PUBLIC SUMMARY DOCUMENT
Product: RIBAVIRIN, tablets, 200 mg, (112 tablets, 140 tablets and 168 tablets) and PEGINTERFERON ALFA-2a, pre-filled syringes, 180 micrograms and RIBAVIRIN, tablets, 200 mg, (168 tablets) and PEGINTERFERON ALFA-2a, pre-filled syringes 135 micrograms, Pegasys RBV®
Sponsor: Roche Products Pty Ltd
Date of PBAC Consideration: July 2010

1. Purpose of Application

To extend the Section 100 listing for the treatment of chronic hepatitis C (CHC) to include patients who have failed one prior attempt at interferon based therapies (non-pegylated or pegylated).

Highly Specialised Drugs (HSD) are medicines for the treatment of chronic conditions that, because of their clinical use or other special features, are restricted to supply through public or private hospitals that have appropriate specialist facilities. To prescribe these medicines under the PBS, medical practitioners must be affiliated with these specialist public hospital units. A medical practitioner or non-specialist hospital medical practitioner, who is not affiliated with the public hospital, may only prescribe HSD to provide maintenance therapy under the guidance of the treating specialist affiliated with the public hospital.

2. Background

At its June 2003 meeting, the PBAC recommended a Section 100 listing for Pegasys RBV for treatment of chronic hepatitis C in patients 18 years of age with compensated liver disease and who have not received prior interferon based therapies who satisfy certain criteria on a cost-minimisation basis compared with ribavirin and peginterferon alfa-2b (Pegatron®). Listing was effective from 1 November 2003.

At the July 2009 meeting, the PBAC rejected a minor submission to extend the listing of Pegasys RBV to include treatment of patients with chronic hepatitis C who have failed one prior attempt at interferon based therapy.

The PBAC considered that both the clinical and economic data to support the request required evaluation, and determined that the request required a major submission.

3. Registration Status

Peginterferon alfa-2a was TGA registered on 31 March 2009 for the following indications:

- Peginterferon alfa-2a monotherapy is indicated for the treatment chronic hepatitis C in patients who have received no prior interferon therapy (treatment naïve patients).
- The combination of peginterferon alfa-2a and ribavirin is indicated for the treatment of chronic hepatitis C in treatment naïve patients and patients who have failed previous treatment with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin.

4. Listing Requested and PBAC's View

Section 100 (Highly Specialised Drugs Program)
Private hospital authority required
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.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

The proposed extension to the listing for Pegasys RBV would provide an additional treatment option for patients with chronic hepatitis C who have failed one previous course of therapy with interferon alfa (non-pegylated or pegylated) with or without ribavirin.

6. Comparator

The submission appropriately nominated peginterferon-alfa-2b plus RBV as the comparator.

7. Clinical Trials

The submission defined four subgroups of eligible patients. The basis of the comparison in each subgroup is outlined below.

1. Non-responders
    i) Previous pegylated interferon plus ribavirin therapy: a comparison of two single arms from different randomised trials (REPEAT, METRO) and one case series for Pegasys RBV (HALT-C); and a case series for Pegatron CT (EPIC-3).
    ii) Previous standard interferon plus ribavirin therapy: one direct randomised trial comparing Pegasys RBV with Pegatron CT (Scotto 2008).

A non-responder was defined as a patient who did not achieve viral suppression (serum hepatitis C virus ribonucleic acid, HCV RNA, remained detectable) despite a minimum of 12 weeks of treatment.

2. Relapsers
    i) Previous pegylated interferon plus ribavirin therapy: an indirect comparison of one case series for Pegasys RBV (WV16143) with a case series for Pegatron CT (EPIC-3).
    ii) Previous standard interferon plus ribavirin therapy: no studies of the effectiveness of Pegasys RBV in this patient subgroup were located; a comparison with Pegatron CT could not be performed.

Scotto (2008) has limited relevance as this study involved prior failure with standard interferon plus ribavirin and not many Australian patients receive standard therapy. Further,

the non-comparative studies are more relevant in the Australian context as most non-responders and relapsers will have failed peginterferon plus ribavirin.

