

5.09 Grazoprevir 100 mg / Elbasvir 50 mg, fixed dose combination tablet, Zepatier[®], Merck Sharp & Dohme Pty Ltd.

1 Purpose of Application

- 1.1 The submission requested a Section 85 Authority Required (STREAMLINED) listing for the fixed dose combination (FDC) of grazoprevir/elbasvir (GRZ/EBR) for treatment of patients infected with genotypes 1, 4 or 6 chronic hepatitis C (CHC), irrespective of previous treatment history and for the treatment of genotype 3 CHC treatment-naïve patients.

2 Requested listing

- 2.1 The submission was originally made before the restrictions of other direct acting antiviral (DAA) treatments were finalised. The requested listings were aligned with the common structure for DAA treatments for hepatitis C. Additions to the proposed restriction are in *italics*, deletions in ~~strikethrough~~.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
GRAZOPREVIR/ELBASVIR Tablet 100 mg/50 mg	28	2	Zepatier [®]	Merck Sharp & Dohme (Australia) Pty Ltd

Category / Program GENERAL – General Schedule (Code GE)

Prescriber type: Dental Medical Practitioners Nurse practitioners Optometrists
Midwives

Chronic hepatitis C infection

~~GT 1, 4 and 6 treatment naïve and treatment experienced relapsers~~

~~GT 1b treatment experienced on treatment failures~~

~~GT 3 treatment naïve~~

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GRAZOPREVIR/ELBASVIR Tablet 100 mg/50 mg	28	3	Zepatier [®]	Merck Sharp & Dohme (Australia) Pty Ltd

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Category / Program Section 100 – Highly Specialised Drugs Program

Public Summary Document – July 2016 PBAC Meeting

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Chronic hepatitis C infection

~~GT 1, 4 and 6 treatment naïve and treatment experienced relapsers~~

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Category / Program Section 100 – Highly Specialised Drugs Program

Prescriber type: Dental Medical Practitioners Nurse practitioners Optometrists
Midwives

~~GT 1a, 4 and 6 treatment experienced on treatment failures~~

Chronic hepatitis C infection

Proposed listing 1:

Restriction	Authority Required
Clinical criteria	<p>Patient must meet the criteria set out in the General Statement for Drugs for the Treatment of Hepatitis C,</p> <p>AND</p> <p>Patient must be taking this drug as part of a regimen set out in the matrix in the General Statement for Drugs for the Treatment of Hepatitis C, based on the hepatitis C virus genotype, patient history and cirrhotic status,</p> <p>AND</p> <p>The treatment must be limited to a maximum duration of 12 weeks.</p>
Population criteria	Patient must be aged 18 years or older
Prescriber instruction	<p>No increase in the maximum quantity or number of units may be authorised.</p> <p>Note:</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>Note:</p> <p>The treatment must be limited to a maximum duration of 12 weeks.</p>

Proposed listing 2

Restriction	Authority Required
Clinical criteria	<p>Patient must meet the criteria set out in the General Statement for Drugs for the Treatment of Hepatitis C,</p> <p>AND</p> <p>Patient must be taking this drug as part of a regimen set out in the matrix in the General Statement for Drugs for the Treatment of Hepatitis C, based on the hepatitis C virus genotype, patient history and cirrhotic status,</p> <p>AND</p> <p>The treatment must be limited to a maximum duration of 16 weeks.</p>
Population criteria	Patient must be aged 18 years or older
Prescriber instruction	<p>No increase in the maximum quantity or number of units may be authorised.</p> <p>Note:</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>Note:</p> <p>The treatment must be limited to a maximum duration of 16 weeks.</p>

Requested changes to the General statement for drugs used in the treatment of hepatitis C

To align the requested listing with other direct acting antivirals for the treatment of hepatitis C, grazoprevir and elbasvir would be inserted into the treatment matrix in the general statement as shown below.

For non-cirrhotic patients:

	Treatment naïve	Treatment experienced
Genotype 1	LEDIPASVIR + SOFOSBUVIR [8 or 12 weeks]	LEDIPASVIR +SOFOSBUVIR [12 weeks]
	OR	OR
	DACLATASVIR and SOFOSBUVIR [12 weeks]	DACLATASVIR and SOFOSBUVIR [12 or 24 weeks]
	OR	OR
	SOFOSBUVIR and PEG-IFN (&) RBV [12 weeks]	SOFOSBUVIR and PEG-IFN (&) RBV [12 weeks]
	OR	OR
	PARITAPREVIR + RITONAVIR + OMBITASVIR (&) DASABUVIR [12 weeks]	PARITAPREVIR + RITONAVIR + OMBITASVIR (&) DASABUVIR [12 weeks]
OR	OR	
	PARITAPREVIR + RITONAVIR +	PARITAPREVIR + RITONAVIR +

Public Summary Document – July 2016 PBAC Meeting

	Treatment naïve	Treatment experienced
	OMBITASVIR (&) DASABUVIR (&) RBV [12 weeks] OR GRAZOPREVIR + ELBASVIR [12 weeks]	OMBITASVIR (&) DASABUVIR (&) RBV [12 weeks] OR GRAZOPREVIR + ELBASVIR [12 weeks] ^a OR GRAZOPREVIR + ELBASVIR [16 weeks] ^b OR GRAZOPREVIR + ELBASVIR (&) RBV [16 weeks] ^c
Genotype 2	SOFOSBUVIR and RBV [12 weeks]	SOFOSBUVIR and RBV [12 weeks]
Genotype 3	DACLATASVIR and SOFOSBUVIR [12 weeks] OR SOFOSBUVIR and RBV [24 weeks] OR SOFOSBUVIR and PEG-IFN/RBV [12 weeks] OR GRAZOPREVIR + ELBASVIR and SOFOSBUVIR [12 weeks]	DACLATASVIR and SOFOSBUVIR [12 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] OR GRAZOPREVIR + ELBASVIR [12 weeks]	SOFOSBUVIR and PEG-IFN/RBV [12 weeks] OR GRAZOPREVIR + ELBASVIR (&) RBV [16 weeks]
Genotype 5	SOFOSBUVIR and PEG-IFN/RBV [12 weeks]	SOFOSBUVIR and PEG-IFN/RBV [12 weeks]
Genotype 6	SOFOSBUVIR and PEG-IFN/RBV [12 weeks] OR	SOFOSBUVIR and PEG-IFN/RBV [12 weeks] OR

^a [GRAZOPREVIR + ELBASVIR] for treatment experienced non-cirrhotic patients, treatment for 12 weeks in patients with genotype 1b CHC.

^b [GRAZOPREVIR + ELBASVIR] for treatment experienced non-cirrhotic patients, treatment for 16 weeks in patients with genotype 1 CHC.

^c [GRAZOPREVIR + ELBASVIR (&) RBV] for treatment experienced non-cirrhotic patients, treatment for 16 weeks in patients with genotype 1a CHC.

Public Summary Document – July 2016 PBAC Meeting

	Treatment naïve	Treatment experienced
	GRAZOPREVIR + ELBASVIR [12 weeks]	GRAZOPREVIR + ELBASVIR (&) RBV [16 weeks]

For cirrhotic patients:

	Treatment naïve	Treatment experienced
Genotype 1	LEDIPASVIR + SOFOSBUVIR [12 weeks]	LEDIPASVIR +SOFOSBUVIR [24 weeks]
	OR	OR
	DACLATASVIR and SOFOSBUVIR [12 weeks]	DACLATASVIR and SOFOSBUVIR [24 weeks]
	OR	OR
	DACLATASVIR and SOFOSBUVIR and RBV [24 weeks]	DACLATASVIR and SOFOSBUVIR and RBV [12 weeks]
	OR	OR
	SOFOSBUVIR and PEG-IFN (&) RBV [12 weeks]	SOFOSBUVIR and PEG-IFN (&) RBV [12 weeks]
	OR	OR
	PARITAPREVIR + RITONAVIR + OMBITASVIR (&) DASABUVIR (&) RBV [12 weeks]	PARITAPREVIR + RITONAVIR + OMBITASVIR (&) DASABUVIR (&) RBV [12 or 24 weeks]
	OR	OR
GRAZOPREVIR + ELBASVIR [12 weeks]	GRAZOPREVIR + ELBASVIR [12 weeks] ^d	
	OR	
	GRAZOPREVIR + ELBASVIR [16 weeks] ^e	
	OR	
	GRAZOPREVIR + ELBASVIR (&) RBV [16 weeks] ^f	
Genotype 2	SOFOSBUVIR and RBV [12 weeks]	SOFOSBUVIR and RBV [12 weeks]
Genotype 3	DACLATASVIR and SOFOSBUVIR [24 weeks]	DACLATASVIR and SOFOSBUVIR [24 weeks]
	OR	OR
	SOFOSBUVIR and RBV	SOFOSBUVIR and RBV

^d [GRAZOPREVIR + ELBASVIR] for treatment experienced cirrhotic patients, treatment for 12 weeks in patients with genotype 1b CHC.

