PUBLIC SUMMARY DOCUMENT
Product: Boceprevir and ribavirin and peginterferon alfa-2b, packs containing:
336 capsules boceprevir 200 mg and 112 capsules ribavirin and 4 single use injection pens containing peginterferon alfa 2b powder for injection 50 micrograms with diluent;
336 capsules boceprevir 200 mg and 112 capsules ribavirin and 4 single use injection pens containing peginterferon alfa 2b powder for injection 100 micrograms with diluent;
336 capsules boceprevir 200 mg and 140 capsules ribavirin and 4 single use injection pens containing peginterferon alfa 2b powder for injection 120 micrograms with diluent;
336 capsules boceprevir 200 mg and 140 capsules ribavirin and 4 single use injection pens containing peginterferon alfa 2b powder for injection 150 micrograms with diluent;
336 capsules boceprevir 200 mg and 168 capsules ribavirin and 4 single use injection pens containing peginterferon alfa-2b powder for injection 150 micrograms with diluent;
336 capsules boceprevir 200 mg and 196 capsules ribavirin and 4 single use injection pens containing peginterferon alfa-2b powder for injection 150 micrograms with diluent;
Victrelis® Pegatron® Combination Therapy,
Sponsor: Merck Sharp & Dohme (Australia) Pty Ltd
Date of PBAC Consideration: November 2012

1. Purpose of Application

The submission requested Section 100 (Highly Specialised Drugs Program) Private Hospital Authority Required and Public Hospital Authority Required (Streamlined) listings for the treatment of chronic hepatitis C in treatment naïve and treatment experienced patients aged 18 years and older who meet certain criteria.

Boceprevir Pegatron Combination Therapy is a composite packaging product, consisting of 4 weeks supply of boceprevir packaged with 4 weeks supply of peginterferon alfa-2b and ribavirin (Pegatron).

Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities.

2. Background

Composite packaging of boceprevir and Pegatron had not previously been considered by the PBAC.

3. Registration Status

Victrelis Pegatron combination therapy was TGA registered on the 3 September 2012 and is indicated for the treatment of chronic hepatitis C genotype 1 infection in adult patients (18 years and older) with compensated liver disease who are previously untreated or who have failed previous therapy.

4. Listing Requested and PBAC's View

Section 100 (Highly Specialised Drugs Program)
Private Hospital Authority Required
Public Hospital Authority Required (STREAMLINED)
Patients naïve to interferon based therapies (non-pegylated or pegylated)

Treatment, managed by an accredited treatment centre, of chronic hepatitis C in combination

with peginterferon alfa and ribavirin 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 genotype 1 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. Patients may only continue treatment after the first 20 weeks of boceprevir treatment if plasma HCV RNA is not detectable by a HCV RNA qualitative assay at treatment week 24.

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.

Private Hospital Authority Required
Public Hospital Authority Required (STREAMLINED)
Patients who have failed prior attempts at interferon based therapies (non-pegylated or pegylated)

Treatment, managed by an accredited treatment centre, of chronic hepatitis C in combination with peginterferon and ribavirin, 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 genotype 1 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. Patients may only continue treatment after the first 8 weeks of boceprevir treatment if plasma HCV RNA is not detectable by an HCV RNA qualitative assay at treatment week 12. Patients should also discontinue all therapy if plasma HCV-RNA is detectable by an HCV-RNA qualitative assay at treatment week 24.

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.

5. Clinical Place for the Proposed Therapy

Infection with hepatitis C virus can lead to chronic hepatitis, a slow progressing condition involving inflammation of the liver that can lead to cirrhosis, hepatocellular carcinoma, and eventually death. There are several hepatitis C virus genotypes, the most common in Australia being genotypes 1, 2 and 3, with genotype 1 representing approximately 55% of all cases.

The submission proposed that boceprevir, in combination with peginterferon alfa and ribavirin, will become standard of care (SOC) for patients with chronic genotype 1 hepatitis C virus infection, including both patients naïve to interferon-based therapies and patients who have failed one prior attempt at interferon based therapies.

6. Comparator

The submission nominated boceprevir plus Pegatron, given as the two individual component packs, as the main comparator. The PBAC considered the choice of comparator appropriate, but the submission did not provide any evidence to support the comparison.

