PUBLIC SUMMARY DOCUMENT
Product: BOCEPREVIR, capsule 200 mg, Victrelis®
Sponsor: Merck Sharp & Dohme (Australia) Pty Ltd
Date of PBAC Consideration: July 2011

1. Purpose of Application

The submission sought a Section 100 (Highly Specialised Drugs Program) Authority required listing for the treatment of chronic hepatitis C in patients 18 years or older who have compensated liver disease and who are naïve or who have failed one prior attempt with interferon alfa or peginterferon alfa treatment for hepatitis C and meet certain criteria.

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

This drug had not been previously considered by the PBAC.

3. Registration Status

Boceprevir was TGA registered on 9 January 2012 for the treatment of chronic hepatitis C (HCV) genotype 1 infection, in a combination regimen with peginterferon alpha and ribavirin, 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
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 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.
The treatment course is determined by the response guided therapy algorithm.

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.

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 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.
The treatment course is determined by a response guided therapy algorithm. 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.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

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

The submission proposed that the place in therapy of boceprevir is as add-on therapy to standard peginterferon alfa and ribavirin therapy (i.e. boceprevir is to form part of triple therapy combination therapy) in clearing the virus. The submission claimed that triple combination therapy will shorten the required treatment duration and improve sustained virological response (SVR) in genotype 1 patients.

6. Comparator

The submission nominated current standard of care (SOC) as the main comparator. Current SOC in genotype 1 CHC patients includes peginterferon alfa and ribavirin (RBV) for up to 48 weeks. This was considered appropriate by the PBAC.

7. Clinical Trials

The basis of the submission is described below.

Treatment naïve patients:
One three-armed direct randomised trial comparing two regimens of boceprevir in addition to peginterferon alfa 2b plus ribavirin (response guided therapy (BOC RGT) and a fixed 48-week regimen (BOC/PR48)) versus placebo in addition to peginterferon alfa 2b and ribavirin for 48 weeks in treatment naïve genotype 1 CHC patients (Trial 216).

Treatment experienced patients:
One three-armed direct randomised trial comparing two regimens of boceprevir in addition to peginterferon alfa 2b plus ribavirin (BOC RGT and BOC/PR48) versus placebo in addition to peginterferon alfa 2b and ribavirin for 48 weeks in treatment experienced genotype 1 CHC patients (Trial 101).

Trials 216 and 101 had not been published at the time of submission.

8. Results of Trials

The primary outcome in both trials was sustained virological response (SVR), defined as undetectable plasma HCV RNA 24 weeks after cessation of treatment.

The comparison of BOC RGT versus placebo/PR48 showed a clinical benefit with boceprevir. The comparison was confounded by the difference in duration of treatment between trial arms. However, when the same duration of treatment is compared between trial arms, a similar clinical benefit with boceprevir was observed.

The results of a post hoc analysis of BOC RGT versus BOC/PR48, performed during the evaluation showed that there appeared to be no difference in SVR according to regimen in treatment naïve patients. The difference for treatment experienced patients was less clear as the analysis was under-powered.

On the basis of these results, the submission claimed that the addition of boceprevir to peginterferon alfa 2b plus ribavirin dual therapy significantly increases the likelihood of achieving a SVR in both treatment naïve genotype 1 CHC patients and genotype 1 CHC patients who have failed previous treatment.

For PBAC's comments on these results, see Recommendation and Reasons.

The PBAC noted that Trial 101 only recruited subjects who had failed to achieve SVR after at least 12 weeks of previous peginterferon-based therapy, but who demonstrated some degree of interferon responsiveness during this qualifying regimen; null responders (less than 2 $\log_{10}$ reduction in HCV RNA by week 12) were excluded. Prior response to treatment is a recognised treatment effect modifier in patients retreated with peginterferon alfa and ribavirin. Therefore, while Trial 101 supported the claim that the addition of boceprevir to peginterferon alfa plus ribavirin dual therapy increases the likelihood of SVR in treatment experienced patients who demonstrated partial response to previous interferon-based therapy, there was no evidence that this is true for null responders.

The submission stated that, in both trials, the incidence of dose modifications due to adverse events (AEs) was higher in the two boceprevir treatment arms than in the placebo/PR48 arm.

In Trial 101, there were also more discontinuations due to AEs with boceprevir compared to placebo. The incidence of serious AEs also tended to be higher in the boceprevir arms compared to the placebo/PR arm in this trial.

In both trials, anaemia and dysgeusia (distortion of the sense of taste) occurred more frequently in both boceprevir triple therapy arms compared to the placebo/PR arm. The most common AE resulting in dose modification was anaemia. In the trials, anaemia was managed with dose modification and/or erythropoietin (EPO); the submission acknowledged that the use of EPO masks the true extent of anaemia. In Australia, EPO is not registered by the TGA for management of CHC treatment-related anaemia, and it is rarely used. It is likely that, in the absence of EPO treatment (i.e. in Australian clinical practice), the difference in the incidence of clinically relevant anaemia between boceprevir containing regimens and SOC may be greater than that observed in the trials.

9. Clinical Claim

The submission described boceprevir and peginterferon alfa plus ribavirin triple therapy as superior in terms of comparative effectiveness and similar in terms of comparative safety over SOC (peginterferon alfa and ribavirin dual therapy), in both treatment naïve and treatment experienced genotype 1 CHC patients.

The PBAC considered the evidence supported 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 SVR in chronic hepatitis C genotype 1 treatment naïve patients and chronic hepatitis C genotype 1 treatment experienced patients who had previously demonstrated a response to peginterferon based therapy.

