PUBLIC SUMMARY DOCUMENT
Product: Ribavirin capsules 200 mg, (various quantities) and peginterferon alfa-2b, single use injection pens containing powder for injection in 50, 80, 100, 120 and 150 micrograms, Pegatron®
Sponsor: Schering-Plough Pty Ltd
Date of PBAC Consideration: July 2008

1. Purpose of Application

The submission sought an extension to the PBS eligibility criteria (currently patients who are interferon alfa or peginterferon alfa naïve) to include those who have failed one previous treatment with interferon alfa (pegylated or non-pegylated) either as combination therapy with ribavirin or as monotherapy.

2. Background

At the March 2002 PBAC meeting, an application to list Pegatron combination therapy was rejected on the basis of uncertain but unfavourable cost-effectiveness.

The economic model was presented in further detail and the number of patients was revised upwards, substantially for the September 2002 submission. However, the application to list Pegatron was rejected on the same grounds as the March 2002 meeting – uncertain but unfavourable cost-effectiveness.

At the March 2003 meeting the PBAC recommended that a weighted price be negotiated for Pegatron® on a cost-effectiveness basis for patients with genotypes 1, 4, 5 or 6 (about 60% patients in Australia) and on a cost-minimisation basis for patients with genotypes 2 or 3 (about 40% patients in Australia).

3. Registration Status

On 3 March 2008, the TGA extended the registration for Pegatron combination therapy to include the treatment of chronic hepatitis C in patients who are who have failed previous therapy with interferon alfa (pegylated or nonpegylated) and ribavirin combination therapy or interferon monotherapy.

Pegatron is currently registered for the following:
The treatment of chronic hepatitis C in patients who are treatment naive or who had failed previous therapy with interferon alfa (pegylated or nonpegylated) and ribavirin combination therapy or interferon monotherapy.

Combination therapy is also indicated for the treatment of adult patients with chronic hepatitis C with stable HIV co-infection, who have not previously received interferon treatment. Patients must be 18 years of age or older and have compensated liver disease.

4. Listing Requested and PBAC's View

Changes to the existing restriction wording are in *italics.*

Section 100
Private hospital authority required

Notes:

Caution:
Treatment with peginterferon alfa has been associated with depression and suicide in some patients. Patients with a history of suicidal ideation or depressive illness should be warned of the risks. Psychiatric status during therapy should be monitored.
Caution:
Ribavirin is a category X drug and must not be given to pregnant women. Pregnancy in female patients or in the partners of male patients must be avoided during treatment and during the 6 months period after cessation of treatment.

Treatment, managed by an accredited treatment centre, of chronic hepatitis C in patients 18 years or older who have compensated liver disease and who have received no *more than one* prior *attempt at* interferon alfa or peginterferon alfa treatment for hepatitis C and who satisfy all of the following criteria:

(1) Documented chronic hepatitis C infection (repeatedly anti-HCV positive and HCV RNA positive);
(2) Female patients of child-bearing age are not pregnant, not breast-feeding, and both patient and their partner are using effective forms of contraception (one for each partner). Male patients and their partners are using effective forms of contraception (one for each partner). Female partners of male patients are not pregnant.

Interferon alfa naïve patients:
For patients with genotype 2 or 3 hepatitis C without hepatic cirrhosis or bridging fibrosis, the treatment course is limited to 24 weeks. For hepatitis C patients with genotype 1, 4, 5 or 6 and those genotype 2 or 3 patients with hepatic cirrhosis or bridging fibrosis, the treatment course is limited to 48 weeks.
Patients with genotype 1, 4, 5 or 6 who are eligible for 48 weeks of treatment may only continue treatment after the first 12 weeks if the result of an HCV RNA quantitative assay (performed at the same laboratory using the same test) shows that the plasma HCV RNA has become undetectable or the viral load has decreased by at least a 2 log drop. (An HCV RNA assay at week 12 is unnecessary for genotype 2 and 3 patients because of the high likelihood of early viral response by week 12).
Patients with genotype 1, 4, 5 or 6 who are viral positive at week 12 but have attained at least a 2 log drop in viral load may only continue treatment after the first 24 weeks of treatment if plasma HCV RNA is not detectable by an HCV RNA qualitative assay at week 24. Similarly, genotype 2 or 3 patients with hepatic cirrhosis or bridging fibrosis may only continue treatment after the first 24 weeks if plasma HCV RNA is not detectable by an HCV RNA qualitative assay at week 24. An HCV RNA qualitative assay at week 24 is unnecessary for those patients with genotype 1, 4, 5 or 6 who became viral negative at week 12.