^e [GRAZOPREVIR + ELBASVIR] for treatment experienced cirrhotic patients, treatment for 16 weeks in patients with genotype 1 CHC.

^f [GRAZOPREVIR + ELBASVIR (&) RBV] for treatment experienced cirrhotic patients, treatment for 16 weeks in patients with genotype 1a CHC.

	Treatment naïve	Treatment experienced
	[24 weeks] OR SOFOSBUVIR and PEG-IFN/RBV [12 weeks] OR <i>GRAZOPREVIR + ELBASVIR and SOFOSBUVIR [12 weeks]</i>	[24 weeks] OR SOFOSBUVIR and PEG-IFN/RBV [12 weeks]
Genotype 4, 5, 6	SOFOSBUVIR and PEG-IFN/RBV [12 weeks] OR <i>GRAZOPREVIR + ELBASVIR [12 weeks]</i>	SOFOSBUVIR and PEG-IFN/RBV [12 weeks] OR <i>GRAZOPREVIR + ELBASVIR (&) RBV [16 weeks]</i>
Genotype 5	SOFOSBUVIR and PEG-IFN/RBV [12 weeks]	SOFOSBUVIR and PEG-IFN/RBV [12 weeks]
Genotype 6	SOFOSBUVIR and PEG-IFN/RBV [12 weeks] OR <i>GRAZOPREVIR + ELBASVIR [12 weeks]</i>	SOFOSBUVIR and PEG-IFN/RBV [12 weeks] OR <i>GRAZOPREVIR + ELBASVIR (&) RBV [16 weeks]</i>

- 2.2 The submission proposed a Special Pricing Arrangement. A dispensed price for maximum quantity (DPMQ) of \$ [REDACTED] for GRZ/EBR is to be published on the PBS website. In the absence of a final decision on the prices for nominated comparators (sofosbuvir (SOF)-containing therapies), the submission used a placeholder ex-manufacturer price (for illustrative purposes) of \$ [REDACTED] per course of GRZ/EBR treatment regardless of CHC genotype treated. This equates to a DPMQ of \$ [REDACTED], assuming patients receiving a 12-week treatment with GRZ/EBR.

The requested separate listings for GRZ/EBR reflected various treatment regimens across the CHC subgroups as proposed in the draft Product Information. The PBAC noted that these regimens may require updating based on the final approved Product Information. Treatment of patients infected with genotype 2 or 5 CHC was not proposed in the submission.

- 2.3 Listing was sought on the basis that GRZ/EBR therapies are cost-minimising to LDV/SOF, SOF+ ribavirin (RBV) or SOF+ pegylated interferon alfa + ribavirin (PR) in the relevant CHC genotype and patient groups (see the “Comparator” section of the Public Summary Document).

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

3 Background

- 3.1 TGA status at time of PBAC consideration: The submission was made under the TGA/PBAC Parallel Process. The TGA Delegate's Overview was available for consideration at the Committee meeting.
- 3.2 This was the first submission of GRZ/EBR to the PBAC for the treatment of CHC.
- 3.3 SOF and RBV were proposed to be used in combination with GRZ/EBR in CHC genotype 3 treatment-naïve patients and in genotype 1a, 4 or 6 patients who have experienced on-treatment virologic failure.

For more detail on PBAC's view, see section 7 "PBAC outcome"

4 Clinical place for the proposed therapy

- 4.1 CHC 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 varices. Currently, genotype 1 or 3 CHC account for 88-92% of infections in Australia.

5 Comparator

- 5.1 The submission nominated:
 - LDV/SOF 8 as the main comparator for genotype 1 treatment-naïve, non-cirrhotic patients;
 - LDV/SOF12 as the main comparator for genotype 1 treatment-naïve, cirrhotic and genotype 1 treatment-experienced (both relapsers and on-treatment virologic failures) patients;
 - SOF24+RBV24 as the main comparator for genotype 3 treatment-naïve patients;
 - SOF12+PR12 as the main comparator for genotypes 4 and 6 treatment-naïve patients; and
 - No treatment as the main comparator for genotypes 4 and 6 treatment-experienced (both relapsers and on-treatment virologic failures) patients.
- 5.2 The PBAC agreed that the nominated comparators for genotypes 1 and 3 were appropriate, with the exception that the treatment duration for LDV/SOF for genotype 1 treatment experienced, cirrhotic patients should be 24 weeks rather than 12, and noting the Department's advice that these comparators are the least expensive of the currently listed treatment regimens for the specified genotype.
- 5.3 At present no interferon-free regimens have been recommended for listing on the PBS for CHC genotypes 4 and 6 patients and the PBAC has previously considered "no treatment" to be the appropriate comparator in these circumstances. However, given the small number of patients with these genotypes, the PBAC considered a

clinical and economic comparison against SOF12+PR12 was reasonable for both treatment naïve and treatment experienced patients.

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 (6), health care professionals (1) and organisations (11) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with grazoprevir and elbasvir including increasing the range of direct acting antiviral treatments for hepatitis C and offering the first interferon-free treatment regimens for genotypes 4 and 6.

6.3 The PBAC noted the advice received from the following clinical groups:

- Hepatitis Australia, supported by state based hepatitis groups in Victoria, South Australia and the Australian Capital Territory;
- Hepatitis New South Wales, supported by Positive Life NSW, the NSW Users and AIDS Association (NUAA), the Network of Alcohol and other Drugs Agencies NSW (NADA) and ACON NSW;
- The Australian Hepatology Association; and
- Haemophilia Foundation Australia (HFA).

The input from all of these groups were strongly supportive of the listing of grazoprevir and elbasvir for the treatment of CHC infection, particularly as it would provide an additional treatment regimen for patients who have failed prior therapies, and would offer the first interferon free treatment regimens for patients with genotypes 4 and 6. A number of these groups also identified grazoprevir and elbasvir as being useful for people who have other medical conditions, such as bleeding disorders or HIV/HCV co-infection.

Clinical trials

6.4 There were no head-to-head comparisons of GRZ/EBR-containing therapies with any of the active CHC therapies. The submission was based on six studies involving GRZ/EBR, four LDV/SOF studies, one SOF+RBV study and two SOF+PR studies. The comparison of GRZ/EBR±RBV or SOF versus LDV/SOF or SOF+PR in the submission was based on unadjusted indirect comparison of the single arms of individual studies. For comparison of GRZ/EBR±RBV versus no treatment, sustained virologic response (SVR) rates were extracted from single arms of GRZ/EBR studies that used the correct regimen. As patients receiving no treatment are unlikely to achieve an SVR, it is probable that any hypothetical trials that included a placebo comparator would provide the same incremental estimate of SVR as the single arm of a GRZ/EBR study against an assumed SVR rate of zero.