The key trials and non-comparative studies published at the time of submission are shown in the table below:

Trial ID/First author	Protocol title/ Publication title	Publication citation
Direct randomised trial – Pegasys RBV vs Pegatron CT		
Scotto 2008 (NR after IFN + RBV) Scotto G et al 2008	Peg-interferon alpha-2a versus peg-interferon alpha-2b in non-responders with HCV active chronic hepatitis: a pilot study.	J Interferon Cytokine Res 2008; 28(10):623-629.
Scotto G et al 2008	Early and sustained virological response in non-responders with chronic hepatitis C: a randomized open-label study of pegylated interferon-alpha-2a versus pegylated interferon-alpha-2b.	Drugs 2008; 68(6):791-801.
Pegasys RBV		
Single arms of randomised trials		
REPEAT (NR after PEG-IFN + RBV) Jensen DM et al 2009	Re-treatment of patients with chronic hepatitis C who do not respond to peginterferon-α2b.	Ann Intern Med 2009; 150(8):528-540.
Jensen DM and Marcellin P 2005	Rationale and design of the REPEAT study: a phase III, randomized, clinical trial of peginterferon alfa-2a (40kDa) plus ribavirin in non-responders to peginterferon alfa-2b (12kDa) plus ribavirin.	Eur J Gastroenterol Hepatol 2005; 17(9):899-904.
METRO (NR after PEG-IFN + RBV) Rustgi VK et al 2009	Merimepodib, pegylated interferon, and ribavirin in genotype 1 chronic hepatitis C pegylated interferon and ribavirin non-responders.	Hepatology 2009; 50(6):1719-1726.
Non-comparative studies		
HALT-C (NR after PEG-IFN or IFN ± RBV) Bonkovsky HL et al 2007	Health-related quality of life in patients with chronic hepatitis C and advanced fibrosis.	Journal of Hepatology 2007; 46(3):420-431.
Everson GT et al 2006	Impact of disease severity on outcome of antiviral therapy for chronic hepatitis C: lessons from the HALT-C trial.	Hepatology 2006; 44(6):1675-1684.
Lee MW et al 2004	Evolution of the HALT-C trial: pegylated interferon as maintenance therapy for chronic hepatitis C in previous interferon nonresponders.	Control Clin Trials 2004; 25(5):472-492.
Shiffman ML et al 2007	Impact of reducing peginterferon alfa-2a and ribavirin dose during retreatment in patients with chronic hepatitis C.	Gastroenterology 2007; 132(1):103-112.
Shiffman ML et al 2004	Peginterferon alfa-2a and ribavirin in patients with chronic hepatitis C who have failed prior treatment.	Gastroenterology 2004;126(4):1015-1023.

Trial ID/First author	Protocol title/ Publication title	Publication citation
WV16143 (Relapsers after PEG-IFN + RBV) Berg C et al 2006	Re-treatment of chronic hepatitis C patients after relapse: efficacy of peginterferon-alpha-2a (40kDa) and ribavirin.	J Viral Hepatitis 2006; 13(7):435-440.
Pegatron CT		
Single arms of randomised trials		
Mathewl 2006 (NR and relapsers after IFN ± RBV) Mathew A et al 2006	Sustained viral response to pegylated interferon α-2b and ribavirin in chronic hepatitis C refractory to prior treatment.	Dig Dis Sci 2006; 51(11):1956-1961.
Mathew A et al 2006	Improvement in quality of life measures in patients with refractory hepatitis C, responding to re-treatment with pegylated interferon alpha-2b and ribavirin.	Health Qual Life Outcomes 2006; 4, article number 30.
Bergmann JF et al 2007 (NR and relapsers after IFN ± RBV)	γ-glutamyltransferase and rapid virological response as predictors of successful treatment with experimental or standard peginterferon-α-2b in chronic hepatitis C non-responders.	Liver Int 2007; 27(9):1217-1225.
Non-comparative studies		
EPIC-3 Poynard T et al 2009 (NR or relapsers after IFN +RBV or PEG-IFN + RBV)	Peginterferon alpha-2b and ribavirin: effective in patients with hepatitis C who failed interferon alfa/ribavirin therapy.	Gastroenterology 2009;136(5):1618-1628.
Carnicer F et al 2005 (NR and relapsers after IFN ± RBV)	Treatment with pegylated interferon alpha 2b and ribavirin in patients unresponsive to previous treatments with standard interferon as monotherapy or combined with ribavirin.	Rev Esp Enferm Dig 2005; 97(5):306-316.
Goncales Jr FL et al 2006 (Treatment naive and NR or relapsers after IFN + RBV)	Weight-based combination therapy with peginterferon α-2b and ribavirin for naive, relapser and non-responder patients with chronic hepatitis C.	Braz J Infect Dis 2006; 10(5):311-316.
Moucari R et al 2007 (NR and relapsers after IFN + RBV)	High predictive value of early viral kinetics in re-treatment with peginterferon and ribavirin of chronic hepatitis C patients non-responders to standard combination therapy.	J Hepatol 2007; 46(4): 596-604.
Myers RP et al 2004 (HIV/HCV co-infected NR and relapsers after IFN ± RBV)	Pegylated interferon alpha 2b and ribavirin in HIV/hepatitis C virus-co-infected non-responders and relapsers to IFN-based therapy.	AIDS 2004; 18(1):75-79.
Supportive trials and studies		
Meta-analysis Pegasys RBV vs Pegatron CT		
Awad T et al 2010 (Meta-analysis mainly treatment-naïve)	Peginterferon alpha-2a is associated with higher sustained virological response than pegatron alfa-2b in chronic hepatitis C: systematic review of randomized trials.	Hepatology 2010; 51(4):1176-1184.