Patients who have failed one prior attempt at interferon alfa based therapy:
The treatment course is limited to 48 weeks. Patients may only continue treatment after the first 12 weeks of treatment if plasma HCV RNA is not detectable by an HCV RNA qualitative assay at week 12.

Note: Treatment centres are required to have access to the following appropriate specialist facilities for the provision of clinical support services for hepatitis C:
(a) a nurse educator/counsellor for patients; and
(b) 24 hour access by patients to medical advice; and

(c) an established liver clinic; and
(d) facilities for safe liver biopsy.
No change is requested to the currently approved packs or the prices per pack.

See Recommendation and Reasons for PBAC's view.

5. Clinical Place for the Proposed Therapy

The proposed change in listing will have no effect on pegylated interferon alfa treatment naïve patients but will make Pegatron available for patients who have failed one previous course of therapy with interferon alfa (pegylated or non-pegylated) with or without ribavirin. Patients who failed an initial attempt at treatment are currently ineligible for any further therapy on the PBS.

6. Comparator

The submission nominated usual standard of care as the main comparator because patients who have failed an initial attempt at interferon alfa monotherapy or interferon alfa combination therapy (pegylated or non-pegylated) are ineligible for any further courses of therapy on the PBS.

The PBAC considered this was appropriate.

7. Clinical Trials

The submission presented nine prospective non-comparative studies:

- five case series of peginterferon α-2b plus ribavirin combination; and
- single arms extracted from four randomised controlled trials comparing different dosage regimens of peginterferon α-2b plus ribavirin combination.

The non-comparative studies and associated reports published at the time of submission are as follows:

Study ID	Protocol title/ Publication title	Publication citation
P02370	Predictors of Sustained Viral Response in the Retreatment of Previous Interferon/Ribavirin Non-responders: Results from the EPIC3 Program.	Poynard T et al. Global Antiviral Journal 2007 (HEP DART 2007 - Frontiers in Drug Development for Viral Hepatitis, Lahaina, Hawaii); Volume 3 (Supplement): abstract Number 110.
	Fibrosis stage is not a pre-determinant of significant adverse events in previous interferon (IFN)-ribavirin (riba) treatment failures receiving Peg-interferon alfa 2b/riba weight-based dosing: results from the EPIC3 Program.	Terg R et al Hepatology 2005 (56th Annual Meeting American Association Study Liver, AASLD, San Francisco, CA, USA); 42(4): Supplement 1, abstract 853, 530-1A
	Interferon (IFN) induced thrombocytopenia is independent of level of fibrosis in patients with chronic hepatitis C (CHC): results from the EPIC 3 Program.	Schiff E et al. Hepatology 2005 (56th Annual Meeting

		American Association Study Liver Disorders, AASLD, San Francisco, CA, USA); 42(4): Supplement 1, abstract 854, 531-2A
	Sustained virologic response (SVR) with PEG-Interferon-alfa 2b/ribavirin weight-based dosing in previous interferon/ribavirin HCV treatment failures; Week 12 virology as a predictor of SVR in the EPIC3 Trials.	Poynard T et al Gastroenterology 2005 (Dig. Dis. Wk., (DDW), Chicago, IL, USA); 128(4), Supplement 2, abstract 5
	Week twelve virology predicts SVR in previous interferon/ribavirin treatment failures receiving PEG-Intron/REBETOL (PR) weight-based dosing (WBD).	Poynard T et al Journal of Hepatology 2005; (40th Annual Meeting of the European Association Study Liver, EASL, Paris, France), 42(2), Supplement, abstract 96
	High early viral response (EVR) with PEGINTRON/ REBETOL (PR) weight-based dosing (WBD) in previous interferon/ribavirin HCV treatment failures; early results of the EPIC3 trial.	Poynard T et al. Hepatology 2004, (55th Annual Meeting American Association Study Liver Disorders (AASLD), Boston, MA, 40(4), supplement 1, abstract 170
Bergmann 2007	(gamma)-glutamyltransferase and rapid virological response as predictors of successful treatment with experimental or standard peginterferon-(alpha)-2b in chronic hepatitis C non-responders.	Bergmann JF et al. Liver International 2007; 27:1217-25
Goncales 2006	Weight-based combination therapy for peginterferon alfa-2b and ribavirin for naive, relapser and non-responder patients with chronic hepatitis C.	Goncales FL, et al. The Brazilian Journal of Infectious Diseases 2006; 10(5):311-16
Hasan 2004	Peginterferon alpha-2b plus ribavirin with or without amantidine for the treatment of non-responders to standard interferon and ribavirin.	Hasan F ,et al. Antiviral Therapy 2004; 9:499-503
Mathew 2006	Improvement in quality of life measures in patients with refractory hepatitis C, responding to re-treatment with Pegylated interferon alpha -2b and ribavirin.	Mathew A, et al. Health and quality of life outcomes 2006 [electronic resource] 4:30.
	Sustained virologic response to pegylated interferon (alpha)-2b and ribavirin in chronic hepatitis C refractory to prior treatment.	Mathew A, et al. Digestive Diseases and Sciences 2006; 51:1956-61
Maynard 2006	Amantadine triple therapy for non-responder hepatitis C patients. Clues for controversies (ANRS HC 03 BITRI).	Maynard M, et al. Journal of Hepatology 2006; 44:484-90
Moucari 2007	High predictive value of early viral kinetics in retreatment with peginterferon and ribavirin of chronic hepatitis C patients non-responders to standard combination therapy.	Moucari R, et al. Journal of Hepatology 2007; 46:596-604

