

5.21 RIBAVIRIN
Tablets, 400mg and 600mg;
Ibavyr[®]; Clinect Pty Ltd.

1 Purpose of Application

1.1 The submission requested a Section 100 Authority Required (STREAMLINED) listing for ribavirin for the treatment of chronic hepatitis C (CHC).

2 Requested listing

2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Genotype 2 treatment naïve patients (initial)

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
RIBAVIRIN RIBAVIRIN 400 MG TABLET, 28	2	2	\$ [REDACTED]	IBAVYR IX Clinect Pty Ltd
RIBAVIRIN RIBAVIRIN 600 MG TABLET, 28	2	2	\$ [REDACTED]	IBAVYR IX Clinect Pty Ltd

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	
Condition:	<i>Chronic hepatitis C infection</i>
PBS Indication:	<i>Chronic hepatitis C infection</i>
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Treatment criteria:	Must be treated in an accredited treatment centre

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<p>Clinical criteria:</p>	<p>Patient must have compensated liver disease,</p> <p>AND</p> <p>Patient must not have received prior <i>interferon alfa or peginterferon alfa treatment for hepatitis C</i> (with or without sofosbuvir or a protease inhibitor),</p> <p>AND</p> <p>The treatment must be in combination with sofosbuvir only,</p> <p>AND</p> <p>The treatment must be limited to a maximum duration of 12 weeks The treatment must be limited to a maximum duration of 24 weeks.</p>
<p>Population criteria:</p>	<p>Patient must be 18 years or older,</p> <p>AND</p> <p>Patient must not be pregnant or breastfeeding. Female partners of male patients must not be pregnant. Patients and their partners must each be using an effective form of contraception if of child-bearing age,</p>
<p>Prescriber Instructions</p>	<p>Evidence of chronic hepatitis C infection (repeatedly anti-HCV positive and HCV RNA positive) must be documented in the patient's medical records,</p> <p>AND</p> <p>A maximum of 2 repeats may be prescribed.</p>
<p>Administrative Advice</p>	<p><u>Note</u> <i>Increased repeats may be requested from the Department of Human Services for patients weighting equal to or greater than 75 kg.</i></p> <p><u>Note</u> 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</p>

2.2 The proposed PBS listing restricted ribavirin to use with sofosbuvir in genotypes 2 and 3 Hepatitis C Virus (HCV). The restriction does not allow the use of ribavirin with agents other than sofosbuvir. The ESC noted that ribavirin has been proposed as adjunctive therapy to improve the SVR or shorten treatment duration for SOF-based and other direct acting antiviral (DAA)-based regimens, which may be precluded with the proposed wording.

2.3 The PBAC recalled the discussion at the Stakeholder meeting (New oral antivirals for the Treatment of Hepatitis C, February 2014) about the setting patients should be

treated in. The PBAC considered that it was appropriate that the new all oral treatment regimens be listed in the General Schedule, to facilitated the longer term objectives for access to treatment, increase treatment rates and outcomes with a view to treat all patients with CHC over time.

- 2.4 The submission did not provide any economic evaluation to support the requested listing. Instead, the submission referred to the sofosbuvir submission for cost-utility analyses of sofosbuvir in combination with ribavirin (SOF+R) in the intended PBS population.

3 Background

- 3.1 **TGA status:** The submission was made under TGA/PBAC Parallel Process. The Clinical evaluation report was provided with the Pre-Sub-Committee Response (PSCR). The sponsor provided the TGA Approval letter with the pre-PBAC response.

- 3.2 The PBAC noted that IBAVYR (ribavirin tablets) was included on the Australian Register of Therapeutic Goods on the 26 February 2015. The indication is for use in combination with other oral agents for the treatment of chronic hepatitis C (CHC) in adults.