HCV=hepatitis C virus; HIV=human immunodeficiency virus; IFN=standard interferon; NR=non-responder; PEG-IFN=pegylated interferon; RBV=ribavirin

8. Results of Trials

As peginterferon alfa (either 2a or 2b) plus ribavirin is the standard of care for treatment naïve CHC patients in Australia, patients who have failed on or relapsed after prior

peginterferon alfa plus ribavirin are likely to represent the most common subgroup of patients eligible for PBS funded re-treatment.

Sustained virological response (SVR) was the primary outcome in the direct randomised trial and the majority of the studies presented in the submission. It was consistently defined as undetectable serum HCV RNA at week 72 (24 weeks after the end of treatment). On the basis of the results for SVR in the direct randomised trial (Scotto 2008), including patients who failed to respond to prior therapy with standard interferon plus ribavirin, the submission concluded that Pegasys RBV for 48 weeks is no worse than Pegatron CT for 48 weeks in terms of effectiveness in the treatment of previously treated CHC in this patient subgroup. As neither Scotto 2008 nor the submission specified a non-inferiority margin, this claim was based on a finding of no statistical difference in treatment effect between the two treatment arms.

The submission noted from the results for SVR from Scotto 2008 and the non-comparative studies, for each of the four patient subgroups (grouped by genotype, since this is a well-established treatment modifier) that the majority of point estimates for SVR rates were higher for Pegasys RBV than for Pegatron CT; in particular, the point estimates were higher for patients with prior peginterferon alfa treatment failure and HCV genotype 1, who represent the most commonly retreated patients in current Australian practice.

The main adverse events (AEs) observed in the direct randomised trial (Scotto 2008) are summarised as follows:

The incidence and severity of adverse events were similar in both peginterferon groups. Four in the Pegasys RBV arm (N=71) and three in the Pegatron CT arm (N=72), experienced severe psychiatric disorders resulting in therapy discontinuation. A further treatment discontinuation was necessary in five patients in the Pegasys RBV arm and three in the Pegatron CT arm due to marked weight loss. One patient in each arm discontinued therapy because of severe headaches and one in the Pegatron CT arm for continuous fever.

Among the remaining patients, an influenza-like syndrome was reported in 42 patients in the Pegasys RBV arm and 44 patients in the Pegatron CT arm. Anaemia (Hb < 10 g/dL) was observed in nine Pegasys RBV and in ten Pegatron CT patients. Thrombocytopenia ($<75{,}000/mm^3$) was reported in 13 patients in the Pegasys RBV arm and 10 in the Pegatron CT arm. Leucopenia ($<3{,}000/mm^3$) was observed in ten Pegasys RBV and seven Pegatron CT patients.

Six patients in the Pegasys RBV group and three in the Pegatron CT group with leucopenia and/or thrombocytopenia required a dose reduction of pegylated interferon, while five subjects in the Pegasys RBV group and three in the Pegatron CT group required a reduction in the dose of ribavirin. No pathological alterations in creatinine and uric acid serum levels were reported, but in all subjects a moderate hyperbilirubinaemia associated with ribavirin-induced haemolysis was observed.

