PUBLIC SUMMARY DOCUMENT
Product: Boceprevir, capsule, 200 mg, Victrelis®
Sponsor: Merck Sharp & Dohme (Australia) Pty Ltd
Date of PBAC Consideration: March 2012

1. Purpose of Application:

The re-submission sought 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 patients 18 years or older who have compensated liver disease and who are treatment naïve or who have failed one prior attempt with interferon based therapies (pegylated or non-pegylated) and who 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 was the second consideration by the PBAC of an application to list boceprevir.

At the July 2011 meeting, the PBAC rejected a submission for listing of boceprevir for the treatment of chronic hepatitis C on the basis of uncertain cost effectiveness. The PBAC considered that any future submission should address areas of uncertainty in the economic model including hepatitis C complications and re-infection.

A copy of the Public Summary Document (PSD) from the July 2011 meeting is available at http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-boceprevir-july11

3. Registration Status

Boceprevir was TGA registered on 9 January 2012 for the treatment of chronic hepatitis C (CHC) genotype 1 infection, in a combination regimen with peginterferon alfa 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
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 one prior attempt 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.

Note
Treatment centers 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 Recommendations and Reasons.

5. Clinical Place for the Proposed Therapy

Chronic hepatitis C virus infection is a slow progressing disease that can lead to cirrhosis of the liver, hepatocellular carcinoma and eventually death. There are several hepatitis C virus genotypes, the most common being genotypes 1, 2 and 3. Patients with genotype 1 hepatitis C make up the majority (55%) of cases in Australia, and are the least responsive to standard therapy (peginterferon with ribavirin) despite prolonged treatment.

The resubmission proposed that the place in therapy for boceprevir is in combination with peginterferon alfa with ribavirin for treatment of chronic hepatitis C genotype 1.

6. Comparator

The re-submission nominated the current standard of care (SOC), i.e. peginterferon with ribavirin for up to 48 weeks, as the main comparator. The PBAC previously considered this was the appropriate comparator.

7. Clinical Trials

The basis of the re-submission was:

- Trial 216 (treatment naïve): Three-armed direct randomised trial comparing two regimens of boceprevir in combination with peginterferon alfa 2b plus ribavirin (response guided therapy and a fixed 48 week regimen), with placebo in combination with peginterferon alfa 2b and ribavirin for 48 weeks, in treatment naïve genotype 1 CHC patients;
- Trial 101 (treatment experienced): Three-armed direct randomised trial comparing two regimens of boceprevir in combination with peginterferon alfa 2b plus ribavirin (response guided therapy and a fixed 48 week regimen), with placebo in combination with peginterferon alfa 2b and ribavirin for 48 weeks, in treatment experienced genotype 1 CHC patients; and
- Trial 685 (treatment experienced): Supplementary two-armed direct randomised trial comparing boceprevir in combination with peginterferon alfa 2a and ribavirin (fixed 48 week regimen), with placebo in combination with peginterferon alfa 2a and ribavirin for 48 weeks, in treatment experienced genotype 1 CHC patients. This trial is presented in support of the effectiveness of boceprevir when administered with the alternative form of peginterferon alfa (peginterferon alfa 2a). This trial did not include a response guided treatment arm.

Trials 216 and 101 were also presented in the previous submission.

Both Trial 101 and Trial 685 only recruited patients 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.

Details of the trials published at the time of submission are in the table below.

Trials and associated reports presented in the submission

Trial ID/First author	Protocol title/ Publication title	Publication citation
Direct randomised trials		
Treatment naïve patients		
Trial 216 Poordad, F et al.	Boceprevir for untreated chronic HCV genotype 1 infection	*New England Journal of Medicine* 2011; 364:1195-206.
Treatment experienced patients		
Trial 101 Bacon B, et al.	Boceprevir for previously treated chronic HCV genotype 1 infection.	*New England Journal of Medicine* 2011; 364:1207-17.

8. Results of Trials

The primary outcome in all three trials was sustained virological response (SVR), defined as undetectable plasma HCV RNA 24 weeks after cessation of treatment. The key results are summarised in the tables below.

