PUBLIC SUMMARY DOCUMENT
Product: Telaprevir, tablet (film coated), 375 mg, Incivo®
Sponsor: Janssen-Cilag Pty Ltd
Date of PBAC Consideration: November 2011

1. Purpose of Application

The submission sought a Section 100 (Highly Specialised Drugs Program) Authority Required listing for the treatment, in combination with peginterferon-alfa and ribavirin (PR), of chronic hepatitis C in a patient 18 years or older who has compensated liver disease and who has received prior treatment with interferon-alfa or peginterferon-alfa for hepatitis C and meets 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 previously been considered by the PBAC.

3. Registration Status

On 6 March 2012, telaprevir was registered by the TGA for the following indication:

Telaprevir, in combination with peginterferon alfa and ribavirin is indicated for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease (including cirrhosis):

- who are treatment-naïve;
- who have previously been treated with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin, including relapsers, partial responders and null responders.

4. Listing Requested and PBAC's View

Section 100
Patients who have failed prior interferon based therapies (pegylated or non-pegylated).

Treatment with telaprevir in combination with peginterferon-alfa and ribavirin, 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 prior treatment with interferon alfa or peginterferon alfa for hepatitis C and who satisfy all of the following criteria:

(1) Documented chronic genotype 1 hepatitis C infection (repeatedly anti-HCV positive and HCV RNA positive);
(2) Female patients of child-bearing age who are not pregnant, not breast-feeding, and both patient and their partner are using effective forms of contraception (one for each partner). Female partners of male patients are not pregnant.

The treatment course is limited to 12 weeks.
Patients may only continue treatment after the first 6 weeks if the results of a HCV RNA quantitative assay at Week 4 (performed at the same laboratory using the same test) shows that the plasma HCV RNA has become ≤ 1000 IU/mL.

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) nurse / educator / councillor 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 C is an inflammation of the liver caused by the hepatitis C virus (HCV). Around 75% of people exposed to hepatitis C develop chronic infection, defined as the presence of the hepatitis C virus in the bloodstream for longer than 6 months. The remaining 25% will spontaneously clear the infection, but will continue to have detectable antibodies. Chronic hepatitis C (CHC) is a lifelong chronic condition that can lead to cirrhosis of the liver and liver cancer.

In 2010, the number of people with (CHC) in Australia was estimated to be 221,000. There are several HCV genotypes. In Australia, the genotype 1 is the most common HCV followed by genotype 3 and genotype 2 which account for 55%, 37% and approximately 5% of all HCV infections, respectively.

The submission proposed that the place in therapy of telaprevir is in combination with interferon-alfa or peginterferon-alfa and ribavirin (PR) for the treatment of a patient with chronic genotype 1 HCV infection who has failed to respond to prior interferon-based therapies.

6. Comparator

In genotype 1 chronic hepatitis C patients who have received only one prior course of interferon-based therapy, the submission nominated peginterferon alfa and ribavarin (PR), without a concomitant direct acting antiviral agent (DAA), as the comparator for telaprevir administered in combination with PR.

In genotype 1 CHC patients who have received more than one prior course of interferon based therapy, the submission nominated placebo (or no active treatment) as the comparator.

The submission also nominated boceprevir, in combination with PR, as a minor comparator, in anticipation that boceprevir is likely to be registered for use in Australia at a similar time to telaprevir. Boceprevir was submitted for consideration by the PBAC at its July 2011 meeting.

The PBAC considered the nominated comparators (placebo added to peg interferon and ribavarin in patients with one prior treatment with interferon-based therapy and placebo for no treatment in patients with more than one prior treatment with interferon-based therapy) to be appropriate. The PBAC also noted the secondary comparison with boceprevir added to peginterferon and ribavarin.

7. Clinical Trials

<u>Telaprevir + PR versus placebo + PR in patients who have failed one prior attempt at interferon based therapy</u>

The submission presented two randomised trials comparing telaprevir in combination with PR, with placebo in combination with PR in patients with genotype 1 CHC patients who have previously failed prior PR therapy:

- REALIZE – a three-armed direct randomised trial comparing two regimens of

12 weeks of telaprevir therapy (with and without a 4 week delayed start), in combination with a 48 week course of peginterferon alfa-2a plus ribavirin, with placebo in combination with 48 weeks of peginterferon alfa-2a plus ribavirin in treatment experienced genotype 1 CHC patients; and

- PROVE 3 – a four-armed direct randomised trial comparing various regimens of telaprevir in combination with peginterferon alfa-2a with or without ribavirin, with placebo in combination with 48 weeks of peginterferon alfa-2a and ribavirin.

