**PUBLIC SUMMARY DOCUMENT**
**Product:** PEGINTERFERON ALFA-2a, injection, single use pre-filled syringe, 135 micrograms and 180 micrograms, Pegasys®
**Sponsor:** Roche Products Pty Ltd
**Date of PBAC Consideration:** November 2005

## 1. Purpose of Application

This submission sought to extend the current Section 100 listing for peginterferon alfa-2a to include the treatment of patients with chronic hepatitis B.

## 2. Background

At the July 2004 meeting the PBAC recommended the Section 100 listing for peginterferon alfa-2a for the treatment of chronic hepatitis C in patients 18 years or older who have compensated liver disease and who have received no prior interferon alfa therapy and have a contraindication to ribavirin, who satisfy certain criteria, on a cost-minimisation basis compared with peginterferon alfa-2b.

Peginterferon alfa-2a has not previously been considered by the PBAC for the treatment of chronic hepatitis B.

## 3. Registration Status

PEG-interferon alfa-2a is registered by the Therapeutic Goods Administration (TGA) for chronic hepatitis C alone or in combination with ribavirin 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. PEG-interferon alfa-2a is also registered for the treatment of chronic hepatitis B in adult in patients with evidence of viral replication and liver inflammation and compensated liver disease.

## 4. Listing Requested and PBAC's View

Section 100 (Highly Specialised Drug) Private hospital Authority required
Patients with chronic hepatitis B and compensated liver disease who satisfy all of the following criteria:

(1) Histological evidence of chronic hepatitis on liver biopsy (except in patients with coagulation disorders considered severe enough to prevent liver biopsy);
(2) Abnormal serum ALT levels in conjunction with documented chronic hepatitis B infection (HBe antigen positive and/or HBV DNA positive);
(3) Female patients of child-bearing age are not pregnant, not breast-feeding, and are using an effective form of contraception;
(4) Are not persons with Child's class B or C cirrhosis (ascites, variceal bleeding, encephalopathy, albumin less than 30 g per L, bilirubin greater than 30 micromoles per L).

The PBAC recommended that treatment be limited to patients who have not received prior treatment with peginterferon alfa for the treatment of hepatitis B (see also Recommendations and Reasons).

## 5. Clinical Place for the Proposed Therapy

Peginterferon alfa-2a would provide an alternative first line treatment to lamivudine and interferon alfa-2a in the treatment of chronic hepatitis B infection.

## 6. Comparator

The PBAC accepted the submission's nomination of lamivudine as the main comparator.

## 7. Clinical Trials

The submission provided two head-to-head, randomised, observer-blind, open-label for peginterferon alfa-2a comparative trials, one in hepatitis B 'e' antigen (HBeAg)-positive patients (WV16240) and one in HBeAg-negative patients (WV16241), comparing peginterferon alfa-2a, lamivudine and peginterferon alfa-2a/lamivudine combination. Both trials had a 48-week treatment period followed by a 24-week follow-up period. The submission presented results for the peginterferon alfa-2a versus lamivudine comparison only.

| Trial/first author | Protocol Publication/Title | Publication citation |
|---|---|---|
| WV16240/ Lau GKK | Peginterferon alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. | New England Journal of Medicine 2005; 352 (26):2682-2695. |
| WV16241/ Marcellin P | Peginterferon alfa-2a alone, lamivudine alone, and two in combination in patients with HBeAg-negative chronic hepatitis B. | New England Journal of Medicine 2004; 351:1206-1217. |

## 8. Results of Trials

The PBAC noted that in HBeAg-positive disease there were statistically significant advantages for peginterferon alfa-2a compared to lamivudine for seroconversion, HBV-DNA suppression, and all secondary outcomes with the exception of histological response, baseline-adjusted mean $\log_{10}$ ALT and baseline-adjusted mean $\log_{10}$ HBeAg+1. For HBeAg-negative disease there were statistically significant advantages for peginterferon alfa-2a compared to lamivudine for ALT normalisation, HBV-DNA suppression, and all secondary outcomes with the exception of the triple endpoint and histological response.