- 3.3 This was the first submission for single agent ribavirin to be listed on the PBS for the treatment of CHC. In July 2014, the PBAC considered the sofosbuvir submission, where for genotypes 2 and 3 HCV, a treatment regimen of sofosbuvir in combination with single agent ribavirin was requested. Ribavirin is only available as a component within a co-package with peginterferon alfa-2a (Pegasys RBV[®], Roche Products) or peginterferon alfa-2b (Pegatron[®], Merck Sharp & Dohme). The proposed regimen of sofosbuvir + ribavirin (SOF+R) in the sofosbuvir submission created a need for ribavirin to be available as a stand-alone medicine to be prescribed along with sofosbuvir for patients who were eligible for peginterferon-free HCV therapy. The sponsor of [REDACTED] has formed an international business partnership with [REDACTED] to distribute an existing formulation [REDACTED]. Clinect Pty Ltd has been appointed as the Australian and New Zealand sponsor for this product. As ribavirin was proposed to be used for a subset of the patient population defined in the sofosbuvir submission which was considered at the July 2014 PBAC meeting, the current ribavirin submission did not replicate the clinical data or economic analyses presented in the sofosbuvir submission; instead, the July 2014 sofosbuvir submission was referred to with the approval from Gilead Sciences.

4 Clinical place for the proposed therapy

- 4.1 HCV infection is a major cause of chronic liver disease. The cycle of viral reproduction within hepatic cells and the response by the host immune system to the infection results in damage to the host's liver. Chronic infection can lead to scarring of the liver and ultimately to cirrhosis. In some cases, patients with liver cirrhosis develop liver failure, liver cancer or life-threatening oesophageal and gastric HCV. Currently, HCV genotypes 2 and 3 account for about 5-8% and 33-42% of infections in Australia respectively.

- 4.2 Ribavirin is an oral synthetic nucleoside analogue with antiviral activity. Ribavirin has shown *in vitro* activity against some ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) viruses. Ribavirin monotherapy is not effective and must only be used in combination with other agents for the treatment of CHC.
- 4.3 Sofosbuvir in combination with ribavirin provides a therapeutic option for treatment naïve and experienced patients with HCV genotypes 2 or 3.

5 Comparator

- 5.1 The submission nominated 'no treatment' as the main comparator for all patients for whom listing was sought for ribavirin, except those with genotype 2 CHC who were eligible for interferon-containing therapy. For this latter population the proposed comparator was peginterferon and ribavirin (PR) for 24 weeks (contingent upon an undetectable result by an HCV RNA assay at week 12).
- 5.2 PR would be an appropriate comparator for those patients who are currently seeking active HCV treatment. However, when assessing other interferon-free treatments the PBAC had previously considered that the appropriate comparator would be 'no treatment' in view of the broader context of infected individuals whose treatment preference is interferon-free therapies (Draft Public Summary Document (PSD) – July 2014 PBAC meeting, 5.17 Sofosbuvir). The PBAC agreed with ESC that the most relevant comparator was no treatment.

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (172), health care professionals (16) and organisations (18) via the Consumer Comments facility on the PBS website. The PBAC noted the correspondence from the Gastroenterological Society of Australia (GESA) on use of DAAs in the treatment of patients with liver cirrhosis and severe portal hypertension, decompensated liver disease, or patients post liver transplant. The large number of comments highlighted the benefit of the availability of a curative treatment that should be made available for all infected individuals and the improved quality of life as well as the side effects associated with the current treatments that would be avoided. The PBAC noted the patient preference for treatments with shorter durations, such as 12 weeks compared to 24 weeks.
- 6.3 Representatives of the PBAC met with Hepatitis Australia, Hepatitis NSW, the Australian Injecting and the Illicit Drug User's League prior to the PBAC meeting, and reported the following key points to the PBAC in relation to the agenda items for the treatment of Hepatitis C.

- The high burden of disease associated with HCV infection was noted, and the urgent need for new treatments acknowledged. The significant adverse reactions associated with interferon-based therapies effectively eliminate these regimens as an option for some patients.
- Concern about not having any treatment (the so-called “warehousing” practice adopted by clinicians), lack of access to transient elastography (including FibroScan®) and the lack of adequate follow-up for patients that are “warehoused” (i.e. where the patient is monitored but treatment is delayed). A complex referral system does not work for many groups of Hepatitis C patients – for example, it was quoted in the meeting that in the ACT only 28 patients have had access to treatment in the previous 12 months.
- Community expectation with regard to the new drugs for Hepatitis C is high, and there is a high level of anticipation with patients keenly aware that these drugs are available in markets outside Australia. It was noted that these expectations were in place for a significant time before the sponsors chose to make reimbursement submissions to the PBAC.
- Co-ordinated treatment of HCV, particularly moving towards the control (and potentially elimination) of the virus, would require health-system-wide approaches that are outside the remit of the PBAC.
- As the PBAC can recommend the circumstances under which PBS subsidy may be granted, elements such as whether to limit prescribing to specialists would be considered in potentially widening access. The PBAC particularly noted the advice of consumer groups that a PBS listing that limited access based on disease severity would not be supported. A listing that allowed broad access was favoured.
- It was also noted that representatives felt that these drugs should be assessed for their capacity for providing a cure within a 12 week period, not as longer term treatment strategies.