6.5 Details of the studies presented in the submission are provided in Table 1.

Table 1: Studies and associated reports presented in the submission

Study ID	Protocol title/ Publication title	Publication citation
Studies involving grazoprevir/elbasvir		
C-EDGE TN	Clinical study report P060V01. A phase III randomized clinical trial to study the efficacy and safety of the combination regimen of grazoprevir (GRZ) and elbasvir (EBR) in treatment-naïve subjects with chronic HCV GT1, GT4, and GT6 infection.	August 2015
	Zeuzem S., Ghalib R., Reddy K. et al. Grazoprevir-elbasvir combination therapy for treatment-naïve cirrhotic and noncirrhotic patients with chronic hepatitis C virus genotype 1, 4, or 6 infection.	<i>Annals of Internal Medicine</i> 2015; 163: 1-13
C-EDGE TE	Clinical Study Report P068V01. A phase III randomized clinical trial to study the efficacy and safety of the combination regimen of GZR/EBR in subjects who have failed prior treatment with pegylated interferon and ribavirin (P/R) with chronic HCV GT1, GT4, and GT6 Infection.	August 2015
C-SWIFT	Clinical Study Report P074V01. A Phase II open-label clinical trial to study the efficacy and safety of the combination regimen of grazoprevir (GZR) and elbasvir (EBR), and sofosbuvir in treatment-naïve subjects with chronic HCV GT1 and GT3 Infection.	April 2015
C-WORTHY	Clinical Study Report P035V01. A phase II randomized clinical trial to study the efficacy and safety of the combination regimen of MK-5172 and MK-8742 ± ribavirin (RBV) in subjects with chronic hepatitis C virus Infection	April 2015
	Lawitz E., Gane E., Pearlman B., et al. Efficacy and safety of 12 weeks versus 18 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin for hepatitis C virus genotype 1 infection in previously untreated patients with cirrhosis and patients with previous null response with or without cirrhosis (C-WORTHY): a randomised, open-label phase 2 trial.	<i>Lancet</i> 2015; 385: 1075-86
	Sulkowski M., Hezode C., Gerstoft J., et al. Efficacy and safety of 8 weeks versus 12 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin in patients with hepatitis C virus genotype 1 mono-infection and HIV/hepatitis C virus co-infection (C-WORTHY): a randomised, open-label phase 2 trial.	<i>Lancet</i> 2015; 385: 1087–97
C-SALVAGE	Clinical study report P048V01. A phase II clinical trial to study the efficacy and safety of the combination regimen of MK-5172 + MK-8742 + ribavirin (R) in subjects with chronic hepatitis C virus infection who failed prior direct acting antiviral therapy.	March 2015
	Buti M., Gordon S., Zuckerman E., et al. Grazoprevir, elbasvir, and ribavirin for chronic hepatitis C virus genotype 1 infection after failure of pegylated interferon and ribavirin with an earlier-generation protease inhibitor: final 24-week results from C-SALVAGE. ^a	<i>Clinical Infectious Disease</i> 2015. [Epub ahead of print]
	Forns X., Gordon S., Zuckerman E., et al. Grazoprevir and elbasvir plus ribavirin for chronic HCV genotype-1 infection after failure of combination therapy containing a direct-acting antiviral agent. ^a	<i>Journal of Hepatology</i> 2015; 63(3): 564-72.
C-SCAPE	Clinical study report P047. A phase II clinical trial to evaluate the efficacy and safety of a combination regimen of MK-5172 with/without MK-8742 and/or ribavirin (RBV) in treatment-naïve subjects with chronic hepatitis C genotype 2, 4, 5 and 6 infection.	April 2015
Studies involving ledipasvir/sofosbuvir		
ION-1	Afdhal N., Zeuzem S., Kwo P., et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection.	<i>New England Journal of Medicine</i> 2014; 370: 1889-98.

Study ID	Protocol title/ Publication title	Publication citation
ION-2	Afdhal N., Reddy K., Nelson D., et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection.	<i>New England Journal of Medicine</i> 2014; 370: 1483-93.
ION-3	Kowdley K., Gordon S., Reddy K., et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis.	<i>New England Journal of Medicine</i> 2014; 370: 1879-88.
LONESTAR	Lawitz E., Poordad F., Pang P., et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial.	<i>Lancet</i> 2014; 383: 515-23.
Studies involving sofosbuvir and ribavirin		
VALENCE	Zeuzem S., Dusheiko G., Salupere R., et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3.	<i>New England Journal of Medicine</i> 2014; 370: 1993-2001.
Studies involving sofosbuvir, peginterferon and ribavirin		
NEUTRINO	Lawitz E., Mangia A., Wyles D., et al. Sofosbuvir for previously untreated chronic hepatitis C infection.	<i>New England Journal of Medicine</i> 2013; 368: 1878-87.
Wehmeyer 2015	Wehmeyer M., Jordan S., Lütha S., et al. Efficacy and safety of sofosbuvir-based triple therapy in hepatitis C genotype 4 infection.	<i>Digestive and Liver Disease</i> 2015; 47: 811–814

^a Papers identified during the evaluation

Source: Table B.2-3, pp66-68 of the submission

6.6 The key features of the included evidence are summarised in Table 2.

Table 2: Key features of the included evidence – indirect comparison

Study	Treatment group ^a	N ^b	Design/ treatment / follow-up post treatment	Risk of bias ^c	Patient population	Outcome
GRZ/EBR±RBV or SOF						
C-EDGE TN	Group 1	316	Single arm of R, DB GRZ/EBR12 24 weeks	High ^d	GT 1/4/6, TN, non-cirr & cirr	SVR12
C-EDGE TE	Group 1	54	Single arm of R, DB GRZ/EBR12 24 weeks	High ^e	GT 1/4/6 PP & GT1b OTVF, non-cirr & cirr	SVR12
	Group 4	42	Single arm of R, DB GRZ/EBR16+RBV16 24 weeks		GT 1a/4/6, OTVF, non-cirr & cirr	
C-SWIFT	Group 6	14	Single arm of R, DB GRZ/EBR12+SOF12 24 weeks	High	GT 3, TE, non-cirr	SVR12
	Group 7	12			GT 3, TE, cirr	
C-WORTHY	Group A3	13	Single arm of R, OL GRZ12+EBR12 ^f 24 weeks	High	GT 1b, TN, non-cirr	SVR12
	Group B3	31			GT 1a, TN, non-cirr	
	Group B5	29			G1, TN, cirr	
	Group C2	29	Single arm of R, OL GRZ8+EBR8 ^f 24 weeks		G1b, TN, F0-F2	
C-SALVAGE	Single-arm	79	NC GRZ12+EBR12 ^f +RBV12 24 weeks	High	GT1, TE, non-cirr & cirr	SVR12
C-SCAPE	Group B3	14	Single arm of R, OL GRZ12+EBR12 ^f	High	GT4/6, TN, non-cirr & cirr	SVR12

Public Summary Document – July 2016 PBAC Meeting

Study	Treatment group ^a	N ^b	Design/ treatment / follow-up post treatment	Risk of bias ^c	Patient population	Outcome
			24 weeks			
LDV/SOF						
ION-1	Group 1	34	Single arm of R, OL LDV/SOF12 24 weeks	High	GT 1, TN, cirr	SVR12
ION-2	Group 1	109	Single arm of R, OL LDV/SOF12 24 weeks	High	GT 1, TE, non-cirr & cirr	SVR12
ION-3	Group 1	215	Single arm of R, OL LDV/SOF8 24 weeks	High	GT 1, TN, non-cirr	SVR12
LONESTAR	Group 1	20	Single arm of R, OL LDV/SOF8 24 weeks	High	GT 1, TN, non-cirr	SVR12
	Group 4	19	Single arm of R, OL LDV/SOF12 24 weeks	High	GT 1, TE, non-cirr & cirr	
SOF+RBV						
VALANCE	Group 4	105	Single arm of R, DB SOF24+RBV24 24 weeks	High	GT 3, TN, non-cirr & cirr	SVR12
SOF+PR						
NEUTRINO	Single-arm	34	NC SOF12+PR12 24 weeks	High	GT 4/6, TN, non-cirr & cirr	SVR12
Wehmeyer	Group 1	11	Single arm of C, OL SOF12+PR12 NR	High	GT 4, TN, non-cirr & cirr	SVR12

C = comparative; Cirr = cirrhotic; DB = double blind; EBR = elbasvir; GRZ = grazoprevir; GT = genotype; LDV = ledipasvir; NC = non-comparative; NR = not reported; OL = open label; OTVF = on-treatment virologic failure; PP = prior relapser; PR = peginterferon and ribavirin; R = randomised; RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virologic response; TE = treatment-experienced; TN = treatment-naive

^a Treatment arms involved patients who were treated with treatment regimens recommended by the PBAC and/or product information documents.

^b Number of patients included for analysis of SVR. In relevant treatment arms, patients who were not the PBS target population and/or did not receive the recommended treatment regimens were excluded from SVR analysis, but included for safety analysis.

^c Refers to bias associated with indirect comparison between GRZ/EBR and active comparators. *There is a high risk of bias associated with the indirect comparison with active HCV therapies, and low risk of bias versus no treatment.*

^d *There is a low risk of bias versus no treatment (for safety outcome).*

^e *Risk of bias is low for the comparison between GRZ/EBR±RBV versus no treatment (for genotype 4 or 6 treatment-experienced patients).*

^f Patients in studies C-WORTHY, C-SALVAGE and C-SCAPE were not given one fixed dose combination tablet of GRZ/EBR (100 mg/50 mg) daily, but took one GRZ tablet (100 mg) plus one EBR tablet (50 mg) every day.

Source: compiled during the evaluation

- 6.7 There were six studies of GRZ/EBR±RBV or SOF. These studies compared GRZ/EBR therapies with placebo (C-EDGE TN), investigated different treatment regimens of GRZ/EBR therapies (C-EDGE TE, C-WORTHY, C-SWIFT and C-SCAPE) or were non-comparative (C-SALVAGE). Of the seven studies of LDV/SOF or SOF+PR, five compared different regimens of SOF-containing therapies (ION-1, ION-2, ION-3, LONESTAR and VALENCE); one compared SOF+PR against PR (Wehmeyer 2015); and one was a single-arm study (NEUTRINO). All of these

studies were treated as non-comparative single arm studies with respect to the estimation of SVR rates.