It was noted by the PBAC that there were statistically significantly more adverse events, serious adverse events, treatment-related adverse events and treatment-related severe/life-threatening adverse events in peginterferon alfa-2a-treated patients compared to lamivudine-treated patients. The submission stated the most common treatment-related adverse events in the peginterferon alfa-2a group were those commonly associated with interferon alfa treatment (i.e. flu-like symptoms, injection-site reactions and alopecia). Severe adverse events were mainly flu-like symptoms.

## 9. Clinical Claim

The submission claimed that peginterferon alfa-2a was significantly more effective than lamivudine and had more toxicity than lamivudine.

*See Recommendations and Reasons for the PBAC's view of this claim.*

## 10. Economic Analysis

Two preliminary economic evaluations were presented in the submission, one for HBeAg-positive disease and one for HBeAg-negative disease. The PBAC considered the choice of a cost-effectiveness approach was valid.

The submission presented two modelled economic evaluations, one for HBeAg-positive disease and one for HBeAg-negative disease. The PBAC considered the cost-effectiveness approach was valid. The structure of the HBeAg-positive and negative models were the same, with the exception of the surrogate clinical outcomes used in each.

The submission linked the surrogate outcomes to the long-term clinical outcomes of cirrhosis, liver transplantation, hepatocellular carcinoma and death. The resources included in both models were the drug alternatives, drugs for salvage therapy if required; non-drug resources including hospitalisation for adverse events, specialists and laboratory investigations; and long-term medical care for each of the health states.

A base case modelled incremental discounted cost per extra discounted life-year gained was between $15,000 to $45,000 for HBeAg-positive disease, and peginterferon alfa-2a dominant (ie more effective and less costly) for HBeAg-negative disease.

A base case modelled incremental discounted cost/extra discounted QALY gained was <$15,000 for HBeAg-positive disease, and peginterferon alfa-2a dominant for HBeAg-negative disease.

## 11. Estimated PBS Usage and Financial Implications

The submission estimated that less than 2,000 patients would be treated in Year 4 of listing.

The net financial cost per year to the PBS in Year 4 was estimated to be between $10 million to $30 million. The submission stated these costs are partially offset by cost savings associated with peginterferon alfa-2a, by avoiding the need for subsequent long-term chronic hepatitis B therapy. The PBAC noted that there were a number of uncertainties associated with these estimates.

## 12. Recommendation and Reasons

The PBAC recommended listing on the basis of acceptable cost-effectiveness compared to lamivudine, concluding that the two head-to-head trials presented in the submission indicate that a course of peginterferon alfa-2a is more effective than lamivudine in the treatment of hepatitis-B, but has slightly more toxicity.

The PBAC considered that, despite a level of uncertainty associated with the modelled economic evaluation presented in the submission, overall the incremental cost per extra discounted life-year gained of between $15,000 to $45,000 was acceptable, and any residual uncertainty would not change the cost-effectiveness beyond the level of acceptability.

The PBAC also considered that the restriction should limit access to monotherapy with a maximum duration of treatment of 48 weeks. Based on the sponsor's comment in its Pre-PBAC Response, that there is no efficacy data for peginterferon alfa-2a re-treatment, the PBAC recommended that treatment be limited to patients who have not received prior treatment with peginterferon alfa for the treatment of hepatitis B. Therefore, treatment would be limited to one course of up to 48 weeks per patient per lifetime.

***Recommendation***

PEGINTERFERON ALFA-2a, injections, single use pre-filled syringe,
135 micrograms and 180 micrograms.

Extend listing to include:

Restriction: (Highly Specialised Drug) Private hospital authority required

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.

Monotherapy in patients with chronic hepatitis B and compensated liver disease who satisfy all of the following criteria:

(1) Histological evidence of chronic hepatitis on liver biopsy (except in patients with coagulation disorders considered severe enough to prevent liver biopsy);
(2) Abnormal serum ALT levels in conjunction with documented chronic hepatitis B infection (HBe antigen positive and/or HBV DNA positive);
(3) Have received no prior peginterferon alfa therapy for the treatment of hepatitis B;
(4) Female patients of child-bearing age are not pregnant, not breast-feeding, and are using an effective form of contraception;
(5) Are not persons with Child's class B or C cirrhosis (ascites, variceal bleeding, encephalopathy, albumin less than 30 g per L, bilirubin greater than 30 micromoles per L).

Treatment is limited to one course of treatment for a duration of up to 48 weeks.

Pack Size: 4 (all strengths)

## 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