6.4 The PBAC noted and welcomed this input.

For more detail on PBAC’s view, see section 7 “PBAC outcome

Clinical trials

6.5 The submission did not provide any clinical evidence in support of the combination treatment of SOF+R for treatment of genotypes 2 and 3 HCV infection, but referred to the sofosbuvir submission considered at the July 2014 PBAC meeting for relevant data on the effectiveness and safety of SOF+R in the proposed PBS population.

Economic analysis

6.6 The submission referred to the sofosbuvir submission for cost-utility analyses of SOF+R in the intended PBS population.

6.7 The proposed price for ribavirin in the submission was not based on any economic analysis; it was derived from external reference pricing (also known as international reference pricing). The limitations of external reference pricing, include the impact of confidential price agreements, the heterogeneous nature of distributors’ profit margins, taxes, supply chain mark-ups, and differences in the burden of disease, indications, willingness and ability to pay and market structure/size.

Drug cost/patient/course

6.8 The costs for ribavirin using the dispensed price for maximum quantity (DPMQ) suggested by the sponsor were estimated to be:

- \$ [redacted] for the 12-week regimen for patients weighing <75kg;
- \$ [redacted] for the 12-week regimen for patients weighing ≥75kg;
- \$ [redacted] for the 24-week regimen for patients weighing <75kg; and
- \$ [redacted] for the 24-week regimen for patients weighing ≥75kg.

Estimated PBS usage & financial implications

6.9 This submission was not considered by DUSC.

6.10 The submission used an epidemiological approach to estimate the expected financial impact of listing single agent ribavirin for use in combination with sofosbuvir. The majority of these data sources and/or assumptions were similar to those in the July 2014 sofosbuvir submission, with some revised estimates concerning the use of the interferon-free regimen in patients with genotype 3 CHC. The estimated use and financial implications are summarised in the table below. At year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be \$10 – \$20 million per year.

Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
In genotype 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
In genotype 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of MQ dispensed					
400 mg x 28; MQ 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
600 mg x 28; MQ 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated net cost to PBS/RPBS^a					
Net cost to PBS/RPBS ^b	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]

MQ = maximum quantity.

^a Not including changes in costs of other drugs, e.g. sofosbuvir and current active treatments

^b Recalculated during the evaluation by rounding up the number of co-payment to the next integer

Source: Tables E-2 and E-3, p54 and p56 of the main submission.

The redacted table above shows that in Year 5, the estimated number of ribavirin scripts dispensed would be 10,000-50,000 and the net cost to Government would be between \$10-\$20 million per year.

6.11 There was potential for the number of patients treated with ribavirin to be greater than estimated in the submission:

- The submission underestimated the system capacity to treat HCV patients. The submission estimated the number of HCV patients (all genotypes) likely to be treated to be less than 10,000 in Year 1, increasing to less than 10,000 in Year 5 of listing. The HCV Stakeholder meeting (February 2014) estimated that 10,000 – 50,000 patients were likely to be treated.
- The proportion of patients with genotype 3 HCV seeking an interferon-free

treatment of SOF+R was estimated to be 66.8% in the submission. This proportion was considered an underestimate in the context of known patient preferences for an interferon free regimen. The PBAC agreed with ESC and DUSC and considered that assuming that 100% of genotype 3 HCV patients will seek the interferon-free regimen of SOF24+R24 is more appropriate.