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

Telaprevir + PR versus placebo + no active treatment (patients who have failed more than one prior attempt at interferon based therapy)

The submission presented the results of an open-label non-comparative, extension study, in which patients who were randomised to the placebo/PR arm of the PROVE 3 trial were subsequently treated with telaprevir + PR. There was no placebo/no active treatment in support of the requested listing for treatment of genotype 1 CHC patients who have failed more than one prior attempt at interferon based therapy.

Telaprevir + PR versus boceprevir + PR

The basis of the submission was an indirect comparison of two randomised controlled trials:

- REALIZE as described above.
- RESPOND 2 – a three-armed randomised trial comparing two regimens of boceprevir (response guided therapy and a fixed 48 week regimen), in combination with peginterferon alfa-2b plus ribavirin, with placebo in addition to 48 weeks of peginterferon alfa-2b plus ribavirin in treatment experienced genotype 1 CHC patients.

Details of the studies published at the time of submission are shown in the following table:

Trial ID/First author	Protocol title/ Publication title	Publication citation
Direct randomised trials		
HCV treatment experienced clinical trials		
PROVE 3 (VX06-950-106)		
McHutchison JG at al 2010	Telaprevir for previously treated chronic HCV infection.	New England Journal of Medicine 2010; 362 (14):1292-1303.
Burney T et al	Overview of the PROVE studies evaluating the use of telaprevir in chronic hepatitis C genotype 1 patients.	Expert Review of Anti-infective Therapy 2011; 9 (2):151-160.
REALIZE (VX-950-TiDP24-C216)		
Zeuzem S et al 2011	Telaprevir for retreatment of HCV infection.	New England Journal of Medicine 2011; 364 (25):2417-2428.
RESPOND 2 Bacon BOC et al 2011	Boceprevir for previously treated chronic HCV genotype 1 infection.	New England Journal of Medicine 2011; 364 (13):1207-1217.
Poordad F et al 2011	Boceprevir combined with peginterferon alfa-2b/ribavirin for treatment-experienced patients with hepatitis C virus (HCV) genotype-1: RESPOND-2 final results.	Hepatology International 2011; 5(3-558): 13.

The submission classified patients who have failed a prior attempt at interferon based therapy as prior relapsers, partial responders, null responders, and patients with prior viral breakthrough, according to the type of treatment failure on prior peginterferon alfa and ribavirin (PR) therapy. The definitions of these subgroups, as used in the submission, are summarised in table below.

Definitions of type of treatment failure on prior PR therapy used in the submission

Prior treatment failure	Definition	
Prior non-responder	A subject who did not achieve undetectable HCV RNA during or at the end of a prior course of at least 42 weeks of PR therapy. This group consists of prior partial-responders and prior null-responders.	
	Prior null-responder	A subject who failed to suppress HCV RNA by at least 2 logs after at least 12 weeks of PR therapy
	Prior partial-responder	A subject who achieved a least a 2 log decrease in HCV RNA level at Week 12 of a prior course of at least 12 weeks of PR treatment, but never achieved undetectable HCV RNA levels.
Prior relapser	A subject who had an undetectable HCV RNA level at the end of a course of PR therapy but did not achieve an SVR.	
Viral breakthrough	A subject who had an undetectable HCV RNA level during prior PR therapy but became detectable ~~HCV RNA~~ again before completion of therapy.	

HCV RNA = Hepatitis C Virus ribonucleic acid; PR= pegylated interferon alfa + ribavirin; SVR = sustained virological response

8. Results of Trials

1. Telaprevir+ PR versus placebo + PR

The submission presented two sets of analyses, because the proposed PR treatment duration for non cirrhotic prior relapsers who attain an eRVR (undetectable HCV RNA at Week 4 and Week 12) is shortened to 24 weeks) whereas prior non-responders, cirrhotic patients and prior relapsers who did not achieve an eRVR receive 48 weeks of PR. The shorter PR treatment regimen is not included in REALIZE:

