PUBLIC SUMMARY DOCUMENT
Product: PEGINTERFERON ALFA-2b, Single use injection pens containing powder for injection in vials of 50, 80, 100, 120 and 150 micrograms and RIBAVIRIN capsules 200 mg, (all pack sizes), Pegatron®, and PEGINTERFERON ALFA-2b, single use injection pens containing powder for injection in vials of 50, 80, 100, 120 and 150 micrograms, PEG-Intron Redipen®,
Sponsor: Schering-Plough Pty Limited
Date of PBAC Consideration: November 2005

1. Purpose of Application
The submission requested the PBAC consider the deletion of the requirement for a liver biopsy in the restrictions for Pegatron and PEG-Intron in order to establish eligibility for PBS subsidised treatment for hepatitis C.

2. Background
At the November 2004 PBAC meeting, the Minister requested the PBAC undertake a review of the current restrictions governing access to PBS-subsidised Hepatitis C therapies in accordance with its usual approach to considering such matters. Relevant pharmaceutical companies were requested to submit applications requesting deletion of the requirement for a liver biopsy.

3. Registration Status
PEG-Intron was registered on 19 November 2001 for the treatment of chronic hepatitis C in patients who have received no prior interferon therapy. Patients must be 18 years of age or older and have compensated liver disease. The optimal treatment for chronic hepatitis C is considered to be the administration of interferon alfa-2b with ribavirin.

The TGA granted approval for the registration of Pegatron Combination Therapy on 16 April 2002 for:

> The treatment of chronic hepatitis C in patients who have not previously received interferon treatment (see Clinical Trials). Patients must be 18 years of age or older and have compensated liver disease.
>
> Interferon alfa monotherapy (including Peg-Intron) is indicated mainly in case of intolerance or contraindication to ribavirin. Rebetol capsules must not be used alone because ribavirin is not effective as monotherapy in the treatment of hepatitis C.

4. Listing Requested and PBAC's View
As currently listed in the Schedule of Pharmaceutical Benefits, but with the requirement for liver biopsy removed.

5. Clinical Place for the Proposed Therapy
Removal of the requirement for liver biopsy would allow treatment to be initiated at an earlier stage of the disease.

6. Comparator
The submission nominated Pegatron therapy in patients with stage F1/A2-A3, F2, F3 and F4 fibrosis (who are currently eligible for PBS-subsidised treatment) as the comparator. This was accepted as appropriate by the PBAC.

7. Clinical Trials

The submission presented no new data. The main evidence in this submission was a series of *post hoc* sub-group analyses of the single key randomised, open-label trial (C/I98-580) comparing peginterferon α-2b plus ribavirin with interferon α-2b plus ribavirin in chronic hepatitis C (CHC) patients over a 1-year period (48-week treatment period and 24-week follow-up period). The outcome measure was sustained virological response (SVR) in patients with mild fibrosis (F0-F1/A0-A1) compared to those with moderate to severe fibrosis (F1/A2-A3, F2-F4) in the treatment arm of peginterferon α-2b (1.5μg/kg QW) plus ribavirin (800mg/day). Three supportive randomised trials were also included as evidence of effectiveness in treating patients with mild CHC.

Summary of trials included in the submission

Trial/author	Title/source
Key randomised trial of peginterferon α-2b plus ribavirin	
C/I98-580 Manns (2001) (Primary publication)	Comparison of PEG-Interferon alpha-2b (PEG-Intron, SCH 54031) plus REBETOL (SCH 18908) vs Interferon alpha-2b (Intron A, SCH 30500) plus REBETOL for treatment of chronic hepatitis C in previously untreated adult subjects. Peginterferon alpha-2b plus ribavirin compared with interferon alpha-2b plus ribavirin for initial treatment of chronic hepatitis C: A randomised trial. Lancet 2001; 358 (9286):958-65.
Supportive RCTs of mild hepatitis C treatment	
Mangia (2004)	Viral clearance in HCV viraemic patients with normal alanine aminotransferase after combination therapy: A controlled, open-labelled study. Aliment Pharmacol Ther 2004; 19:331-7.
Verbaan (2002)	High sustained response rate in patients with histologically mild (low grade and stage) chronic hepatitis C infection. A randomized, double blind, placebo controlled trial of interferon alpha-2b with and without ribavirin. Eur J Gastroenterol & Hepatol 2002; 14:627-33.
Wright (2005a) Wright (to be published in 2005)	Treatment of histologically mild hepatitis C virus infection with interferon and ribavirin: A multicentre randomized controlled trial. Journal of Viral Hepatitis 2005; 12: 58-66. NCCHTA Project No:95/24/03. Health benefits of anti-viral therapy for mild chronic hepatitis C: Randomised control trial and economic evaluation.