- 6.12 The PBAC considered that the advice received from the Australian Liver Association, namely Bruggmann et al. (2014), was the most appropriate the source of HCV genotype distribution in Australia.
- 6.13 A sensitivity analysis was performed during the evaluation by increasing the number of patients treated to 10,000 – 50,000 (as suggested in the HCV Stakeholder Meeting) and assuming 100% genotype 3 HCV patients seeking the interferon-free regimen of SOF24+R24. The total number of patients prescribed single agent ribavirin would be less than 10,000 and the cost impact of ribavirin to the PBS would be \$30 – \$60 million per year (note: this estimate did not include the cost of co-administered sofosbuvir and the cost offset arising from the substitute of current active treatments (only in a small proportion of the target population)). The PSCR (p3) presented alternative sensitivity analysis based on 100% of genotype 3 patients and 10,000 – 50,000 total treated patients indicates an estimated net cost to the PBS of between \$10 - \$20 million per year to \$20 - \$30 million per year. The ESC considered usage of RBV proposed in the submission may have been underestimated based on the National HCV Strategy targets for treatment and the preference for SOF24+R24 over SOF12+RP12 for GT3.
- 6.14 The PBAC noted the estimates by DUSC, during the consideration of items 5.03, 5.06, 5.13 and 7.04. The following number of patients of all genotypes estimated to be treated over the first five years of listing of new treatments.

Year 1	Year 2	Year 3	Year 4	Year 5
6,600	9,900	15,000	15,000	15,000

Quality Use of Medicines

- 6.15 Single agent ribavirin is not listed on the PBS. Ribavirin is only available co-packaged with peginterferon from the PBS. In the absence of PBS subsidised single agent ribavirin, clinicians may have to resort to prescribing the currently available combination products involving peginterferon and ribavirin and discarding the peginterferon. If a Genotype 3 patient received 12 weeks of SOF plus peginterferon with ribavirin and then discarded the peginterferon, they would be treated with a sub-optimal course of SOF12+ R12. In addition, such a practice would represent substantial wastage.

7 PBAC Outcome

- 7.1 The PBAC rejected the submission for the Section 100 (Highly Specialised Drugs Program) Authority Required (Streamlined) listing for ribavirin for the treatment of chronic hepatitis C Genotype 2 and 3 on the basis that the submission had not justified the incremental cost effectiveness of ribavirin compared to the currently listed ribavirin based items.

- 7.2 The PBAC noted the clinical need for a stand-alone ribavirin (RBV) for the treatment of genotype 2 and 3 patients if sofosbuvir is listed on the PBS. The PBAC noted that ESC highlighted that there was evidence that RBV was used as adjunctive therapy to improve the SVR or shorten treatment duration of DAA-based regimens.
- 7.3 The PBAC recalled the discussion at the Stakeholder meeting (February 2014) about the setting patients should be treated in. The PBAC considered that it was appropriate that the new all oral treatment to be listed in the General Schedule, to facilitated the longer term objectives for access to treatment, increase treatment rates and outcomes and acknowledging initiatives such as The Fourth National Hepatitis C Strategy 2014-2017 and NSW Hepatitis C Strategy 2014-2020 to support a greater role of primary care in the prescribing and monitoring of the newer generation of antivirals, that have reduced side effects and more simplified dosing schedules. The PBAC noted that treatment of patients would initially remain in tertiary settings but expand as clinician experience grows.
- 7.4 The PBAC noted that the Commentary stated that an alternative approach to determine the ribavirin price could have been to establish the cost-effective price for SOF+R as a combination therapy and then suggest a negotiation between the sponsors of the two products with regard to the disaggregated reimbursed prices for sofosbuvir and ribavirin that they would be willing to have listed on the PBS.
- 7.5 The PBAC reiterated their view that the appropriate comparator was no treatment in view of the broader context of infected individuals whose treatment preference is interferon-free therapies.
- 7.6 The PBAC considered that the approach presented in the submission, based on international reference pricing was not informative for valuing ribavirin in the Australian context. The PBAC noted that the submission presented an analysis of the 'shadow price' of ribavirin on the PBS. The PBAC considered that, though mathematically correct to use negative unit costs for deriving a weighted price, it was more appropriate to exclude negative costs in this analysis. The PBAC noted that the submission presented data that showed that there were more services of Pegasys RBV than Pegatron during 2013-2014. The PBAC noted that based on Pegasys RBV analysis, the cost of a 200mg tablet of ribavirin was calculated to range between \$████ and \$████.
- 7.7 The PBAC were of a mind to approve listing if stand-alone ribavirin was cost-minimised to the ribavirin in the co-pack with peg-interferon most likely to be replaced, based on current usage, and that as a component of a CHC treatment course, that the cost of the total treatment course remained in the acceptable willingness-to-pay threshold for a CHC patient weighting less than 75kg.
- 7.8 The PBAC noted that this submission is eligible for an Independent Review.
- 7.9 The PBAC wished to advise the Minister that:
- While interferon-free oral direct acting antiviral (DAA) agents provide safe and effective treatment options for patients with CHC, there is a substantial opportunity cost associated with the potential listing of these medicines. The lower estimate of this opportunity cost is more than \$3 billion over 5 years, at the prices proposed in