7. Clinical Trials

As noted above, the submission provided no clinical evidence about the use of the co-pack. It presented two randomised trials comparing boceprevir plus Pegatron, administered concomitantly as the two component products (not co-packaged), versus Pegatron alone: one trial in treatment naïve patients with genotype 1 chronic hepatitis C (CHC) (Trial 216), and the other in genotype 1 CHC patients who have previously failed interferon-based therapy (partial responders and relapsers) (Trial 101). Both of these trials were included in the July 2011 PBAC submission and the March 2012 re-submission for listing of boceprevir for treatment of genotype 1 CHC, in combination with peginterferon alfa and ribavirin.

For PBAC's view, see Recommendation and Reasons.

8. Results of Trials

The PBAC has previously considered that the evidence supports the claim that boceprevir in combination with peginterferon alfa and ribavirin is of superior efficacy to peginterferon alfa with ribavirin, in terms of the primary outcome of an increase in sustained virological response, in chronic hepatitis C genotype 1 treatment naïve or treatment experienced patients who have previously demonstrated a response to peginterferon based therapy.

9. Clinical Claim

The submission implied that co-packaged boceprevir/Pegatron is non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety to boceprevir and Pegatron given as the individual component products.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost-minimisation analysis based on the assumption of non-inferiority (co-packaged boceprevir/Pegatron). However, the cost-minimisation approach was not supported by the clinical evidence presented in the submission.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated a net cost per year to the PBS of less than $10 million in Year 5.

The PBAC noted the potential financial benefit for patients of the co-pack in terms of fewer patient co-payments. However the PBAC considered that no evidence had been presented to support a benefit of the co-pack in terms of health outcomes. The PBAC also considered that a clinical need for this product had not been demonstrated.

12. Recommendation and Reasons

The PBAC accepted boceprevir plus Pegatron (ribavirin and peginterferon alfa-2b) given as the two individual component packs as the most appropriate main comparator. However, the Committee noted that the submission did not present any clinical data for this comparison.

The PBAC considered that the trials presented in the submission comparing boceprevir plus Pegatron administered concomitantly as the two component products versus Pegatron alone in treatment naïve patients (Study 216) and in patients who have previously failed interferon based therapy (Study 101) were not relevant to the evaluation of the boceprevir/Pegatron co-pack compared with the individual components given concomitantly.

The PBAC considered that while it may be reasonable to assume non-inferior comparative effectiveness and safety between co-packaged boceprevir/Pegatron and boceprevir and Pegatron given as the individual component products, the evidence presented in the submission did not support the claim of non-inferiority. Therefore, the cost-minimisation analysis was not valid.

The PBAC also noted the adverse effect profile of boceprevir as discussed in the Hepatitis C stakeholder meeting and the advice from that meeting that anaemia would be managed by titration of ribavirin rather than administration of erythropoietin. A monthly pack may not allow for sufficiently rapid changes in ribavirin dose in response to monitoring of anaemia.

The PBAC noted that the cost-minimisation analysis resulted in a net cost to the PBS due to the reduced number of patient co-payments. The PBAC considered that further costs to the PBS could occur if co-packaged boceprevir/Pegatron were to substitute for boceprevir administered with Pegasys RBV® (ribavirin and peginterferon alfa-2a) as the weighted price per pack for Pegatron is higher than that for Pegasys RBV. The Committee was mindful that under subsection 101(3B) of the *National Health Act 1953*, it is not able to recommend to the Minister that a drug or medicinal preparation be made available as a Pharmaceutical Benefit if it is substantially more costly than an alternate therapy or therapies unless for some patients, it provides a significant improvement in efficacy or reduction of toxicity over the alternate therapy or therapies.

The PBAC noted the potential financial benefit for patients of the co-pack in terms of fewer patient co-payments. However the PBAC considered that no evidence had been presented to support a benefit of the co-pack in terms of health outcomes. The PBAC also considered that a clinical need for this product had not been demonstrated.

The PBAC noted that the proposed composite pack does not fully meet the guidelines for listing of fixed dose combination products:

- Criterion (g) requires that the combination product should not result in inappropriate dosing of either component, nor contain components which require individual dose titration - The PBAC considered that there is a potential that this product may not result in optimal treatment for those patients that require ribavirin dose titration.
- Criterion (h) requires that the combination product should not result in unnecessary proliferation of product and/or dose forms – The PBAC considered that there is an expected net PBS cost in that the weight-based dosing of ribavirin and peginterferon may lead to unnecessary proliferation of dose forms.

The PBAC therefore rejected the submission on the basis of no demonstrated clinical benefit or unmet clinical need and inadequate comparative clinical evidence to support the cost-minimisation claim.

Recommendation:
Reject

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 did not provide further comment.