- A review of the results of the REALIZE trial [12 weeks telaprevir therapy in combination with 48 weeks peginterferon alfa and ribavarin regimen (T12/PR48) and telepravir placebo for 12 weeks in combination with 48 weeks peginterferon alfa and ribavarin regimen (Pbo12/PR48) treatment arms], which are applicable to all prior partial responders and null responders and to prior relapsers who have cirrhosis or who fail to achieve an eRVR;
- A comparison of the results for prior relapsers, stratified by eRVR status, in the T12/PR48 treatment arm of the REALIZE trial (relevant to prior relapsers who have cirrhosis or who fail to achieve an eRVR) and the T12/PR24 (12 weeks telaprevir therapy in combination with 24 weeks peginterferon alfa and ribavarin regimen) treatment arm of the PROVE 3 trial (representative of the proposed duration of treatment in non-cirrhotic prior relapsers who achieve an eRVR).

REALIZE

The results of the primary outcome in the REALIZE trial, $SVR24_{planned}$, for both the full analysis set (FAS), and categorised by prior treatment response are presented in the following table:

Results for the primary outcome, $SVR24_{planned}$*, in the REALIZE trial

	Telaprevir/PR arm n/N (%)	Placebo/PR arm n/N (%)	Absolute difference[b] % (95% CI)	Relative Risk (95% CI)	Odds Ratio (95% CI)
REALIZE	**T12/PR48**	**PboPR48**			
FAS	171/266 (64.3)	22/132 (16.7)	46.8 (36.8, 56.7)	*3.9 (2.6, 5.7)*	*9.0 (5.4, 15.1)*
Prior non-responders					
All prior non-responders	50/121 (41.3)	6/64 (9.4)	35.0 (22.9, 47.0)	4.4 (2.0, 9.7)	6.8 (2.7, 17.0)
Null-responder	21/72 (29.2)	2/37 (5.4)	24.7 (11.6, 37.7)	5.4 (1.3, 21.8)	7.2 (1.6, 32.7)
Partial responder	29/49 (59.2)	4/27 (14.8)	44.1 (24.7, 63.6)	4.0 (1.6, 63.6)	8.3 (2.5, 27.8)
Prior relapsers					
All prior relapsers	121/145 (83.4)	16/68 (23.5)	60.5 (48.8, 72.2)	3.6 (2.3, 5.5)	16.4 (8.1, 33.4)

CI = confidence interval; eRVR = extended rapid virological response; FAS = full analysis set; NR = not reported; Pbo = placebo; PR = peginterferon alfa and ribavirin; T = telaprevir

[a] [b]The results reported in the table are the adjusted absolute difference, as reported in the CSR

* $SVR24_{planned}$ is defined as the proportion of patients with undetectable HCV RNA levels 24 weeks after the last planned dose of study drug (i.e. at Week 72). The results for SVR_{actual}, defined as the proportion of patients with undetectable HCV RNA levels 24 weeks after the last actual dose of study medication, were identical.

Telaprevir administered in combination with PR significantly increased the proportion of patients achieving SVR, in both the FAS population and in each category of prior treatment response (prior relapsers, partial responders and null responders).

Comparison of prior relapsers in REALIZE and PROVE 3

The submission presented an unadjusted comparison of single arms extracted from each trial T12/PR48 (12 weeks telaprevir therapy in combination with 48 weeks peginterferon alfa and ribavarin regimen) versus T12/PR24 (12 weeks telaprevir therapy in combination with 24 weeks peginterferon alfa and ribavarin regimen). It was not possible to perform an adjusted indirect comparison between the subgroup of prior relapsers who attained an eRVR as no patients in the placebo/PR treatment group in the PROVE 3 trial achieved an eRVR.

The submission presented this comparison to justify the reduction in the duration of PR treatment (when given in combination with telaprevir) from 48 weeks to 24 weeks in non-cirrhotic relapsers who attain an eRVR. The submission implied that both regimens are equally effective in this specific subgroup of patients.

Study C107 was a supportive premodelling single-arm study in which 82 patients who had previously been treated in the PR arm of the PROVE 3 study were given telaprevir/PR. This represented 70.1% of all patients in the PR arm of the PROVE 3 study

For PBAC's view, see Recommendation and Reasons.

2. Telaprevir +-PR versus boceprevir + PR

The submission presented an indirect comparison of the T12/PR48 arm of the REALIZE trial and both boceprevir + PR regimens included in the RESPOND 2 trial: boceprevir + PR response guided therapy (RGT) and boceprevir + PR fixed duration therapy. The control arm of each of the two trials was used as the common-reference arm for the indirect comparison.