the submissions. Given this large opportunity cost, the cost of a course of treatment should be set irrespective of the duration, and that other pricing policies be considered.

- The impact of the new antivirals on patients currently infected has been modelled by Sievert et al. (2014). This modelling shows that the number of people with chronic hepatitis C (CHC) will be reduced by 60% in 2030 compared to the base case of current treatment. The assumptions in the model include up to 13,500 people (including all fibrosis stages) are treated annually by 2018 and the DAA agents are expected to have rates of sustained virologic response (measured at 12 weeks, SVR12) up to 90% for genotype 1 and 80% for genotype 3 by 2016. The analyses accounted for mortality but did not consider re-infection.
- Advice from the Australian Liver Association (ALA) indicated that of the estimated 233,000 people living with Hepatitis C virus (HCV), 193,000 patients have been diagnosed. Listing of oral DAA agents may increase public and clinician awareness of the disease potentially leading to increased testing and diagnosis.
- The DUSC analysis shows that approximately 60 000 patients would be treated over 5 years, based on treatment targets in the Fourth National Hepatitis C Strategy 2014-2017, together with the advice from the ALA and February 2014 Stakeholder meeting (New oral antivirals for the Treatment of Hepatitis C). However, it is not clear how many people living with CHC will seek treatment, particularly if patients have to be seen in specialist liver clinics or wait for a referral to a liver clinic. Prescribing is likely to continue to be delivered through specialist clinics in the short-term until clinicians in other settings have learned how to use the DAA agents. Patients may still be required to go through the hospital system as part of their clinical management, which could be a limiting factor to uptake.
- Given the very large opportunity cost, one option would be to restrict access to treatment to those with the highest clinical need. The PBAC considered that it was inappropriate to restrict access, given the likely benefit of the DAA agents across the full spectrum of patients with CHC, from those with early disease to those patients with existing liver cirrhosis and severe portal hypertension, decompensated liver disease, or patients post liver transplant. The benefits in terms of avoidance or delay of decompensated cirrhosis, hepatocellular carcinoma and morbidity are likely to be seen earlier in the most severely ill, but population benefits, such as reduction in transmission of the disease, are likely to occur with wide access to treatment. These and other benefits may be also realised via other community-based programmes and strategies, such as those described in the Fourth National Hepatitis C Strategy 2014-2017.
- The high response (sustained virologic response measured at 12 weeks, SVR12) observed in the clinical trials may only be realised if the adherence of patients in Australia to treatment is similar to those in the clinical trials. While there is a patient preference for shorter treatments, and new shorter treatment regimens are currently being tested, for some patients, 24 weeks of treatment are necessary. Therefore it is critical that appropriate prescribing education be put in place to ensure that the benefits to the Australian community are maximised.
- The treatment landscape of HCV treatment is changing rapidly, as new DAA agents or new combinations of DAA agents become available and treatment guidelines are regularly updated. It is likely that new DAA agents will be produced over the next 2 to 3 years that may further increase treatment options.

- In this context, the current treatment for CHC, such as peginterferon and ribavirin alone and in combination with telaprevir, boceprevir or simeprevir, are no longer cost-effective as currently listed especially given the higher rate of adverse effects observed in clinical practice for some treatment combinations compared to those observed in the clinical trials. The Minister may wish to review the listing of these products. The PBAC advised the Department to bring this consideration to the attention of the sponsor of these products. The Commonwealth currently pay approximately \$87 million for these treatments.

Outcome:

Rejected

8 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.

9 Sponsor's Comment

The sponsor had no comment.