

**6.15 SOFOSBUVIR with VELPATASVIR,
Tablet containing 400 mg sofosbuvir with 100 mg
velpatasvir,
Epclusa[®], Gilead Sciences Pty Ltd**

1 Purpose of Application

- 1.1 The minor submission requested the PBAC review its advice that sofosbuvir with velpatasvir should be treated as interchangeable on an individual patient basis with other direct-acting antiretroviral (DAA) treatment regimens under Section 101(3BA) of the *National Health Act 1953* (the Act).

2 Requested listing

- 2.1 The submission did not request changes to the recommended restriction, which is consistent with other listings for DAA regimens and the General Statement for Drugs for the Treatment of Hepatitis C.

3 Background

- 3.1 Under Section 101(3BA) of the *Act*, if the Committee makes a positive recommendation for a drug or medicinal preparation, it must specify whether the drug or medicinal preparation and another drug or medicinal preparation should be treated as interchangeable on an individual patient basis.
- 3.2 Sofosbuvir with velpatasvir is TGA registered for the treatment of chronic hepatitis C virus infection – genotypes 1, 2, 3, 4, 5 or 6 (all genotypes).
- 3.3 At its November 2016 meeting, the PBAC recommended the listing of sofosbuvir with velpatasvir for the treatment of chronic hepatitis C (CHC) infection. As part of that recommendation, the PBAC advised that sofosbuvir with velpatasvir should be treated as interchangeable on an individual patient basis with the other direct acting antiviral treatment regimens¹:

¹ Sofosbuvir with velpatasvir PBAC November 2016 Public Summary Document, p 20

- Ledipasvir with sofosbuvir, and paritaprevir with ritonavir with ombitasvir and dasabuvir +/- ribavirin (RBV) for genotype 1 (GT1) CHC;
- Sofosbuvir in combination with RBV for genotypes 2 (GT2) and 3 (GT3) CHC;
- Daclatasvir and sofosbuvir for GT3 CHC; and
- Grazoprevir with elbasvir +/- RBV for genotype 4 (GT4) CHC.

3.4 For the purposes of providing advice under Section 101(3BA) of the Act regarding interchangeability, the PBAC considers material relating to the health outcomes of treatment with each drug. Advice under this Section does not mean that two or more drugs are appropriate for every circumstance for every patient – rather, that the outcomes are comparable at a whole-of-population level for those treatments. Further, such advice does not influence a clinician’s choice of treatment for an individual patient.

3.5 Section 101(3BA) was introduced into the Act as part of the 2007 PBS reforms. The Revised Explanatory Memorandum to the National Health Amendment (Pharmaceutical Benefits Scheme) Bill 2007 does not provide any guidance on how the phrase “should be treated as interchangeable on an individual patient basis” should be interpreted, but does indicate that *“this advice may be taken into account by the Minister is [sic] deciding whether to place the drugs or medicinal preparations in a therapeutic group (see proposed section 84AG).”*²

3.6 The Department made a submission to a Senate Community Affairs References Committee inquiry into consumer access to pharmaceutical benefits (therapeutic groups) in April 2010. In its submission to the Committee, the Department commented that³:

- In general terms, interchangeability means drugs that are pharmaceutically related, have the same mechanism of action and provide similar therapeutic outcomes.
- The question of interchangeability of drugs (in therapeutic groups) differs from a finding by the TGA that generic brands of a drug are sufficiently bioequivalent to be treated as identical. It was announced in the Budget in 1997 that the new policy (at that time) meant specified medicines with very similar clinical activity would have the same pricing consequences as had previously been in place for drugs with identical chemical make-up.

² National Health Amendment (Pharmaceutical Benefits Scheme) Bill 2007 (Cth), Revised Explanatory Memorandum. Available from http://www.aph.gov.au/Parliamentary_Business/Bills_Legislation/Bills_Search_Results/Result?bld=r2801

³ Australian Department of Health (2010). Submission to the Australian Government Senate Community Affairs References Committee Inquiry Into Consumer Access to Pharmaceutical Benefits. Canberra; pp 14-15

- Material available to the PBAC members when considering interchangeability includes published peer-reviewed journals and studies, submissions by pharmaceutical companies and others, Product Information documents for the relevant drugs, and the expert analysis that underpins the PBAC deliberations.
- The submissions from pharmaceutical companies for PBAC listing recommendations include comparisons with other drugs, including details about similarity of action, clinical effect and similarity or differences in safety.