The PBAC considered that boceprevir in combination with peginterferon alfa and ribavirin has an inferior safety profile to peginterferon alfa with ribavirin alone.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented separate economic evaluations for the treatment naïve population and the treatment experienced population. Both models were stepped economic evaluations presenting cost-utility analyses. The models followed patients until death (to a maximum of 120 years of age).

Patient characteristics used in the analyses were based on the average characteristics of the subjects enrolled in the trials. For each model, the submission defined a number of patient identities based on gender, race, age, and baseline fibrosis level. These identities were then weighted according to the prevalence in the trial populations and used to populate the models. Patients who attained an end of treatment response (ETR), including those who discontinue treatment early, entered a transitional stage that lasts one cycle. At the end of this cycle, patients with undetectable HCV RNA attain SVR and are considered permanently cured. These patients remain in the SVR health state until death; it is assumed that they do not develop any HCV-related complications. Patients who fail to attain an ETR, or who attain an ETR but subsequently relapse, return to the chronic HCV health states.

The outcome of the model was the incremental cost per quality-adjusted life year (QALY) gained. The model is a semi-Markov model. The extrapolation of treatment effects beyond the trial period was the key driver of the model.

The incremental cost-effectiveness ratios (ICER) for both treatment naïve and treatment experienced patients from the modelled economic evaluation were between $15,000 and $45,000 per quality adjusted life year (QALY) gained.

Sensitivity analyses indicated that the model was most sensitive to the time horizon (the ICERs for both treatment naïve and treatment experienced patients increased to between $45,000 and $75,000 per QALY gained when the time horizon was limited to 20 years) and the baseline severity of liver fibrosis in the patient population, with boceprevir being more cost-effective in patients with more advanced liver pathology.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated the net cost per year to the PBS to be between $30 and $60 million in Year 5.

12. Recommendation and Reasons

The PBAC considered that the restriction should state that boceprevir must be used in combination with peginterferon and ribavirin, consistent with the proposed TGA indication. The PBAC however noted the sponsor's pre-Sub Committee response stating that the omission of stipulation of combination therapy in the requested restriction was unintended.

The PBAC noted that the requested restriction for treatment experienced patients included non-responders to prior interferon based treatment, but Trial 101 included treatment experienced patients only, including patients who had demonstrated some degree of response to previous interferon based therapy. The PBAC hence considered that the clinical evidence presented for treatment experienced patients did not fully represent the requested patient population. The PBAC further considered that the inclusion of non-responders to prior interferon based treatment would include use of boceprevir treatment as functional monotherapy for treatment experienced patients in the requested listing (as the peginterferon would not be eliciting a sustained viral response in this subgroup) and thereby increase the risk of developing boceprevir resistant variants.

The PBAC noted that the requested restriction was based on response guided treatment. The PBAC noted that the sustained viral response (SVR) in treatment naïve patients appeared to be similar in the response guided therapy and fixed duration treatment regimen groups, however that it was uncertain if the two regimens resulted in a similar SVR in treatment experienced patients.

The PBAC considered the comparator of current standard of care, including peginterferon alfa with ribavirin for up to 48 weeks in patients with chronic hepatitis C genotype 1, appropriate.

The submission presented Trial 216 (treatment naive patients) and Trial 101 (treatment experienced patients), each a three arm trial comparing the efficacy of a response guided

treatment regimen and a fixed duration treatment regimen of boceprevir in combination with peginterferon alfa and ribavirin to placebo in combination with peginterferon alfa and ribavirin. The PBAC considered the evidence supported 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 patients and chronic hepatitis C genotype 1 treatment experienced patients who had previously demonstrated a response to peginterferon based therapy.

The PBAC considered that boceprevir in combination with peginterferon alfa and ribavirin has an inferior safety profile to peginterferon alfa with ribavirin alone. The PBAC noted there was an increase in the frequency of anaemia in the boceprevir containing arms in each of trials 216 and 101 and that in Trial 101 there were more discontinuations due to adverse events and a higher incidence of serious adverse events in the boceprevir arms.

The submission presented a cost-utility analysis. The PBAC considered that the omission of hepatitis C virus complications for patients who attain a SVR to be inappropriate and to be the greatest source of uncertainty in the economic model. The PBAC agreed with the ESC that the ICER outcome from the model which depended on downstream costs and outcomes, beyond 20 years, was uncertain. The PBAC also noted that the treatment of chronic hepatitis C was likely to change in the near future, further adding to the uncertainty of the extrapolation in the model of the treatment effects of boceprevir well beyond the trial period. The PBAC further noted that the sensitivity analyses exploring the time horizon of the model demonstrated that the ICER was highly sensitive to the time horizon, and that limiting the model to a 20 year time horizon approximately doubled the ICER.

The PBAC noted that the model inputs for the sensitivity analysis were not provided in the submission and hence that the outcomes of the model could not be verified during the evaluation. The PBAC considered that the costs associated with adverse events should have been included in the model. The PBAC also noted that re-infection was not accounted for in the model and considered that this further added to the uncertainty in the economic model The PBAC hence considered that the cost effectiveness was uncertain.

The PBAC therefore rejected the submission on the basis of uncertain cost effectiveness. The PBAC considered that any future submission should address the areas of uncertainty in the economic model noted above including hepatitis C complications and re-infection.

The PBAC acknowledged and noted the consumer comments received in its consideration of boceprevir.

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

MSD thanks the PBAC for their comments and is working to address the uncertainties in the economic model. MSD will work hard with the PBAC to ensure that patients with genotype 1 chronic hepatitis C will soon have access to this important medicine.