- 6.8 Only data from treatment arms representing the proposed PBS population and the recommended dose regimens were considered during the evaluation, with the exception of C-SALVAGE. It was noted that the treatment regimen in C-SALVAGE for genotype 1 treatment-experienced patients was not consistent with the treatment details recommended in the draft PI and the proposed listings (GRZ12+EBR12+RBV12 in C-SALVAGE versus the recommended treatment regimen of GRZ/EBR12 or GRZ/EBR16+RBV16 depending on genotype 1 subtype and type of treatment failure on prior CHC treatment (see the “Requested listing” section)). However, as C-SALVAGE was the only study which investigated patients who had failed previous direct acting antiviral therapies, namely simeprevir, boceprevir and telaprevir, which have the same mechanism of action (NS3/4 protease inhibitor) as one component of the assessed FDC, ie GRZ, this study has also been presented as key evidence.
- 6.9 GRZ/EBR therapies were compared to the active therapies by extracting the point estimates of SVR or adverse event (AE) rates from single arms of studies that lacked a common reference arm. Comparisons were, therefore, unadjusted and indirect. Patients in the GRZ/EBR studies and those in the LDV/SOF or SOF+PR studies differed in respect to the severity of hepatic impairment, the IL28B genotype, the baseline HCV RNA level, the racial distribution and the distribution of Metavir scores. The evaluation considered that overall, the risk of bias associated with such indirect comparisons was very high because the patient baseline risks, methods used in the studies or quality of the studies may not be exchangeable. There was uncertainty with regard to the magnitude of the differences observed and/or calculated between the study arms in the outcomes evaluated.
- 6.10 The evaluation considered the comparison of GRZ/EBR versus no treatment, in terms of efficacy measured by sustained virologic response (SVR) was less likely to be biased, as it could be assumed that patients receiving no treatment would not achieve an SVR. The study populations may not, however, have been representative of the target PBS population. Given the availability of the double-blind placebo-controlled trial of GRZ/EBR (C-EDGE TN), the uncertainty associated with the assessment of safety, relative to no treatment, was reduced.
- 6.11 The submission presented two pre-modelling studies. C-SURFER investigated the effectiveness and safety of GRZ/EBR12 for treatment of CHC genotype 1 patients with advanced chronic kidney disease. C-EDGE CO-INFXN assessed the treatment effect of GRZ/EBR12 in treatment of genotype 1, 4 or 6 treatment-naïve patients who were co-infected with human immunodeficiency virus (HIV). Results from both studies showed that GRZ/EBR was effective in the overall study populations, although some subgroups, eg the cirrhotic subgroup and the treatment-experienced subgroup, were too small to reliably estimate the SVR rates in these traditionally difficult-to-treat CHC subpopulations. GRZ/EBR was generally well-tolerated. For CHC patients with advanced kidney disease, GRZ/EBR was associated with increased risks of abdominal pain, flatulence, decreased appetite, back pain, night sweats, and cough, compared with placebo.

- 6.12 The ESC considered that the study populations were likely to be reasonably comparable, but noted the viral load for genotype 1 participants was different between studies and that patients with hepatic impairment were excluded from most GRZ/EBR studies.
- 6.13 The ESC noted that the difference in the in baseline characteristics between studies for hepatic impairment, the proportion of treatment-naïve/treatment-experienced patients, the proportion of cirrhotic patients and the CHC genotypes, which are all traditionally recognised as predictors of response to pegylated interferon alfa + ribavirin (PR)-including treatment regimens, could have affected the exchangeability in indirect comparisons. The ESC noted that to minimise the potential for confounding, comparisons between studies should, if possible, be stratified by these subgroups.

Comparative effectiveness

- 6.14 Table 3 summarises the results for the primary outcome, sustained virologic response 12 weeks after end of treatment (SVR12), as reported in the relevant treatment arms in the studies involving GRZ/EBR.

Table 3: Results of SVR rates in relevant populations across GRZ/EBR studies

Population	Study / treatment arm	Treatment regimen	SVR12 % (n/N)	[95% CI]
GT1, treatment-naive, non-cirrhotic	C-EDGE TN, Group 1	GRZ/EBR12	94.1% (207/220)	[90.1%, 96.8%]
	C-WORTHY, Arms A3 and B3	GRZ12+EBR12	97.7% (43/44)	[88.0%, 99.9%]
	C-WORTHY, Arm C2 ^a	GRZ8+EBR8	96.6% (28/29)	[82.2%, 99.9%]
GT 1, treatment-naive, cirrhotic	C-EDGE TN, Group 1	GRZ/EBR12	97.1% (66/68)	[89.8%, 99.6%]
	C-WORTHY, Group B5	GRZ12+EBR12	96.6% (28/29)	[82.2%, 99.9%]
GT1, relapser, non-cirrhotic	C-EDGE TE, Group 1	GRZ/EBR12	100% (24/24) ^b	[85.8%, 100%] ^b
GT1, relapser, cirrhotic	C-EDGE TE, Group 1	GRZ/EBR12	100% (9/9) ^b	[66.4%, 100%] ^b
GT1, on-treatment failure, non-cirrhotic	C-EDGE TE, Group 1 ^c	GRZ/EBR12	100% (14/14) ^b	[76.8%, 100%] ^b
	C-EDGE TE, Group 4 ^d	GRZ/EBR16+RBV16	86.4% (19/22) ^b	[65.1%, 97.1%] ^b
GT1, on-treatment failure, cirrhotic	C-EDGE TE, Group 1 ^c	GRZ/EBR12	100% (5/5) ^b	[47.8%, 100%] ^b
	C-EDGE TE, Group 4 ^d	GRZ/EBR16+RBV16	100% (15/15) ^b	[78.2%, 100%] ^b
GT3, treatment-naive, non-cirrhotic	C-SWIFT, Group 6	GRZ/EBR12+SOF12	100% (14/14)	[76.8%, 100%]
GT3, treatment-naive, cirrhotic	C-SWIFT, Group 7	GRZ/EBR12+SOF12	83.3% (10/12)	[51.6%, 97.9%]
GT4 & 6, treatment-naive, non-cirrhotic	C-EDGE TN, Group 1	GRZ/EBR12	92.3% (24/26) ^b	[74.9%, 99.1%] ^b
	C-SCAPE, Group B3	GRZ12+EBR12	85.7% (12/14) ^b	[57.2%, 98.2%] ^b
GT4 & 6, treatment-naive, cirrhotic	C-EDGE TN, Group 1	GRZ/EBR12	100% (2/2) ^b	[15.8%, 100%] ^b
GT4 & 6, relapser, non-cirrhotic	–	GRZ/EBR12	No evidence	–
GT4 & 6, relapser, cirrhotic	C-EDGE TE, Group 1	GRZ/EBR12	100% (2/2) ^b	[15.8%, 100%] ^b
GT4 & 6, on-treatment failure, non-cirrhotic	C-EDGE TE, Group 4	GRZ/EBR16+RBV16	100% (1/1) ^b	[2.5%, 100%] ^b
GT4 & 6, on-treatment failure, cirrhotic	C-EDGE TE, Group 4	GRZ/EBR16+RBV16	100% (4/4) ^b	[39.8%, 100%] ^b

CI = confidence interval; EBR = elbasvir; GT = genotype; GRZ = grazoprevir; RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virologic response

^a For GT1b patients with limited fibrosis (F0-2)

^b Data on the number of patients achieving SVR12 were extracted from respective clinical study reports during the evaluation as they were not provided in the submission. Confidence intervals were calculated using Stata®13.1 – exact confidence intervals were calculated using *cii* in Stata.