The PBAC noted that no minimal clinically important difference to determine non-inferiority was specified. In addition, the width of the confidence intervals suggested that many of the comparisons were inadequately powered for testing non-inferiority. Combined with concerns regarding the exchangeability of the trials, [for example the boceprevir trial (RESPOND 2) did not include prior null responders and the teleprevir trial (REALIZE) contained more cirrhotic patients] the PBAC considered it difficult to draw conclusions regarding the relative efficacy of telaprevir/PR and boceprevir/PR in treatment experienced genotype 1 CHC patients who are either prior relapsers or prior partial responders.

For PBAC's view of these results, see Recommendation and Reasons.

During the overall treatment phase, telaprevir + PR was associated with a greater incidence of grade 3 AEs and more AEs that required a dose reduction of peginterferon alfa and/or ribavirin, compared to placebo+ PR. The incidence of serious AEs also tended to be higher in the telaprevir + PR treatment arm compared to the placebo + PR arm.

9. Clinical Claim

The submission described telaprevir in combination with PR as superior in terms of comparative effectiveness over PR alone. The submission acknowledged that telaprevir in combination with PR is inferior in terms of comparative safety to PR alone during the 12 week telaprevir treatment phase, but argued that, across the entire course of therapy, the comparative safety trends towards being non-inferior.

The PBAC considered that the results of the REALIZE trial were supportive of the claim of superior efficacy of telaprevir in combination with peginterferon and ribavirin (48 weeks) over placebo in combination with peginterferon and ribavirin (48 weeks) in patients with chronic HCV who have failed one prior attempt at interferon based therapy, as measured by the proportion of patients achieving a sustained virological response (SVR). The PBAC further considered that telaprevir in combination with PR is of inferior safety to PR alone.

In addition, the submission claimed that overall, the comparative efficacy of boceprevir in prior relapser and prior partial responder patients is non-inferior to telaprevir, when both are administered in combination with PR.

The PBAC considered that the comparison of the relative efficacy of telaprevir + PR with boceprevir + PR in treatment experienced prior relapsers or partial responders was uncertain due to concerns with the exchangeability of the trials and lack of power to test non-inferiority.

10. Economic Analysis

The submission presented two stepped economic analyses of telaprevir to reflect the different comparators for patients who have received one, and those who have received more than one prior treatment with interferon based therapies. The models were cost-utility analyses that adopted a health care sector perspective. The trial based outcome, sustained virological response (SVR), was translated into health outcomes by applying different transition probabilities to patients who achieve SVR and to those who do not.

The base case incremental cost/extra QALY gained for both patient groups was between $15,000 and $45,000.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The net financial cost to the PBS (excluding treatment naïve patients) was estimated by the submission to be between $30 - $60 million in Year 5. This estimate was uncertain and may be an underestimate.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC considered that the appropriateness of the requested restriction was uncertain noting that evaluation by the TGA was still in process and the final indication, recommended treatment duration with peg/interferon and ribavirin, and the number of quantitative hepatitis C virus (HCV) RNA assays required were all factors that will inform the appropriateness of the requested restriction. The PBAC and Sponsor also noted that there could be flow on changes required to the restrictions for peg/interferon with ribavirin treatments for CHV currently listed on the PBS if telaprevir was recommended for PBS listing. However, these changes cannot be assessed in the absence of completion of the TGA evaluation and a TGA Delegate's overview. In relation to the two quantitative HCV RNA assays included in the requested restriction, the PBAC noted that these would be subsidised under the current Medical Benefits Schedule (MBS). However, if further quantitative HCV RNA assays were to be included in the restriction, requiring MBS subsidy, then a joint co-dependent technology submission would be required for evaluation by both the Medical Services Advisory Committee (MSAC) and the PBAC.

The PBAC also considered that the restriction should exclude use of telaprevir in patients who have failed to respond to other HCV N3S 4A protease inhibitors.

The PBAC considered the nominated comparators (placebo added to peg/interferon and ribavirin in patients with one prior treatment with interferon-based therapy and placebo for no treatment in patients with more than one prior treatment with interferon-based therapy) to be appropriate. The PBAC also noted the secondary comparison with boceprevir added to peg/interferon and ribavirin.