Myers 2004	Pegylated interferon alpha 2b and ribavirin in HIV/hepatitis C virus-co-infected non-responders and relapsers to IFN-based therapy.	Myers RP, et al. AIDS 2004; 18:75–9
Taliani 2006	Pegylated interferon alfa-2b plus ribavirin in the retreatment of interferon-ribavirin nonresponder patients.	Taliani G, et al. Gastroenterology 2006; 130:1098-106

8. Results of Trials

The key results are summarised in the table below.

Sustained virological response (SVR) reported in the studies[a]

Study	N	SVR n (%)	CI[b]
P02370	1,336	303 (22.7)	99% CI (19.7-25.6)
Australian subgroup	76	26 (34.2)	NR
Non-Australian subgroup	1,265	256 (20.2)	NR
Goncales 2006	66	31 (46.9)	NR
Moucari 2007	154	44 (28.6)	NR
Taliani 2006	141	28 (19.6)	NR
Bergmann 2007	30	11 (36.7)	NR
Hasan 2004	21	1 (4.8)	NR
Mathew 2006	72	15 (20.8)	NR
Maynard 2006	99	16 (16.2)	NR
Myers 2004	32	5 (15.6)	NR

[a] defined as undetectable plasma HCV-RNA after 24 weeks follow up post treatment; [b] standard deviations or standard error are not reported in the published reports; CI = confidence interval; NR = not reported; SVR = sustained virological response

Twenty-two percent of subjects in study P02370 achieved a SVR, which the submission attributed to peginterferon α-2b and ribavirin combination therapy. SVR varied between 4.8% and 46.9% across the studies.

In study P02370, 97.2% (1,304) of subjects experienced a treatment emergent adverse event (AE) and 8.8% (118) of subjects reported a serious adverse event (SAE). 6.6% (89) of subjects discontinued treatment due to adverse events. The following reported adverse events had the greatest incidence: headache (43%); pyrexia (41%); myalgia (34%); fatigue (32%); nausea (25%); asthenia (24%); insomnia (23%); neutropenia (22%); chills (21%); and influenza-like illness (20%). The most frequently reported SAEs were: pneumonia (0.6%); neutropenia (0.4%), chest pain (0.4%), and suicidal ideation (0.4%). Despite the lack of a safety comparison with standard care, it was clear that most patients will experience adverse events when receiving peginterferon α-2b and ribavirin combination therapy.

For PBAC's comments on these trials, see Recommendations and Reasons.

9. Clinical Claim

The submission claimed peginterferon α-2b and ribavirin combination therapy as superior in terms of comparative effectiveness and inferior in terms of comparative safety over standard care.

For PBAC's view, see Recommendations and Reasons.

10. Economic Analysis

The submission presented a stepped economic evaluation. The economic evaluation took a health care sector perspective and utilised a Markov model, constructed using TreeAge Pro

2007 Suite®. A cohort expected value analysis was employed. The model had a 53-year duration (lifetime), with an annual cycle length.

The model compared standard care or peginterferon α-2b and ribavirin combination therapy for the treatment of patients with CHC and moderate to severe fibrosis who have failed a previous course of interferon based therapy, simulating the course of the disease using fifteen health states. Patients entered the model in either the viral positive moderate or cirrhotic stage. Patients with mild fibrosis were not included in the model. As in the previous submissions, the model was structured so that only patients who were treated can become viral negative. Patients transition from viral positive to viral negative status in the first cycle only.

