

6.12 RIBAVIRIN

tablet 400 mg, tablet 600 mg

Ibavyr®, Clinect Pty Ltd

1 Purpose of Application

- 1.1 The minor submission requested an extension to the listing of ribavirin for the treatment of chronic hepatitis C (CHC) infection to include treatment regimens of daclatasvir + sofosbuvir + ribavirin (DAC/SOF/RBV) for 12 or 24 weeks for the use in HCV Genotypes (GT) 2, 3, 4, 5 and 6 for patients with decompensated liver disease.

2 Requested listing

- 2.1 The submission requested changes to the existing listings of ribavirin for the treatment of HCV in combination with other direct acting antiviral agents.
- 2.2 Treatment regimens for HCV infection are not contained within individual prescribing rules for medicines used for this indication. The minor submission requested an amendment to the treatment matrix within the General statement for drugs for the treatment of hepatitis.

3 Background

- 3.1 Single agent ribavirin was registered by the TGA for treatment, in combination with other oral agents, of chronic hepatitis C on 26 February 2015.
- 3.2 The PBAC previously considered treatment regimens for the various CHC genotypes in 2015, and did not recommend treatment regimens containing daclatasvir and sofosbuvir +/- ribavirin for GT 4/5/6 on the basis of limited evidence to support them.
- 3.3 The PBAC has previously considered ribavirin for treatment of CHC as part of a regimen containing direct acting antivirals on several occasions. These previous considerations are summarised below:
- March 2015, PBAC rejected the submission for S100 (Highly Specialised Drugs Program) listing of ribavirin co-prescribed with sofosbuvir for the treatment of GT 2 or 3 HCV on the basis of inadequately justified incremental cost effectiveness compared to the existing ribavirin and peg-interferon combination items.
 - July 2015, PBAC deferred the submission for standalone ribavirin on the basis of uncertain use in association with other oral interferon-free regimens, and as the requested listing may have inappropriately restricted availability of ribavirin to patients infected with other HCV genotypes.
 - November 2015, PBAC recommended the listing of ribavirin in combination with other direct-acting antivirals.

4 Current situation

- 4.1 The current treatment regimen matrices for cirrhotic patients are included below (source: General Statement for Drugs for the Treatment of Hepatitis C).

	Treatment naïve	Treatment experienced
Genotype 1	LEDIPASVIR + SOFOSBUVIR [12 weeks] OR DACLATASVIR and SOFOSBUVIR [24 weeks] OR DACLATASVIR and SOFOSBUVIR and RBV [12 weeks] OR SOFOSBUVIR and PEG-IFN (&) RBV [12 weeks] OR PARITAPREVIR + RITONAVIR + OMBITASVIR (&) DASABUVIR (&) RBV [12 weeks]	LEDIPASVIR +SOFOSBUVIR [24 weeks] OR DACLATASVIR and SOFOSBUVIR [24 weeks] OR DACLATASVIR and SOFOSBUVIR and RBV [12 weeks] OR SOFOSBUVIR and PEG-IFN (&) RBV [12 weeks] OR PARITAPREVIR + RITONAVIR + OMBITASVIR (&) DASABUVIR (&) RBV [12 or 24 weeks]
Genotype 2	SOFOSBUVIR and RBV [12 weeks]	SOFOSBUVIR and RBV [12 weeks]
Genotype 3	DACLATASVIR and SOFOSBUVIR [24 weeks] OR SOFOSBUVIR and RBV [24 weeks] OR SOFOSBUVIR and PEG-IFN/RBV [12 weeks]	DACLATASVIR and SOFOSBUVIR [24 weeks] OR SOFOSBUVIR and RBV [24 weeks] OR SOFOSBUVIR and PEG-IFN/RBV [12 weeks]
Genotype 4, 5, 6	SOFOSBUVIR and PEG-IFN/RBV [12 weeks]	SOFOSBUVIR and PEG-IFN/RBV [12 weeks]

5 Consideration of the Evidence

Sponsor hearing

- 5.1 There was no hearing for this item as it was a minor submission.

Consumer comments

- 5.2 The PBAC noted that no consumer comments were received for this item.

Drug cost per patient per course: \$ [REDACTED], based on a treatment course of 24 weeks.

5.3 The duration of treatment proposed was 24 weeks, in combination with daclatasvir and sofosbuvir. Patients weighing less than 75 kg would receive 1,000 mg/ day, while patients over 75 kg will receive 1,200 mg/ day. The cost per course was averaged between a 50/50 split of patients above and below the dose/weight threshold. The sponsor did not provide a treatment cost for a 12 week regimen as they estimated less than one patient per year for genotypes 2, 4, 5 or 6 would be eligible for treatment.

Estimated PBS usage & financial implications

5.4 The submission estimated a total treated population of 10,000 – 50,000per year in years 1-3, decreasing to less than 10,000in year 4, and less than 10,000in year 5. It was predicted that the proposed change to listing would add less than 10,000 patients per year in years 1-3, less than 10,000 patients in year 4, and less than 10,000 patients in year 5.