Results for the primary outcome, sustained virological response, across the direct randomised trials, BOC RGT vs Placebo/PR48

Trial ID	BOC RGT n/N (%)	Placebo/PR48 n/N (%)	Absolute difference % (95% CI)	Relative Risk (95% CI)	Odds Ratio[a] (95% CI)
Treatment naïve patients					
Trial 216 Cohort 1	211/316 (66.8)	125/311 (40.2)	26.6 (19.1, 34.1)	1.7 (1.4, 1.9)	3.3 (2.4, 4.7)
Treatment experienced patients					
Trial 101 FAS	95/162 (58.6)	17/80 (21.3)	37.4 (25.7, 49.1)	2.8 (1.8, 4.3)	7.3 (3.7, 14.5)

BOC = Boceprevir; CI = confidence interval; FAS = full analysis set; PR48 = peginterferon alfa 2b plus ribavirin for 48 weeks; RGT = response guided therapy.
[a] Odds ratio estimate using multivariate stepwise logistic regression, which included adjustment for genotype (1a vs 1b), ethnic group, baseline viral load and fibrosis score.
Figures calculated during the evaluation.

Results for the primary outcome, sustained virological response, across the direct randomised trials, BOC/PR48 vs Placebo/PR48

Trial ID	BOC/PR48 n/N (%)	Placebo/PR48 n/N (%)	Absolute difference % (95% CI)	Relative Risk* (95% CI)	Odds Ratio[a] (95% CI)
Treatment naïve patients					
Trial 216[b] Cohort 1	213/311 (68.5)	125/311 (40.2)	28.3 (20.8, 35.8)	*1.7 (1.5, 2.0)*	3.5 (2.5, 4.9)
Treatment experienced patients					
Trial 101[b] FAS	107/161 (66.5)	17/80 (21.3)	45.2 (33.7, 56.8)	*3.1 (2.0, 4.8)*	10.5 (5.2, 21.1)

BOC = boceprevir; CI = confidence interval; FAS = full analysis set; PR48 = peginterferon alfa 2b plus ribavirin for 48 weeks; RGT = response guided therapy.
[a] Odds ratio estimate using multivariate stepwise logistic regression, which included adjustment for genotype (1a vs 1b), ethnic group, baseline viral load and fibrosis score.
[b] PR = peginterferon alfa 2b and ribavirin (Pegatron®)
**Figures calculated during the evaluation.*

The PBAC noted that as in Trials 216 and 101, the results of Trial 685 demonstrated that boceprevir in combination with peginterferon alfa 2a and ribavirin, when administered according to a fixed 48 week regimen, is superior to 48 weeks of placebo in combination with peginterferon alfa 2a and ribavirin in treatment experienced genotype 1 CHC patients.

In order to assess if there was a treatment effect depending on the type of pegylated interferon used (peginterferon alfa 2a versus peginterferon alfa 2b), the submission presented a comparison of the results of the BOC/PR48 arm of Trial 101 and Trial 685.

Comparison of results from Trial 101 and Trial 685 suggested that the virological response to boceprevir/PR48 in treatment experienced patients is similar, irrespective of the form of peginterferon alfa with which it is administered; no evidence was presented for co-administration with peginterferon alfa 2a in treatment naïve genotype 1 CHC patients, or for the RGT regimen in either treatment naïve or treatment experienced patients.

The toxicity key results from trials 216 and 101 are summarised below. The re-submission also presented additional toxicity data from Trial 685.

Summary of adverse events, dose modifications, discontinuations and death

	BOC RGT n (%)	BOC/PR48 n (%)	Placebo/PR n (%)
Treatment naïve patients Trial 216, Cohort 1 and 2	**N=368**	**N=366**	**N=363**
Treatment emergent AEs	365 (99)	364 (99)	356 (98)
Treatment related AEs	364 (99)	363 (99)	353 (97)
Serious AEs	42 (11)	45 (12)	31 (9)
Life-threatening emergent AEs	5 (1)	4 (1)	4 (1)
Death	1 (<1)	1 (<1)	4 (1)
Discontinued due to AEs	45 (12)	60 (16)	57 (16)
Dose modification due to AEs[a]	146 (40)	129 (35)	94 (26)
Treatment experienced patients			
Trial 101	**N=162**	**N=161**	**N=80**
Treatment emergent AEs	160 (99)	161 (100)	77 (96)
Treatment related AEs	159 (98)	161 (100)	77 (96)
Serious AEs	16 (10)	23 (14)	4 (5)
Life-threatening emergent AEs	4 (2)	5 (3)	0
Death	1 (1)	0	0
Discontinued due to AEs	13 (8)	20 (12)	2 (3)
Dose modification due to AEs[a]	47 (29)	53 (33)	11 (14)

AE = adverse event; BOC = boceprevir; PR = peginterferon alfa and ribavirin; RGT = response guided therapy

[a] Subjects who had a dose modification and study drug discontinuation due to an AE were counted only in the 'discontinuation due to AE' category.

Both the type and frequency of adverse events observed in Trial 685 were generally comparable to those observed in Trials 216 and 101.