Patients accrued costs and quality adjusted life years (QALYs) in each cycle of the model until death. QALYs were calculated from the utility weights for each health state. Progression through the health states was dependant upon viral status and disease stage. A disutility weighting was applied in the first cycle of the model to account for the reduced quality of life while undergoing peginterferon α-2b and ribavirin combination therapy. The utility values and transition probabilities applied in the model were subject to uncertainty. The costs of drug therapy were incurred in the first cycle of the Markov model only. In subsequent cycles, the costs incurred relate to the cost of management of CHC only. The resources included were drug costs and non-drug costs (outpatient visit, FBE, ALT, TSH, HCV genotype assay, pregnancy test, and PCR tests).

The incremental cost/extra QALY gained was estimated to be less than $15,000.

Inspection of the expanded report in the TreeAge model for each treatment arm by cycle indicated that the main contributors to the overall incremental cost between the treatment arms were: (i) the costs of peginterferon α-2b and ribavirin combination therapy; (ii) the costs associated with hepatocellular carcinoma; and (iii) the costs associated with the management of post-liver transplant. The incremental QALY was mainly driven by: (i) the disutility associated with peginterferon α-2b and ribavirin combination therapy during the first year of the model; (ii) the utility associated with viral positive and viral negative status; and (iii) the difference in mortality, which was largely due to the difference in deaths due to liver disease between the treatment arms.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated to be less than 10,000 in Year 3. The submission suggested that the treatment of CHC with peginterferon and ribavirin combination therapies had reached a maximum due to capacity constraints in the health system in Australia for the treatment of patients with CHC. Financial estimates were based on the assumption that services for the treatment of CHC would be expanded in line with the recommendations in the Hepatitis C Virus Projections Working Group 2006 (HCVPWG) report.

The financial cost per year to the PBS was estimated to be in the range of $30-60 million in Year 1 beyond the current level of use for peginterferon and ribavirin combination therapies, including but not limited to, the combination for which listing is sought.

12. Recommendation and Reasons

The PBAC recommended the listing of ribavirin and peginterferon alfa-2b on the PBS for the treatment of chronic hepatitis C in patients who have failed one prior attempt at interferon based therapies (non-pegylated or pegylated) on the basis of acceptable cost-effectiveness compared with usual standard care. The PBAC noted that the requested price was higher than the current price, but considered that although the cost-effectiveness of re-treatment was acceptable at the higher price, the weighted average price proposed by the sponsor in its pre-PBAC response relies on acceptance of the assumption that a pre-determined proportion of hepatitis C patients will be eligible for initial treatment and for re-treatment. These proportions cannot be monitored in the future due to the operation of S100 listing and an as such, the pricing strategy proposed by the submission presents some financial risk to the government.

The PBAC agreed that standard care was the appropriate comparator but that this assumes that the health system is not subject to capacity constraints. However, the PBAC noted that capacity constraints in the delivery of care may limit the uptake of hepatitis C treatment and that such constraints would impact on the calculation of costs to the Government arising from the extension of treatment to include patients who have failed previous therapy. Capacity restraints may also impact on clinicians between faced with the choice of treating a patient with one treatment failure or treating a treatment naïve patient.

The PBAC agreed that although there is some uncertainty in relation to the design of the studies presented in the submission (non-comparative, open-label, non consecutive selection of cases) and differences in the baseline characteristics between the Australian cases in study P02370 and the population for whom PBS listing is sought, the evidence provided supports the claim that peginterferon alfa-2b and ribavirin combination therapy is superior in terms of comparative effectiveness and inferior in terms of comparative safety over standard care. The PBAC considered that the method applied to stratify the proportion of patients with a SVR for Australian cases in study P02370 was appropriate provided that fibrosis stage is unrelated to genotype and fibrosis stage is equally distributed across the genotypes.

The PBAC noted that the costs of managing and treating adverse events associated with peginterferon alfa-2b and ribavirin combination therapy were not included in the Markov model and therefore treatment costs may be underestimated. Both the quality of evidence used to derive the SVR rates and the exclusion of costs for treating adverse events limit the validity of the ICER. The model assumptions were considered reasonable but most sensitive to model duration (53 years). The overall cost-effectiveness was nonetheless acceptable.