^c Include GT 1b patients only

^d Include GT1a patients only

Source Table B.6-2, p172 and Table B.6-12, p195 of the submission

- 6.15 SVR12 rates associated with the recommended treatment regimens of GRZ/EBR±RBV or SOF ranged from 83.3% to 100% across CHC populations except for genotype 4 or 6 cirrhotic prior relapsers for whom no results were available. The sample size in some patient populations, eg genotype 4 or 6 treatment-naïve cirrhotic patients (n=2), genotype 4 or 6 treatment-experienced subgroup (n=7) and genotype 3 patients (n=26), was too small to provide an accurate estimate of the clinical benefit.
- 6.16 In C-SALVAGE, 96.2% (76/79) of patients who had failed previous protease inhibitor therapy achieved SVR12 after being treated with GRZ/EBR12+RBV12. Similar SVR results were reported for prior relapsers and those patients who had experienced on-treatment virologic failure (96.2% vs 95.0%). At baseline, the overall prevalence of

NS3/4A resistance-associated variants (RAVs) at the specified loci was 43.6% (34/78). Even though all subjects had not been previously exposed to an NS5A inhibitor, a total of eight subjects (10.1%) had a NS5A baseline polymorphism at these loci prior to treatment. This could be a reflection of the relatively low barrier to the development of resistance. For both NS3/4A and NS5A RAVs, SVR rates were apparently lower in patients harbouring viruses with baseline RAVs than those without (91.2% vs 100% for NS3/4 variants; 75.0% vs 98.6% for NS5A variants). However, no firm conclusion could be drawn regarding the impact of baseline RAVs on the efficacy of GRZ/EBR primarily due to the small number of patients who did not achieve SVR12 in C-SALVAGE (n=3).

- 6.17 In order to compare GRZ/EBR therapies with LDV/SOF, SOF+(P)R or no treatment, where possible the study results were pooled and have been presented in Tables 4, 5 and 6.

Table 4: Unadjusted indirect comparison of SVR12 between GRZ/EBR±RBV with LDV/SOF in GT1 patients

Comparison	GRZ/EBR±RBV n/N (k=no. of studies) ^a % [95%CI]	LDV/SOF n/N (k=no. of studies) ^a % [95%CI]
Treatment-naïve		
Non-cirrhotic	GRZ/EBR8 or GRZ/EBR12 ^b 278/293 (k=2 ^c) 95.1% [92.2%, 97.3%] ^a	LDV/SOF8 221/235 (k=2 ^d) 94.8% [91.3%, 97.6%] ^a
Cirrhotic	GRZ/EBR12 94/97 (k=2 ^e) 97.1% [92.3%, 99.8%] ^a	LDV/SOF12 32/34 (k=1 ^f) 94.1% [80.3%, 99.3%] ^a
Treatment-experienced		
Non-cirrhotic	GRZ/EBR12 or GRZ/EBR16+RBV16 ^g 57/60 (k=1 ^h) 95.0% [86.1%, 99.0%] ^a	LDV/SOF12 83/87 (k=1 ⁱ) 95.4% [88.6%, 98.7%] ^a
Cirrhotic	GRZ/EBR12 or GRZ/EBR16+RBV16 ^g 29/29 (k=1 ^h) 100% [88.1%, 100%] ^a	LDV/SOF12 19/22 (k=1 ⁱ) 86.4% [65.1%, 97.1%] ^a

CI = confidence interval; EBR = elbasvir; GT = genotype; GRZ = grazoprevir; LDV = ledipasvir; RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virologic response

^a SVR rates for GRZ/EBR±RBV and LDV/SOF were recalculated during the evaluation based on available data. Exact confidence intervals were calculated using the confidence intervals for proportions command in Stata® 13.1 – exact confidence intervals were calculated using cii in Stata when only one study provided data. When multiple studies were used to generate a pooled estimate, this was performed using a random effects meta-analysis of proportions, with exact confidence intervals and adjusted using the Freeman-Tukey transformation in Stata® 13.1.

^b GRZ/EBR12 is the recommended treatment for all genotype 1 treatment-naïve patients. GRZ/EBR8 can be considered for GT1b treatment-naïve patients with limited fibrosis (F0-2).

^c SVR data from Groups A3, B3 and C2 in C-WORTHY (71/73) and from Group 1 in C-EDGE TN (207/220).

^d SVR data from Group 1 in ION-3 (202/215) and from Group 1 in LONESTAR (19/20)

^e SVR data from Group 1 in C-EDGE TN (66/68) and from Group B5 in C-WORTHY (28/29)

^f SVR data from Group 1 in ION-1

^g GRZ/EBR12 is recommended for genotype 1 relapsers and genotype 1b on-treatment virologic failures. GRZ/EBR16+RBV16 is recommended for genotype 1a on-treatment virologic failures

^h SVR data from Groups 1 and 4 in C-EGDE TE

ⁱ SVR data from Group 1 in ION-2. SVR results of LONESTAR are not presented in the table as SVR data stratified by cirrhotic status are not available. The SVR12 rate was 94.7% (18/19) for all genotype 1 treatment-experienced patients.

Source: Table compiled during the evaluation

Table 5: Unadjusted indirect comparison of SVR12 between GRZ/EBR+SOF with SOF+RBV in GT3 patients

Comparison	GRZ/EBR12+SOF12 n/N (k=no. of studies) % [95%CI]	SOF24+RBV24 n/N (k=no. of studies) % [95%CI]
Treatment-naïve		
Non-cirrhotic	14/14 (k=1 ^a) 100% [76.8%, 100%]	87/92 (k=1 ^b) 94.6% [87.8%, 98.2%]
Cirrhotic	10/12 (k=1 ^c) 83.3% [51.6%, 97.9%]	12/13 (k=1 ^b) 92.3% [64.0%, 99.8%]

CI = confidence interval; EBR = elbasvir; GT = genotype; GRZ = grazoprevir; RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virologic response

^a SVR data from Group 6 in C-SWIFT

^b SVR data from Group 4 in VALENCE

^c SVR data from Group 7 in C-SWIFT

Source: Table B.6-12, p195 of the submission

Table 6: Unadjusted indirect comparison of SVR12 between GRZ/EBR±RBV with SOF+PR or no treatment in GT4 or 6 patients

Comparison	GRZ/EBR±RBV n/N (k=no. of studies) % [95%CI] ^a	SOF+PR or no treatment n/N (k=no. of studies) % [95%CI] ^a
Treatment-naïve		
Non-cirrhotic	GRZ/EBR12 36/40 (k=2 ^b) 90.4% [78.4%, 98.4%] ^a	SOF12+PR12 44/45 (k=2 ^{c, d}) 98.6% [91.4%, 100%] ^a
Cirrhotic	GRZ/EBR12 2/2 (k=1 ^e) 100% [15.8%, 100%] ^a	
Treatment-experienced		
Non-cirrhotic	GRZ/EBR12 or GRZ/EBR16+RBV16 ^f 1/1 (k=1 ^g) 100% [2.5%, 100%]	No treatment 0%
Cirrhotic	GRZ/EBR12 or GRZ/EBR16+RBV16 ^f 6/6 (k=1 ^h) 100% [54.1%, 100%] ^a	

CI = confidence interval; EBR = elbasvir; GT = genotype; GRZ = grazoprevir; PR = peginterferon and ribavirin; RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virologic response

^a SVR rates for GRZ/EBR±RBV and SOF+PR were recalculated during the evaluation based on available data. Exact confidence intervals were calculated using the confidence intervals for proportions command in Stata[®] 13.1. – exact confidence intervals were calculated using cii in Stata when only one study provided data. When multiple studies were used to generate a pooled estimate, this was performed using a random effects meta-analysis of proportions, with exact confidence intervals and adjusted using the Freeman-Tukey transformation in Stata[®] 13.1.

^b SVR data from Group 1 in C-EDGE TN (24/26) and from Group B3 in C-SCAPE (12/14)

^c SVR data from NEUTRINO (33/34) and from Group1 in Wehmeyer 2015 (11/11)

^d Data on SVR12 rates stratified by cirrhotic status are not available for genotypes 4 and 6 patients in the two SOF+PR studies.

^e SVR data from Group 1 in C-EDGE TN.

^f GRZ/EBR12 is recommended for genotype 4 or 6 relapsers. GRZ/EBR16+RBV16 is recommended for genotype 4 or 6 on-treatment virologic failures

^g SVR data from Group 4 in C-EDGE TE

^h SVR data from Groups 1 and 4 in C-EDGE TE

Source: Table compiled during the evaluation

- 6.18 Adjustment for population baseline risk could not be undertaken due to the lack of a control arm/common reference in these studies. The evaluation considered that the results of the indirect comparisons between GRZ/EBR therapies and the other active CHC treatments are highly uncertain due to exchangeability concerns. However, as

the SVR rates are presented in subgroups that represent the main influencers of treatment success (cirrhotic status and treatment experience), some of the confounding that may influence study population exchangeability in an indirect comparison has been controlled for.