ALT, alanine aminotransferase; IFN, interferon; MU, million units; RBV, ribavirin; TIW, three times a week

8. Results of Trials

The results of the key trial are summarised in the table below.

Sustained Virological Response (SVR) rates in PEG1.5/R treatment arm: response by ITT population of key trial C/198-580 at end of treatment and end of follow-up (carry forward analysis)

HCV genotype	End of treatment SVR rate – n/N (%)	End of follow-up (carry forward) SVR rate – n/N (%)
All subjects	333/511 (65%)	274/511 (54%)
1	188/348 (54%)	145/348 (42%)
2/3	136/147 (93%)	121/147 (82%)
4/5/6	9/16 (56%)	8/16 (50%)

SVR rates in ITT treatment arm PEG1.5/R and high-dose sub-group PEG1.5/R>10.6 of key trial C/I98-580 - response by genotype

Genotype	PEG1.5/R treatment arm		PEG1.5/R>10.6 sub-group		
	SVR rate – n/N (%)		SVR rate – n/N (%)		
All	274/511 (53.6%)		114/188 (60.6%)		
G2/3	121/147 (82.3%)		51/58 (87.9%)		
non-G2/3	153/364 (42.0%)		63/130 (48.5%)		

SVR = sustained virologic response

The submission claimed that there was no significant difference in SVR rates after peginterferon α-2b and ribavirin treatment between the currently ineligible and eligible patients in the PEG1.5/R>10.6 sub-group, regardless of the genotype. The PBAC noted that this claim was based on a secondary sub-group analysis that could not be replicated during the evaluation as the data describing the stages of fibrosis in the patients in the remainder of the overall group were not supplied. It was therefore also not possible to carry out a verification of the validity of the sub-group analyses, such as a test for interaction.

The PBAC noted that although the data presented might not represent the strongest basis for making a recommendation with respect to the change in restriction sought, it was nevertheless reassuring that the additional group do not appear to have a reduced SVR to treatment and it seemed reasonable to apply the Intention to Treat (ITT) results of the trial to both this group and the group currently being treated following liver biopsy.

9. Clinical Claim

The submission described peginterferon α-2b and ribavirin treatment in patients with no or mild hepatitis C as being no worse than treatment in patients with moderate to severe hepatitis C in terms of effectiveness and toxicity.

See Recommendations and Reasons for the PBAC's view.

10. Economic Analysis

A modelled economic evaluation was presented adopting a cost-utility approach. The type of model used was a Markov model.

The base case modelled incremental discounted cost/extra discounted QALY gained was between $15,000 - $45,000. The submission also presented a number of sensitivity analyses.

For the PBAC's view of the economic analysis, see Recommendations and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated up to 10,000 patients in Year 5 of listing assuming constant liver clinic capacity.

The estimated financial net cost/year to the PBS was up to $10 to $30 million in Year 5 of listing assuming constant liver clinic capacity.

The PBAC considered that there is likely to be an increase in the number of people treated once the requirement of the liver biopsy was removed. There was uncertainty in regard to what the exact number would be because liver biopsy was not the only rate-limiting step in the current restriction. There are other factors which would continue to limit the number of patients who receive therapy, including the requirement that patients are managed within

liver clinics. The PBAC remained firmly of the view that this requirement should be retained in the restriction to maintain compliance at the rates reported in the submission.

12. Recommendation and Reasons

The PBAC recommended a change to the restrictions for ribavirin with peginterferon alfa-2b to remove the requirement for liver biopsy to establish eligibility for PBS subsidised treatment for hepatitis C. The Committee considered that the evidence presented in the submission indicated that peginterferon alfa with ribavirin has similar effectiveness in patients regardless of their stage of fibrosis when treated, and that the requirement for liver biopsy to determine disease severity should not be required. The PBAC thus agreed that the extent of liver damage does not appear to be an important treatment effect modifier.

The PBAC accepted the conclusions from the modelled evaluation that treating hepatitis C patients earlier would be associated with an increase in both costs and outcomes per patient and that the incremental cost per extra QALY gained was acceptable and robust to important sources of uncertainty examined in the sensitivity analyses.

The PBAC recommended that this change to the restriction should apply to all peginterferon alfa with/without ribavirin products listed on the PBS for the treatment of hepatitis C.

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