Scotto (2008) was insufficiently powered to reliably assess the relative safety of Pegasys RBV versus Pegatron CT. There were no comparative safety data in special patient subgroups, such as patients with HIV/HCV co-infection, and patients with renal impairment.

9. Clinical Claim

The submission described Pegasys RBV for 48 weeks as non-inferior, in terms of both comparative effectiveness and comparative safety, to Pegatron CT for 48 weeks for re-treatment of CHC patients who have failed one prior attempt at interferon based therapies.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost minimisation analysis. The base-case analysis presented the average cost per patient of a course of treatment with Pegasys RBV and Pegatron CT, accounting for the proportion of patients who discontinue treatment at week 12, and assuming those continuing treatment receive a total of 48 weeks of therapy.

The equi-effective doses were considered to be those recommended in the respective Product Information (PI) documents for prior treatment failure. The economic evaluation used the doses recommended in the relevant PI's, and a treatment duration of 48 weeks for all patients. However, the recommended duration of treatment for patients with genotype 1 or 4 infection in the Pegasys RBV PI is up to 72 weeks.

Drug acquisition costs were the only costs included in the cost-minimisation analysis.

The submission's cost minimisation analysis indicated that Pegasys RBV was cost saving compared with Pegatron CT for the treatment of CHC patients who had failed prior interferon based therapy. The evaluation considered that there was considerable uncertainty in the proportion of patients who would meet the continuation criterion and receive the full 48 week course of therapy; the magnitude of any saving was largely dependent on this proportion.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients/year was estimated by the submission to be less than 10,000 in Year 5. The financial savings per year to the PBS were estimated by the submission to be less than $10 million in Year 5. The submission's estimates were considered uncertain.

12. Recommendation and Reasons

The PBAC recommended the Section 100 Highly Specialised Drug listing of peginterferon alfa-2a with ribavirin (Pegasys RBV) be extended to include the treatment of patients with hepatitis C who have failed one prior attempt at interferon based therapies (non-pegylated or pegylated). Listing was recommended on a cost-minimisation basis with peginterferon alfa-2b with ribavirin (Pegatron), for 48 weeks of treatment.

The PBAC noted that the evidence for the comparative effectiveness of Pegasys RBV versus Pegatron CT for a treatment course of 48 weeks in genotype 1, 2, 3 and 4 infection, in both non-responders and relapsers to pegylated interferon plus ribavirin, who are likely to represent the majority of re-treated patients in Australia, is derived from non-comparative studies, with considerable potential for confounding and major biases. Nonetheless, the Committee accepted that it was very unlikely that Pegasys RBV would be less effective than Pegatron CT.

The PBAC further considered that the comparative evidence to support the claim that Pegasys RBV is non-inferior to Pegatron in terms of safety in chronic hepatitis C patients who have previously failed prior non-pegylated interferon based therapy is equally limited. However, there are no biological grounds that would be expected to result in differences and the PBAC agree that the submissions claim that Pegasys RBV is non-inferior in terms of safety to Pegatron CT is reasonable.

The PBAC noted that at the prices proposed in the submission, Pegasys RBV will be cost-saving compared to Pegatron CT. This is because the doses of ribavirin in the Pegasys RBV regimen, and the doses of both peginterferon alfa-2b and ribavirin in the Pegatron CT regimen, are dependent on patient bodyweight. The distribution of bodyweight in the eligible population influences the outcome of the cost-minimisation analysis, as the incremental cost of Pegatron CT versus Pegasys RBV increases with increasing bodyweight, and it is apparent that the proportion of patients with higher body weight utilising Pegatron CT is higher than was estimated at the time of listing. The PBAC requested that the Minister and Pricing Authority be advised that it is appropriate to review the prices of Pegatron across all indications to align them with the lower prices of Pegasys.

Recommendation:
RIBAVIRIN, tablets, 200 mg, (112 tablets, 140 tablets and 168 tablets) and PEGINTERFERON ALFA-2a, pre-filled syringes, 180 micrograms and
RIBAVIRIN, tablets, 200 mg, (168 tablets) and PEGINTERFERON ALFA-2a, pre-filled syringes 135 micrograms, Pegasys RBV®

Extend the current restriction to include:

Restriction:

Highly Specialised Drugs Program
Authority Required (STREAMLINED)
Private hospital authority required
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.

Maximum quantity: 2
Repeats: 5

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 had no further comment.