Recommendation

RIBAVIRIN capsules 200 mg, (all the currently listed various quantities and the new recommended pack size of 196 capsules) and PEGINTERFERON ALFA-2b, single use injection pens containing powder for injection in 50, 80, 100, 120 and 150 micrograms.

Restriction :	Section 100 Private hospital authority required
	Notes:
	Caution:

Treatment with peginterferon alfa has been associated with depression and suicide in some patients. Patients with a history of suicidal ideation or depressive illness should be warned of the risks. Psychiatric status during therapy should be monitored.
Caution:
Ribavirin is a category X drug and must not be given to pregnant women. Pregnancy in female patients or in the partners of male patients must be avoided during treatment and during the 6 months period after cessation of treatment.

Patients naïve to interferon based therapies (non-pegylated or pegylated)
Treatment, managed by an accredited treatment centre, of chronic hepatitis C in patients 18 years or older who have compensated liver disease and who have received no prior interferon alfa or peginterferon alfa treatment for hepatitis C and who satisfy all of the following criteria:
(1) Documented chronic hepatitis C infection (repeatedly anti-HCV positive and HCV RNA positive);
(2) Female patients of child-bearing age are not pregnant, not breast-feeding, and both patient and their partner are using effective forms of contraception (one for each partner). Male patients and their partners are using effective forms of contraception (one for each partner). Female partners of male patients are not pregnant.
For patients with genotype 2 or 3 hepatitis C without hepatic cirrhosis or bridging fibrosis, the treatment course is limited to 24 weeks. For hepatitis C patients with genotype 1, 4, 5 or 6 and those genotype 2 or 3 patients with hepatic cirrhosis or bridging fibrosis, the treatment course is limited to 48 weeks.
Patients with genotype 1, 4, 5 or 6 who are eligible for 48 weeks of treatment may only continue treatment after the first 12 weeks if the result of an HCV RNA quantitative assay (performed at the same laboratory using the same test) shows that the plasma HCV RNA has become undetectable or the viral load has decreased by at least a 2 log drop. (An HCV RNA assay at week 12 is unnecessary for genotype 2 and 3 patients because of the high likelihood of early viral response by week 12).
Patients with genotype 1, 4, 5 or 6 who are viral positive at week 12 but have attained at least a 2 log drop in viral load may only continue treatment after the first 24 weeks of treatment if plasma HCV RNA is not detectable by an HCV RNA qualitative assay at week 24. Similarly, genotype 2 or 3 patients with hepatic cirrhosis or bridging fibrosis may only continue treatment after the first 24 weeks if plasma HCV RNA is not detectable by an HCV RNA qualitative assay at week 24. An HCV RNA qualitative assay at week 24 is unnecessary for

	those patients with genotype 1, 4, 5 or 6 who became viral negative at week 12. Note: Treatment centres are required to have access to the following appropriate specialist facilities for the provision of clinical support services for hepatitis C: (a) a nurse educator/counsellor for patients; and (b) 24 hour access by patients to medical advice; and (c) an established liver clinic; and (d) facilities for safe liver biopsy.
Restriction:	Section 100 Private hospital authority Patients who have failed one prior attempt at interferon based therapies (non-pegylated or pegylated) Treatment, managed by an accredited treatment centre, of chronic hepatitis C in patients 18 years or older who have compensated liver disease and who have received no more than one prior treatment with interferon alfa or peginterferon alfa for hepatitis C and who satisfy all of the following criteria: (1) Documented chronic hepatitis C infection (repeatedly anti-HCV positive and HCV RNA positive); (2) Female patients of child-bearing age are not pregnant, not breast-feeding, and both patient and their partner are using effective forms of contraception (one for each partner). Male patients and their partners are using effective forms of contraception (one for each partner). Female partners of male patients are not pregnant. The treatment course is limited to 48 weeks. Patients may only continue treatment after the first 12 weeks of treatment if plasma HCV RNA is not detectable by an HCV RNA qualitative assay at week 12. Note: Treatment centres are required to have access to the following appropriate specialist facilities for the provision of clinical support services for hepatitis C: (a) a nurse educator/counsellor for patients; and (b) 24 hour access by patients to medical advice; and (c) an established liver clinic; and (d) facilities for safe liver biopsy.
Pack size:	1 (with the capsule + syringe pack combinations to be the same as those listed for treatment naïve patients, together with the newly recommended pack containing containing 196 x 200 mg capsules and 4 x single use injection pens containing peginterferon alfa-2b powder for injection 150 micrograms with diluent)

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The sponsor chose not to comment.