The re-submission stated that, in all three trials, the incidence of dose modifications due to adverse events (AEs) was higher in the boceprevir treatment arms compared to the placebo/PR48 arm. In Trial 101 and Trial 685, there were also more discontinuations due to AEs with boceprevir compared to placebo.

In all the trials, anaemia and dysgeusia (distortion of the sense of taste) occurred more frequently in the boceprevir triple therapy arms compared to the placebo/PR arm. In Trial 685, the incidence of neutropenia also tended to be higher in the boceprevir treatment 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 free use of EPO masked the true extent of anaemia. The PBAC noted that in Australia, EPO is not registered by the TGA for management of CHC treatment-related anaemia. The PBAC considered it 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 re-submission described boceprevir and peginterferon alfa plus ribavirin triple therapy as superior in terms of comparative effectiveness over SOC (peginterferon alfa 2b or

peginterferon alfa 2a plus ribavirin dual therapy) in both treatment naïve and treatment experienced genotype 1 CHC patients. In contrast to the previous submission, the re-submission described boceprevir/PR triple therapy as inferior in terms of comparative safety over SOC. The PBAC considered that the claim that boceprevir/PR is inferior in terms of comparative safety was appropriate.

The clinical claim of superiority over the comparator was well supported and had been previously accepted by the PBAC. However, the PBAC noted that there was no evidence presented to support a claim of superior comparative effectiveness for patients who had a null response to prior peginterferon alfa-based therapy.

10. Economic Analysis

An updated modelled economic evaluation was presented. The stepped economic evaluations were similar to those presented in the previous submission (reported in the July 2011 Public Summary Document).

See *Recommendation and Reasons* for the key differences between the re-submission and the previous submission.

The PBAC noted the revised base case ICERs were between $15,000 - $45,000/QALY for treatment naïve patients and were lower but within the same range for treatment experienced patients.

From the results of the sensitivity analyses, the PBAC noted that the model was most sensitive to the time-horizon, baseline distribution of fibrosis scores and to the effect of discounting. Given HCV is a chronic condition, the PBAC considered a lifetime model was reasonable. However, the PBAC acknowledged that an ICER that is largely determined by downstream costs and outcomes beyond 20 years is inherently uncertain.

For the patient's baseline fibrosis score the analyses were incomplete because the SVR rate had not been estimated specifically for each fibrosis stage; rather the same averaged SVR rate had been applied to all fibrosis stages. Fibrosis stage is likely to be an effect modifier and thus the overall impact of baseline fibrosis score on the ICER was unclear. Additionally, there was a lack of data confirming that the baseline distribution of liver disease by fibrosis level in the trials was representative of the proposed Australian CHC patients.

During the evaluation, additional sensitivity analyses were conducted to investigate the effect on the ICERs when the disutility associated with viral positive states (5%) was removed.

The PBAC noted that the sensitivity analyses showed that the ICERs increased by between $10,000 and $15,000/QALY for the treatment naïve population and for the treatment experienced population.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The re-submission estimated the likely number of treatment naïve patients treated to be less than 10,000 and treatment experienced patients to be less than 10,000 in Year 5 of listing, at an estimated total net cost to the PBS in the range of $60 - $100 million in Year 5 of listing.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC noted that boceprevir is now TGA registered and that the requested PBS listing differs from the approved Product Information (PI) in that the approved PI recommends an increase in the duration of treatment for cirrhotics and prior null-responders to 44 weeks and an additional qualitative HCV RNA assay at treatment week 24 for treatment experienced patients and patients with cirrhosis.

The PBAC considered the comparator of peginterferon alfa and ribavirin alone for up to 48 weeks was appropriate.

The PBAC considered that the lack of evidence of effectiveness of boceprevir in combination with peginterferon alfa and ribavirin (boceprevir/PR) in treatment experienced patients who had no response to prior interferon based treatment remained an area of clinical uncertainty as well as uncertainty in the assessment of the overall cost-effectiveness of boceprevir.

The PBAC noted that the re-submission presented an updated modelled economic evaluation with the following key differences to the previous submission:

- the model structure was simplified to use the average patient characteristics;
- allowance for progression from sustained viral response (SVR) to liver complications among cirrhotic patients was included;
- treatment of anaemia via blood transfusions among a proportion of patients was included;
- the modelled time horizon, as the maximum allowable age was changed from 120 years to 100 years;
- the treatment duration and SVR data applied to the comparator arm of the treatment naïve model were considered in line with the existing PBS restriction concerning peginterferon/ribavirin;
- the requested price of boceprevir was reduced; and
- the revised base case ICERs for treatment naive patients and for treatment experienced patients were in the range of $15,000 - $45,000/QALY.