The minor submission estimated a net cost to the PBS of less than \$10 million per year in Year 1 of listing, with a total net cost to the PBS of less than \$10 million over the first 5 years of listing. This is summarised in the table below.

Table 1: Estimated extent of use and financial implications

Use and cost of IBAVYR to the PBS/RPBS	Year 1	Year 2	Year 3	Year 4	Year 5
Total treated population	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Genotype 1	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Genotype 2	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Genotype 3	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Genotypes 4,5,6	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Incremental patients prescribed IBAVYR per proposed amendment					
Genotype 3, with decompensated disease	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
-weighing up to 75 kg, 1,000mg/ day	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
-weighing more than 75 kg, 1,200 mg/ day	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Cost at DPMQ	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
PBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Co-payments	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
PBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net Cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net Cost to PBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net Cost to RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Ribavirin submission, p. 6.

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be less than \$10 million per year.

For more detail on PBAC's view, see section 6 "PBAC outcome"

6 PBAC Outcome

- 6.1 The PBAC recommended the listing of ribavirin in combination with daclatasvir and sofosbuvir as a 12 week treatment course for the treatment of Genotype 3 CHC in treatment naïve and treatment experienced cirrhotic patients. The PBAC also recommended a footnote be added to the GT3 daclatasvir with sofosbuvir 24 week regimen to allow for the addition of ribavirin to this regimen when clinically appropriate, for example in patients with decompensated liver disease. In making this recommendation, the PBAC noted that new direct-acting antiviral treatment regimens for CHC are available both as General Schedule items and under special arrangements under Section 100. The PBAC recommended the special arrangements currently in place for new drugs for CHC listed under the Highly Specialised Drugs Program should apply to any new Section 100 listings for ribavirin.
- 6.2 The PBAC noted that the sponsor and some clinicians had informally stated they had requested ribavirin from the sponsor on compassionate grounds to treat CHC patients with decompensated liver disease outside current PBS listings.
- 6.3 The PBAC considered that while no new data was presented in the submission, results from the published ALLY-3+ study¹, demonstrated that treatment with 12 weeks of ribavirin in combination with daclatasvir and sofosbuvir in GT3 patients with cirrhosis was well tolerated and resulted in similar response rates to currently subsidised treatment regimens.
- 6.4 The PBAC noted the "*Hepatitis C Virus Infection Consensus Statement Working Group. Australian recommendations for the management of hepatitis C virus infection: a consensus statement 2016. Melbourne: Gastroenterological Society of Australia, 2016*" identified patients with decompensated liver disease as a special population where limited evidence was available, and agreed to allow prescribers to add ribavirin to the current 24 week daclatasvir and sofosbuvir treatment regimen in GT3 patients with cirrhosis where that was considered clinically appropriate.
- 6.5 The PBAC did not consider it appropriate to extend the listing of ribavirin in combination with daclatasvir and sofosbuvir to GT 2, 4, 5 or 6 at this time. The Committee acknowledged that there is a clinical need for further treatment options for these less common genotypes, and indicated it would continue to review this recommendation as new evidence becomes available.

¹ Nelson DR, *et al.* (2015) All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. *Hepatology*. 2015 Apr;61(4):1127-35.
Leroy V, *et al.* (2016) Daclatasvir, sofosbuvir, and ribavirin for hepatitis C virus genotype 3 and advanced liver disease: A randomized phase III study (ALLY-3+). *Hepatology*. 2016 May;63(5):1430-41.

- 6.6 The PBAC considered that these changes could be given effect without any impact on the cost to Government of subsidising the new treatments for CHC. The PBAC reached this view because although a small number of patients with GT3 disease would have ribavirin added to their treatment regimen, a similarly small number would now be treated with a 12 week treatment course of ribavirin with daclatasvir and sofosbuvir in place of the currently subsidised 24 week treatment course of daclatasvir and sofosbuvir.
- 6.7 The PBAC advised there should be no change to the status of ribavirin for nurse practitioner prescribing.
- 6.8 The PBAC advised there should be no change to the status of ribavirin with regards to the early supply rule.
- 6.9 The PBAC noted that this submission was not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

7 Recommended listing

- 7.1 Amend existing/recommended listing as follows:

General statement for drugs used for the treatment of hepatitis C

For cirrhotic patients with GT3:

	Treatment naïve	Treatment experienced
Genotype 3	DACLATASVIR and SOFOSBUVIR [24 weeks] ²	DACLATASVIR and SOFOSBUVIR [24 weeks] ²
	OR	OR
	SOFOSBUVIR and RBV [24 weeks]	SOFOSBUVIR and RBV [24 weeks]
	OR	OR
	SOFOSBUVIR and PEG-IFN/RBV [12 weeks]	SOFOSBUVIR and PEG-IFN/RBV [12 weeks]
	OR	OR
	<i>DACLATASVIR and</i>	<i>DACLATASVIR and</i>

² Consider adding ribavirin where clinically appropriate

	Treatment naïve	Treatment experienced
	<i>SOFOBUVIR and RBV [12 weeks]</i>	<i>SOFOBUVIR and RBV [12 weeks]</i>

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.