- 6.19 The ESC noted that no direct comparisons with active comparators were presented in the submission, but considered that GRZ/EBR had a similar evidence base to other agents.
- 6.20 The SVR12 rates with GRZ/EBR±RBV were consistently high across all genotype 1 subgroups and appeared non-inferior to those of LDV/SOF.
- 6.21 The SVR rate with GRZ/EBR12 in genotype 4 or 6 treatment-naïve, non-cirrhotic patients was numerically lower than the comparator arm (90.4% [78.4%, 98.4%] in non-cirrhotic patients vs 98.6% [91.4%, 100%] in a mixed non-cirrhotic and cirrhotic population). The wide confidence intervals indicate that the subgroups were statistically underpowered. This, in addition to the exchangeability concerns, suggests that it is not possible to reliably determine the comparative efficacy of GRZ/EBR versus SOF+PR in genotype 4 or 6 treatment-naïve, non-cirrhotic patients.
- 6.22 Limited clinical data were available on patients receiving GRZ/EBR±RBV or SOF in genotype 3 treatment-naïve patients (n=26), in genotype 4 or 6 treatment-naïve cirrhotic patients (n=2) and in genotype 4 or 6 treatment-experienced patients (n=7).
- 6.23 The PSCR (p.3) argued that despite the limited clinical data for genotypes 4 and 6, patient populations are small and recommending GRZ/EBR for genotypes 4 and 6 would enable patients to access interferon free treatment on the PBS. The ESC considered there was limited data for genotypes 3, 4 and 6, however acknowledged the small patient populations in these groups created barriers to additional data collection.
- 6.24 SVR rates in patients who had failed prior protease inhibitor therapy were comparable between the GRZ/EBR study (96.2% (76/79) in C-SALVAGE) and the LDV/SOF studies (93.9% (62/22) in ION-2 and 94.7% (18/19) in LONESTAR). Any interpretation of the results should consider the exchangeability concerns raised previously, along with the fact that the treatment regimen in C-SALVAGE (GRZ/EBR12+RBV12) is not recommended by the draft PI.
- 6.25 It is not possible to make a comparison of SVR results in patients infected with viruses harbouring RAVs between GRZ/EBR and LDV/SOF, due to the lack of relevant data for patients receiving LDV/SOF.

Comparative harms

- 6.26 The safety data of GRZ/EBR from the placebo-controlled trial of C-EDGE TN are summarised in Table 7.

Table 7: Summary of AEs reported in C-EDGE TN

	GRZ/EBR12 n (%)	Placebo n (%)	Risk difference [95% CI] ^a	Relative risk [95% CI] ^a
N	316	105		
Overall				
Any AEs	213 (67.4%)	72 (68.6%)	-1.2% [-11.4%, 9.1%]	0.98 [0.85, 1.14]
Drug-related AEs ^b	114 (36.1%)	41 (39.0%)	-3.0% [-13.7%, 7.8%]	0.92 [0.70, 1.22]
Serious AEs	9 (2.8%)	3 (2.9%)	-0.0% [-3.7%, 3.7%]	1.00 [0.28, 3.61]
Serious drug-related AEs	0 (0%)	0 (0%)	–	–
Deaths	2 (0.6%)	0 (0%)	0.6% [-0.2%, 1.5%]	–
Discontinuation due to AEs	3 (0.9%)	1 (1.0%)	-0.0% [-2.2%, 2.1%]	1.00 [0.11, 9.48]
Discontinuation due to drug-related AEs	2 (0.6%)	1 (1.0%)	-0.3% [-2.4%, 1.7%]	0.67 [0.06, 7.26]
Common AEs				
Headache	52 (16.5%)	19 (18.1%)	-1.6% [-10.1%, 6.8%]	0.91 [0.57, 1.47]
Fatigue	49 (15.5%)	18 (17.1%)	-1.6% [-9.9%, 6.6%]	0.91 [0.55, 1.48]
Nausea	28 (8.9%)	8 (7.6%)	1.2% [-4.7%, 7.2%]	1.16 [0.55, 2.47]
Hepatic events ^c				
Hepatic events of clinical interest ^d	5 (1.6%)	0 (0%)	1.6% [0.2%, 3.0%]	–
ALT or AST > 5xULN	4 (1.3%)	0 (0%)	1.3% [0.0%, 2.5%]	–

AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; EBR = elbasvir; GRZ = grazoprevir; ULN = upper limit of normal

^a Relative risks and risk differences were calculated during the evaluation.

^b Determined by investigator to be related to the drug

^c Data on hepatic events were extracted from the clinical study report, as they were not provided in the submission

^d Hepatic laboratory events of clinical interest were defined as the following: 1) ALT or AST >500 IU/mL regardless of baseline ALT/AST (not associated with virologic failure); or 2) ALT or AST >3x baseline and >100 IU/mL (not associated with virologic failure); or 3) alkaline phosphatase >3x ULN (not associated with virologic failure).

Source: Table B.6-15, pp206-207 and Table B.6-17, pp209-210 of the submission

- 6.27 In C-EDGE TN, rates of any AEs and drug-related AEs were comparable between the GRZ/EBR12 arm and the placebo arm. GRZ/EBR was generally well tolerated. There was a low incidence of serious AEs (2.8%) and a low incidence of treatment discontinuation due to AEs (0.9%). Two patients receiving GRZ/EBR died during the study. Neither death was considered to be drug-related by the investigators. However, it is unknown whether the investigators were blinded to treatment allocation when they determined the relationship between death and the study drug in C-EDGE TN. The most common AEs in both treatment groups were headache, fatigue, and nausea. With regard to hepatic events, five subjects (1.6%) treated with GRZ/EBR, but none in the placebo arm, had elevated transaminases that were considered events of clinical interest (for definition, see the note below Table 7). The difference between the two arms was statistically significant.
- 6.28 Safety data for the treatment arms relevant to the proposed GRZ/EBR listings, as well as the active comparators, were pooled during the evaluation and are summarised below.

Table 8: Summary of AEs across GRZ/EBR-containing therapies and SOF-containing therapies^a

Treatment combination	AEs, n (%)					
	GRZ/EBR	GRZ/EBR +RBV	GRZ/EBR +SOF	LDV/SOF ^e	SOF+RBV	SOF+PR
Duration of treatment	8 or 12 weeks	12 or 16 weeks	12 weeks	8 or 12 weeks	24 weeks	12 weeks
N	543^b	185^c	26^d	577^e	250^f	327^g
Overall						
Any AEs	376 (69.2%)	158 (85.4%)	6 (23.1%)	403 (69.8%)	229 (91.6%)	310 (94.8%)
Serious AEs	15 (2.8%)	8 (4.3%)	0 (0%)	6 (1.0%)	10 (4.0%)	4 (1.2%)
Discontinuation due to AEs	5 (0.9%)	6 (3.2%)	0 (0%)	0 (0%)	1 (0.4%)	5 (1.5%)
AEs of interest						
Anaemia	2 (0.4%)	23 (12.4%)	2 (7.7%)	2 (0.3%)	15 (6.0%)	68 (20.8%)
Neutropenia ^h	2 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.2)	1 (0.4%)	54 (16.5%)
Rash ⁱ	11 (2.0%)	11 (5.9%)	0 (0%)	21 (3.9%)	NA	59 (18.0%)
Pruritus ^h	10 (1.8%)	14 (7.6%)	0 (0%)	13 (3.0%)	67 (26.8%)	54 (16.5%)
Hepatic events with clinical interest ^j	6 (1.1%)	0 (0%)	0 (0%)	NA	NA	NA

AE = adverse event; EBR = elbasvir; GRZ = grazoprevir; LDV = ledipasvir; PR = peginterferon and ribavirin; RBV = ribavirin; SOF = sofosbuvir; ULN = upper limit of normal

^a Data on AEs were pooled and calculated during the evaluation.

^b Including the following treatment arms: Group 1 in C-EDGE TN, Group 1 in C-EDGE TE, Groups 3, B3, B5 and Group C2 in C-WORTHY, and Group B3 in C-SCAPE

^c Including Group 4 in C-EDGE TE and the subjects in C-SALVAGE

^d Including Groups 6 and 7 in C-SWIFT

^e Including the following treatment arms: Group 1 in ION-1, Group 1 in ION-2, Group 1 in ION-3 and Groups 1 and 4 in LONESTAR

^f Including Group 4 in VALENCE

^g Including the subjects in NEUTRINO. Data on the number of patients experiencing AEs among patients receiving SOF+PR in Wehmeyer were not provided.

^h Relevant safety data were not reported for ION-2 and LONESTAR

ⁱ Relevant safety data were not reported for LONESTAR and VALENCE

^j Relevant safety data were not reported for all comparator studies. Hepatic laboratory events of clinical interest were defined as the following: 1) ALT or AST >500 IU/mL regardless of baseline ALT/AST (not associated with virologic failure); or 2) ALT or AST >3x baseline and >100 IU/mL (not associated with virologic failure); or 3) alkaline phosphatase >3x ULN (not associated with virologic failure).