The PBAC considered the results of the REALIZE trial were supportive of the claim of superior efficacy of telaprevir in combination with peginterferon and ribavirin (48 weeks) over placebo in combination with peginterferon and ribavirin (48 weeks) in patients with chronic HCV who have failed one prior attempt at interferon based therapy, as measured by the proportion of patients achieving a sustained virological response (SVR). The PBAC considered the comparison of the results for prior relapsers, (stratified by extended rapid virological response (eRVR) status), in the telaprevir with peginterferon and ribavirin (PR) 48 week treatment arm of the REALIZE trial (relevant to prior relapsers who have cirrhosis or who fail to achieve an eRVR) and the telaprevir/PR 24 treatment arm of the PROVE 3 trial (representative of the proposed duration of treatment in non-cirrhotic prior relapsers who achieve an eRVR) was uncertain. The comparison was inadequately powered for statistical testing of non-inferiority and the PBAC noted that it was a comparison of subgroup results

from single treatment arms from two separate trials, with no common reference group. The PBAC hence considered the estimated comparative efficacy of the reduction in the duration of PR treatment (when given in combination with telaprevir) from 48 weeks to 24 weeks in non-cirrhotic relapsers who attain an eRVR was uncertain.

The PBAC noted that the REALIZE trial included an unknown proportion of subjects who had previously failed more than one prior attempt at interferon-based therapy. The PBAC considered that it is likely that the evidence presented is applicable to previously treated patients overall and considered that the data presented from the C107 study were supportive.

The PBAC considered that telaprevir in combination with PR is of inferior safety to PR alone. The PBAC noted that telaprevir + PR was associated with a greater incidence and severity of rash and anaemia (including anaemia requiring blood transfusion) than PR alone.

The PBAC noted two stepped economic analyses were presented to reflect the different comparators for patients who have received one or more than one prior treatment with interferon based therapies. The PBAC noted that the economic analyses assumed that patients in viral positive health states have a lower quality of life than those who achieve sustained virological response and that this assumption is responsible for more than a third of the incremental QALYs in the telaprevir arm. The PBAC considered that this was a source of uncertainty. However, the PBAC noted that the scenario presented in the sponsor's Pre-PBAC Response that modified this assumption that the utility of patients who achieve a SVR is equivalent to the utility of patients without an SVR. The result of this analysis was a cost/QALY of between $15,000 and $45,000 for patients who had received one prior treatment with interferon based therapy. The PBAC also considered that the possibility of re-infection among patients who achieve a SVR and the development of viral resistance to telaprevir/PR should have been included in the economic evaluation.

The PBAC considered the sensitivity analyses presented in the submission were limited and did not involve combinations of changes to variables that would result in higher ICERs. The PBAC noted that high ICERs can be generated by using plausible values as calculated during the evaluation. The PBAC considered that the presentation of more extensive sensitivity analyses would have been informative. The PBAC also noted that Markov traces of the ICER over time would have been informative.

The PBAC considered the submission's utilisation estimates to be highly uncertain. The PBAC noted that the submission assumed that telaprevir would be listed on the PBS for the treatment of genotype 1 CHC patients naïve to interferon based therapies at the same time as the listing for treatment experienced patients. The PBAC also noted that the submission subsequently assumed that, as telaprevir + PR would be standard care for treatment naïve patients, there would be no new treatment experienced patients eligible for retreatment with telaprevir. Hence the estimated cost to the PBS was based only on the prevalent treatment experienced patient pool at the time of listing, who are assumed to be subsequently retreated over the first 5 years of listing. The PBAC noted that utilisation figures for telaprevir/PR in treatment experienced patients only (for the prevalent population) were provided in the sponsor's Pre-Sub-Committee Response. However, the PBAC considered the utilisation remained uncertain and noted the difference in the results calculated during the evaluation based on the inclusion of both prevalent and incident treatment-experienced patients.

The PBAC therefore rejected the submission on the basis of uncertainty about the impact of the final product information resulting from the evaluation by the TGA on all aspects of the submission with resultant uncertain cost effectiveness and highly uncertain utilisation.

The PBAC considered there is a clinical need for additional treatment options for chronic HCV. The PBAC considered that consultation with clinicians would assist in determining the place in therapy in chronic HCV of direct acting anti-viral agents, noting that the standard of care in chronic HCV is currently an area of rapid change.

The PBAC noted that the Highly Specialised Drugs (HSD) Working Party considered that telaprevir did not meet all the criteria for the HSD Program and hence did not support the listing as a HSD under Section 100.

The PBAC acknowledged and noted the consumer comments on this item.

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 had no further comment.