniques.pdf
[10] Roudot-Thoraval F. Évolution des caractéristiques épidémiologiques de l'hépatite C. Gastroenterol Clin Biol 2002 ;26 :B138-B143
[11] Institution d'un traitement anti-viral (a) chez les patients ARN positif nouvellement pris en charge par les pôles de référence 2004-2006. http://www.invs.sante.fr/surveillance/hepatite_c/poleref_volontaire/anti_viral.pdf

It should be possible to estimate the number of people in the group of individuals already treated who might benefit from re-treatment (in the extension of the indication):

- a recent European study[12] conducted on the basis of IMS data estimates that 16% of individuals with HCV in France (prevalence of antibody seropositivity) have already been treated, i.e. 60,000 patients (43,000 to 74,000).

- according to the ADEQUATION and HECOS observational studies[13], around 30 to 40% of patients who have treatment either do not respond or relapse (i.e. 30 000 to 70 000 patients).

As relapsing patients were already included in the previous indication, the target population for the extension of indication can be estimated at no more than 30,000 to 70,000 patients.

4.5. Transparency Committee recommendations

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

4.5.1. Packaging: Appropriate for the prescription conditions

4.5.2. Reimbursement rate: 65 %

[12] Lettmeier B. et al. Market uptake of new antiviral drugs for the treatment of hepatitis C. J Hepatol. 2008 Oct;49(4):528-36.

[13] See the appendix to the Transparency Committee's opinion dated 17 September 2008 on VIRAFERONPEG: Opinion of the Public Health Benefit group on the studies submitted.