Source: Table constructed during the evaluation.

- 6.29 The comparative safety results across treatment regimens via indirect comparisons are indicative, given the lack of exchangeability across studies. The incidence of serious AEs and treatment discontinuation as a result of AEs was low in patients receiving GRZ/EBR or LDV/SOF. GRZ/EBR therapies were associated with hepatic events of clinical interest; but relevant data were not provided for the active comparators in the submission. The key differences in AE rates between treatment arms containing RBV versus those without RBV were rash and anaemia related events, both of which are known AEs related to the use of RBV. The use of interferon in addition to DAAs raises more safety issues, eg neutropenia.
- 6.30 The PSCR (p.4) stated that the majority of patients treated with GRZ/EBR do not require RBV, and only a small proportion of GT 1a, 4 and 5 patients who have failed prior treatment will require GRZ/EBR + RBV. The ESC noted the higher rates of adverse events in patients given GRZ/EBR + RBV compared to GRZ/EBR alone or LDV/SOF.

- 6.31 The PSCR (p.4) argued that data on hepatic events for the active comparators was not provided as the information was not contained in publically available publications or Product Information (PI) documents, and was therefore unable to provide it. The PSCR also noted the PI for Viekira Pak stated that hepatic events of interest occurred in about 1% of all subjects, and argued it was similar to the rate of hepatic events found with GRZ/EBR (0.8%) and that the types of events observed were similar. The ESC noted that guidelines are now in place for the use of new hepatitis C medicines in practice, and considered that these measures would be appropriate and adequate for GRZ/EBR.
- 6.32 There were limited data on the safety of GRZ/EBR administered in combination with SOF.

Benefits/harms

- 6.33 A summary table of benefits and harms cannot be formulated, given:
- 1) the lack of comparative evidence from head-to-head trials;
 - 2) concerns regarding unadjusted indirect comparisons of clinical studies with potential exchangeability issues;
 - 3) the lack of statistically significant differences in SVR rates between GRZ/EBR therapies and the active comparators; and
 - 4) the small size of the genotype 4 or 6 treatment-experienced subgroup (n=7), which means that the magnitude of the clinical benefits associated with GRZ/EBR±RBV *versus* no treatment unable to be reliably estimated.

Clinical claim

- 6.34 The submission described:
- GRZ/EBR12 as non-inferior to LDV/SOF8 in terms of comparative effectiveness and safety in genotype 1 treatment-naïve non-cirrhotic patients (GRZ/EBR8 could be considered in subjects with genotype 1b with minimal fibrosis (F0-F2));
 - GRZ/EBR12 as non-inferior to LDV/SOF12 in terms of comparative effectiveness and safety in genotype 1 treatment-naïve cirrhotic patients, genotype 1 treatment-experienced relapsers and genotype 1b patients who have experienced on-treatment virologic failure;
 - GRZ/EBR16+RBV16 as non-inferior to LDV/SOF12 in terms of comparative effectiveness and safety in genotype 1a patients who have experienced on-treatment virologic failure;
 - GRZ/EBR12+SOF12 as non-inferior to SOF24+RBV24 in terms of comparative effectiveness and safety in genotype 3 treatment-naïve patients;
 - GRZ/EBR12 as non-inferior to SOF12+PR12 in terms of comparative effectiveness and safety in genotypes 4 and 6 treatment-naïve patients;
 - GRZ/EBR12 as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety to no treatment in genotypes 4 and 6 treatment-experienced relapsers; and
 - GRZ/EBR16+RBV16 as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety to no treatment in genotypes 4 and 6 patients who have experienced on-treatment virologic failure.

- 6.35 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable for genotypes 1, 4 and 6, albeit noting the small patient numbers for genotypes 4 and 6. The PBAC considered the claim of non-inferior comparative effectiveness was not adequately supported by the data for genotype 3.
- 6.36 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

- 6.37 The submission took a cost-minimisation approach. The equi-effective doses presented in the submission and based on the requested PBS listings for GRZ/EBR and clinical studies presented in Section B(i), are:
- GRZ/EBR (100 mg/50 mg) once daily for 12 weeks is equivalent to LDV/SOF (90 mg/400 mg) once daily for 8 weeks in genotype 1 treatment-naïve non-cirrhotic patients;
 - GRZ/EBR (100 mg/50 mg) once daily for 12 weeks is equivalent to LDV/SOF (90 mg/400 mg) once daily for 12 or 24 weeks in genotype 1 treatment-naïve cirrhotic patients, genotype 1 prior relapsers and genotype 1b patients who have experienced on-treatment virologic failure;
 - GRZ/EBR (100 mg/50 mg) once daily plus RBV⁹ for 16 weeks is equivalent to LDV/SOF (90 mg/400 mg) once daily for 12 weeks in genotype 1a patients who have experienced on-treatment virologic failure;
 - GRZ/EBR (100 mg/50 mg) once daily plus SOF 400 mg once daily for 12 weeks is equivalent to SOF 400 mg once daily plus RBV 1,000 mg daily (in patients with a body weight of <75kg) or 1,200 mg daily (in patients with a body weight of ≥75kg) for 24 weeks in genotype 3 treatment-naïve patients; and
 - GRZ/EBR (100 mg/50 mg) once daily for 12 weeks is equivalent to SOF 400 mg once daily plus RBV 1,000 mg daily (in patients with a body weight of <75kg) or 1,200 mg daily (in patients with a body weight of ≥75kg) plus peg-interferon (PegIFN) alfa-2a 180µg weekly for 12 weeks in genotypes 4 and 6 treatment-naïve patients.
- 6.38 The submission claimed that GRZ/EBR12 (for relapsers) or GRZ/EBR16+RBV16 (for on-treatment virologic failures) has superior effectiveness and non-inferior safety *versus* no treatment in genotype 4 or 6 treatment-experienced patients. No cost-effectiveness analysis was presented in the submission on basis of this clinical claim.
- 6.39 In the absence of information on the effective prices of the DAA comparators, eg LDV/SOF and SOF, the submission used a placeholder price (for illustrative purposes) of \$ [REDACTED] ex-manufacturer per course of GRZ/EBR treatment regardless of CHC genotype treated. The submission expected that the majority (> [REDACTED]%) of PBS target patients will take GRZ/EBR for 12 weeks (requiring 3 packs of GRZ/EBR), with a small proportion of patients receiving either 8 weeks (some genotype 1b treatment-naïve patients with limited fibrosis) or 16 weeks (1a, 4 or 6 patients who have experienced on-treatment failures) of therapy. Using the placeholder price per patient of \$ [REDACTED], the indicative GRZ/EBR ex-manufacturer price per pack was calculated to

⁹ In GRZ/EBR studies, the dose of RBV was weight-based: 800mg/day for patients weighing <66kg; 1,000mg/day for 66-80kg; 1,200mg/day for 81-105kg and 1,400mg/day for >105kg.

be \$ [REDACTED] (= \$ [REDACTED]/3) per pack. In the recent considerations of treatments for Hepatitis C, the PBAC advised the Minister that there was no basis on which to recommend that any one treatment be more expensive than another. Drug prices for concomitant SOF and RBV should be taken into account in the cost-minimisation analysis while calculating the price per GRZ/EBR pack when the overall cost per course of CHC therapy in the comparator arm has been determined.

- 6.40 The sponsor acknowledged the final reimbursed price would depend on the conditions for listing for the other DAAs and was prepared to negotiate accordingly with the PBAC and the Australian Government.
- 6.41 Irrespective of the final agreed cost per patient course, the sponsor requested a Special Pricing Arrangement with a published ex-manufacturer price of \$ [REDACTED] per 12 week course as a condition of listing.

Drug cost/patient/course: \$ [REDACTED] (placeholder price, regardless of treatment duration)

Estimated PBS usage & financial implications

- 6.42 This submission was not considered by DUSC.
- 6.43 The submission used an epidemiological approach and a market share approach to estimate the financial implications of listing GRZ/EBR for treatment of CHC genotype 1, 4 or 6 both treatment-naïve and treatment-experienced patients and genotype 3 treatment-experienced patients. The number of CHC patients likely to receive interferon-free treatments was sourced from the DUSC estimates when the DUSC considered LDV/SOF, SOF+PR and DCV+SOF ([REDACTED] in Year 1 and [REDACTED] in Years 2-5). The submission assumed that the uptake rate (market share) of GRZ/EBR would be [REDACTED]% in Year 1 of listing, increasing to [REDACTED]% in Year 5. A placeholder DPMQ of \$ [REDACTED] and an average treatment duration of 12 weeks for GRZ/EBR were used in the financial analysis. The submission assumed that GRZ/EBR, once listed, would substitute for other recommended interferon-free treatment combinations, against which the price for GRZ/EBR will be determined on a cost-minimisation basis.