The PBAC however agreed that there are a number of remaining uncertainties in the economic model, including:

- The time horizon of 50 years. The PBAC noted that the incremental cost effectiveness relies on benefits and costs that accrue 20 years or more in the future. The PBAC noted that the treatment of chronic hepatitis C is an evolving area which is likely to change substantially in the near future, which adds to the uncertainty in the long time horizon in the economic model. The PBAC further noted the sensitivity analyses presented in the submission demonstrated that the model was highly sensitive to the time horizon with a 30 year time horizon resulting in less favourable ICERs in both the treatment naive and treatment experienced patient populations.
- The transition probabilities. The PBAC noted that the accuracy of available diagnostic methods and available treatments have changed over time and hence the data used in the model from studies published in 1986, 1989 and 1992 to estimate transition probabilities is likely to overestimate the likelihood of progression compared to present rates. Further, the PBAC noted that the route and source of infection may affect the

rate of progression and that the studies used to estimate the transition probabilities had a much lower percentage of patients with community acquired hepatitis C virus (HCV) than in the Australian HCV population today. The PBAC noted that this was likely to result in an overestimation of the cost effectiveness of boceprevir.

- The utility values. The PBAC noted there is variability in the utilities associated with HCV in the published literature and hence that the utilities applied in the model are uncertain. The PBAC also noted a disutility for viral positive states was included.
- Re-infection is not captured in the model. The PBAC however noted the sensitivity analysis of a 1 % re-infection rate among patients attaining SVR each year, which resulted in an increase in the ICERs in both naïve and treatment experienced patients. The PBAC accepted this was an appropriate sensitivity analysis because re-infection is most likely in the 3-5% of patients who actively continue IV drug injecting and the available data suggest a re-infection rate of 3-5/100 person years in this subgroup.

The PBAC noted that revised models were presented in the Pre-Sub-Committee Response applying a longer treatment duration in cirrhotic patients and previous null responders (in line with the treatment duration in the final TGA-approved PI), using fibrosis-specific data for all baseline health states. The PBAC noted that this increased the ICERs in both models. The PBAC however noted that the structure of the treatment experienced model was changed and the outputs of the revised model had not been fully evaluated, given the time-frame in which they were received.

The PBAC noted the price reduction offered in the Pre-PBAC Response and the associated claimed lower ICERs of which remained in the range of $15,000 - $45,000/QALY for treatment naive patients and treatment experienced patients (using the 44 weeks treatment duration for null responders and cirrhotics as per the final TGA-approved PI).

The PBAC considered the utilisation estimates and hence the estimated financial cost to the PBS were highly uncertain. The PBAC considered the estimated uptake of boceprevir/PR to be uncertain, noting the capacity constraints in the current HCV treatment infrastructure in Australia and that the treatment of chronic hepatitis C will change rapidly in the near future

The PBAC further noted the availability of interleukin (IL) 28B genotype (genotypes CC, CT and TT) testing on the private market. The PBAC noted that patients with different IL28B genotypes may have a different response to treatment with boceprevir/PR, hence adding to the uncertainty in the cost effectiveness of boceprevir/PR.

The PBAC considered that an additional quantitative HCV RNA assay at week 4 may be utilised by clinicians, however that reference to a quantitative HCV RNA assay at week 4 is not included in the dosage recommendations in the TGA-approved PI, and was not included in the submission's requested PBS restriction for this reason. The PBAC noted that this was also an additional source of uncertainty in the cost effectiveness of boceprevir.

The PBAC therefore considered that the cost-effectiveness ratio was unacceptably high and uncertain and the utilisation estimates were also highly uncertain. The PBAC noted that the inputs to the economic model were the key sources of this uncertainty. However, the PBAC acknowledged that more applicable data to input into the model are not currently available. The PBAC also acknowledged the clinical need for additional treatment options for the

treatment of chronic hepatitis C and noted the comment received from the Australian Liver Association, the Australasian Society for HIV Medicine and the Australasian Society for Infectious Diseases regarding the clinical place in therapy of boceprevir in the treatment of chronic hepatitis C.

The PBAC therefore deferred the submission so that discussion could take place with the sponsor regarding price, noting that a substantial further price reduction would be required in order to reduce the impact of uncertainty in the cost effectiveness ratio. The PBAC also considered that a Stakeholder meeting would be of benefit to more clearly ascertain the clinical place of boceprevir, the place of quantitative and qualitative HCV RNA and IL28B testing and to identify those patients who would most likely benefit from this drug.

In making this recommendation the PBAC noted the consumer comments on this item.

Recommendation:
Defer

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 is working with the PBAC to ensure that boceprevir is listed on the PBS at the earliest possible opportunity.