Table 9: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Scripts ^a	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated net cost of GRZ/EBR to PBS/RPBS					
Net cost of GRZ/EBR to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Estimated total net cost					
Net cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

^a Assuming 3 scripts per patient as estimated in the submission.
Source: Table E.3-1, p252 of the submission.

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

- 6.44 The ESC recalled the previous PBAC recommendation of LDV/SOF in March 2015, where it was considered that the cost of a course of treatment should be set irrespective of treatment duration. The ESC noted the submission had proposed pricing irrespective of treatment duration and offered to join the existing Risk Share Arrangement for all DAAs.

Financial Management – Risk Sharing Arrangements

- 6.45 As part of the conditions of approval for LDV/SOF, SOF, DCV and Viekira PAK, the PBAC recommended all new DAAs come under a Risk Share Arrangement. The sponsor indicated its understanding that, should GRZ/EBR be approved for reimbursement, it will be required to join the arrangement negotiated with the sponsors of other DAAs.

For more detail on PBAC's view, see section 7 "PBAC outcome"

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of GRZ/EBR +/- RBV for the treatment of treatment-naïve and treatment experienced genotypes 1, 4 and 6 CHC on a cost minimisation basis with LDV/SOF for GT1 disease and on a cost-minimisation basis with SOF+PR for GT 4 and 6 disease.
- 7.2 The PBAC rejected the requested listing of GRZ/EBR and SOF for treatment-naïve genotype 3 CHC as it considered there was insufficient data to support recommending listing for this group.
- 7.3 In making this recommendation, the PBAC noted that new DAA treatment regimens for CHC are available both as General Schedule items and under special arrangements under Section 100. The PBAC recommended that GRZ/EBR be listed in the same way as existing DAA listings for CHC.
- 7.4 The PBAC noted that the submission proposed the following equi-effective doses for the recommended genotypes:
- GRZ/EBR (100 mg/ 50 mg) once daily for 12 weeks equals LDV/SOF (90 mg/ 400 mg) once daily for 8 weeks in genotype 1 treatment-naïve non-cirrhotic patients.
 - GRZ/EBR (100 mg/ 50 mg) once daily for 12 weeks equals LDV/SOF (90 mg/ 400 mg) once daily for 12 weeks in genotype 1 treatment-naïve cirrhotic patients.
 - GRZ/EBR (100 mg/ 50 mg) once daily for 12 weeks equals LDV/SOF (90 mg/ 400 mg) once daily for 12 weeks in genotype 1b treatment-experienced patients.
 - GRZ/EBR (100 mg/ 50 mg) once daily for 16 weeks plus RBV for 16 weeks equals LDV/SOF (90 mg/ 400 mg) once daily for 12 weeks in genotype 1a treatment-experienced patients.
 - GRZ/EBR (100 mg/ 50 mg) +/- ribavirin once daily for 12 or 16 weeks equals SOF 400 mg once daily plus RBV 1,000 mg (patients with a body weight less than 75 kg) or 1,200 mg (patients with a body weight greater than 75 kg) plus

Peg-interferon alfa-2a 180 µg weekly for 12 weeks in genotype 4 and 6 patients.

- 7.5 The PBAC noted that the treatment duration for LDV/SOF for genotype 1 treatment experienced, cirrhotic patients should be 24 rather than 12 weeks, and that Product Information for GRZ/EBR has not been finalised by TGA and agreed that the above GRZ/EBR regimens should be updated for consistency with the final TGA approved Product Information.
- 7.6 The PBAC considered there was a high clinical need for interferon-free treatment regimens for CHC genotypes 4 and 6, and that recommending GRZ/EBR for these genotypes would allow this small patient group access to PBS-subsidised IFN-free therapy.
- 7.7 The PBAC noted that no head-to-head trials with the nominated comparators were presented in the submission. The Committee reaffirmed its opinion that there was no basis on which to recommend one particular CHC treatment over another.
- 7.8 The PBAC also recommended that GRZ/EBR enter the risk sharing arrangement currently in place for other drugs used for the treatment of CHC.
- 7.9 The PBAC considered that GRZ/EBR would only substitute for other DAA containing treatment regimens for CHC infection and would not grow the total market. The PBAC considered the utilisation estimates presented in the submission were reasonable and agreed that the listing of GRZ/EBR would be cost neutral.
- 7.10 The PBAC noted the correspondence received from individuals, health professionals and organisations, all supportive of the listing of GRZ/EBR. The PBAC noted that the listing of GRZ/EBR would provide patients with PBS-subsidised access to interferon-free treatments for some CHC genotypes for the first time.
- 7.11 The PBAC advised that GRZ/EBR, similar to other DAAs for CHC, are not suitable for prescribing by nurse practitioners at this time.
- 7.12 The PBAC recommended that the Early Supply Rule should not apply as it does not apply to other DAA listings for CHC.
- 7.13 The PBAC noted that this submission was not eligible for an Independent Review because it received a positive recommendation.
- 7.14 The PBAC advised, under Section 101(3BA) of the *National Health Act 1953*, that grazoprevir with elbasvir should be treated as interchangeable on an individual patient basis with ledipasvir with sofosbuvir and paritaprevir with ritonavir with ombitasvir and dasabuvir +/- RBV when used in the treatment of GT1 CHC.

Outcome:

Recommended: genotypes 1, 4 and 6

Rejected: treatment-naïve genotype 3

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
GRAZOPREVIR/ELBASVIR Tablet 100 mg/50 mg	28	2	Zepatier [®]	Merck Sharp & Dohme (Australia) Pty Ltd

Category / Program GENERAL – General Schedule (Code GE)

Prescriber type: Dental Medical Practitioners Nurse practitioners Optometrists
Midwives

Chronic hepatitis C infection

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
GRAZOPREVIR/ELBASVIR Tablet 100 mg/50 mg	28	3	Zepatier [®]	Merck Sharp & Dohme (Australia) Pty Ltd

Category / Program GENERAL – General Schedule (Code GE)

Prescriber type: Dental Medical Practitioners Nurse practitioners Optometrists
Midwives

Chronic hepatitis C infection

Public Summary Document – July 2016 PBAC Meeting

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
GRAZOPREVIR/ELBASVIR Tablet 100 mg/50 mg	28	2	Zepatier®	Merck Sharp & Dohme (Australia) Pty Ltd

Category / Program Section 100 – Highly Specialised Drugs Program

Prescriber type: Dental Medical Practitioners Nurse practitioners Optometrists
Midwives

Chronic hepatitis C infection

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
GRAZOPREVIR/ELBASVIR Tablet 100 mg/50 mg	28	3	Zepatier®	Merck Sharp & Dohme (Australia) Pty Ltd

Category / Program Section 100 – Highly Specialised Drugs Program

Prescriber type: Dental Medical Practitioners Nurse practitioners Optometrists
Midwives

Chronic hepatitis C infection

Proposed listing 1:

Restriction	Authority Required
Clinical criteria	<p>Patient must meet the criteria set out in the General Statement for Drugs for the Treatment of Hepatitis C,</p> <p>AND</p> <p>Patient must be taking this drug as part of a regimen set out in the matrix in the General Statement for Drugs for the Treatment of Hepatitis C, based on the hepatitis C virus genotype, patient history and cirrhotic status,</p> <p>AND</p> <p>The treatment must be limited to a maximum duration of 12 weeks.</p>
Prescriber instruction	<p>No increase in the maximum quantity or number of units may be authorised.</p> <p>Note:</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>Note:</p> <p>The treatment must be limited to a maximum duration of 12 weeks.</p>

Proposed listing 2

Restriction	Authority Required
Clinical criteria	<p>Patient must meet the criteria set out in the General Statement for Drugs for the Treatment of Hepatitis C,</p> <p>AND</p> <p>Patient must be taking this drug as part of a regimen set out in the matrix in the General Statement for Drugs for the Treatment of Hepatitis C, based on the hepatitis C virus genotype, patient history and cirrhotic status,</p> <p>AND</p> <p>The treatment must be limited to a maximum duration of 16 weeks.</p>
Prescriber instruction	<p>No increase in the maximum quantity or number of units may be authorised.</p> <p>Note:</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>Note:</p> <p>The treatment must be limited to a maximum duration of 16 weeks.</p>

Additions to the General statement for drugs used for the treatment of hepatitis C to be finalised based on the final TGA approved regimens.

9 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.

10 Sponsor's Comment

The sponsor had no comment.