3.7 As part of the recent Medicines Australia strategic agreement, the Minister undertook not to determine any new therapeutic groups during the 5 year term of the agreement. The agreement further commits the Government and Medicines Australia to working together to develop a new framework for potential therapeutic group formation.⁴

3.8 All the non-interferon containing DAA treatment regimens recommended by the PBAC for subsidy for CHC have broadly similar efficacy results in terms of sustained virologic response (SVR). All regimens are associated with broadly similar rates of adverse events, when used without ribavirin. The addition of ribavirin to a CHC treatment regimen is associated with additional adverse events including anaemia, rash, cough, dyspnoea, insomnia and anxiety⁵.

4 Current situation

4.1 The sponsor (Gilead Sciences Pty Ltd) argued that the PBAC, in its consideration of whether sofosbuvir with velpatasvir should be treated as interchangeable on an individual patient basis with other DAA regimens, incorrectly provided such advice on the basis of HCV genotype alone.

4.2 The sponsor argued that the advice of the PBAC with regards to Section 101(3BA) was flawed and not founded on the evidence base. The sponsor argued that well defined characteristics independent of genotype define whether individual patients or the majority of patients can reasonably be expected to achieve the same health outcome with each of the regimens the PBAC advised should be treated as interchangeable on an individual patient basis.

⁴ Commonwealth Department of Health (2017). Strategic Agreement – Commonwealth of Australia and Medicines Australia Limited 2017, p. 16. Available on [Publication available on Department of Health Website](#).

⁵ Hepatitis C Virus Infection Consensus Statement Working Group. Australian recommendations for the management of hepatitis C virus infection: a consensus statement (January 2017), p 21. Melbourne: Gastroenterological Society of Australia, 2017

- 4.3 The sponsor stated that the selection and use of DAA regimens is based on the published guidelines of the Gastroenterological Society of Australia (GESA), which clearly define patients by characteristics that can confer different health outcomes with different DAA regimens and that, therefore, the apparent PBAC advice on interchangeability on an individual patient basis has not been made in consideration of all these factors. These other characteristics generally relate to patient safety when considering the choice of DAA regimen.
- 4.4 The sponsor provided a summary of the indications, contraindications, precautions and drug interactions which may impact patient outcomes and a prescriber's selection of therapy. The table is reproduced at Table 1 below.

Table 1: Summary of indications, contraindications, precautions and drug interactions for PBS listed DAA regimens

Characteristic establishing distinct populations	Regimen						
	Epclusa (sofosbuvir with velpatasvir)	Harvoni ¹ (ledipasvir with sofosbuvir)	Viekira Pak ² (+/- RBV ⁶) (paritaprevir with ritonavir with ombitasvir and dasbuvir)	Sovaldi ³ (+ RBV ⁶) (sofosbuvir)	Daklinza ⁴ (+ SOF ³) (daclatasvir)	Zepatier ⁵ (+/-RBV ⁶) (grazoprevir with elbasvir)	Ibavyr ⁶ (ribavirin; RBV)
HCV genotype⁷							
Genotype 1	✓	✓	✓				✓
Genotype 2	✓			✓			✓
Genotype 3	✓			✓	✓		✓
Genotype 4	✓					✓	✓
Genotype 5	✓						
Genotype 6	✓						
Mechanism of action							
	NS5B RNA polymerase inhibitor	NS5B RNA polymerase inhibitor	NS3/4A protease inhibitor + NS5A inhibitor + non-nucleoside inhibitor of NS5B RNA polymerase	NS5B RNA polymerase inhibitor	NS5A replication complex inhibitor	NS5A inhibitor + NS3/4A protease inhibitor	Nucleoside analogue
Hepatic disease							
Use in moderate hepatic impairment/Child-Pugh B decompensated cirrhosis	✓	✓	Not recommended	✓	✓	Contraindicated	Not evaluated
Use in severe hepatic impairment/Child-Pugh C decompensated cirrhosis	✓	✓	Contraindicated	✓	✓	Contraindicated	Not evaluated
Renal disease							

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Characteristic establishing distinct populations	Regimen						
	✘	✘	✓	✘	✓	✓	✘ if Cl _{Cr} < 50mL/min
Teratogenicity							
Use in pregnancy	Category B1 (Category X with RBV)	Category B1	Category B3 (Category X with RBV)	Category B1 (Category X with RBV)	Category B3	(Category X with RBV)	Category X Contraindicated
Treatment experience							
Prior PI therapy			Caution				
Established drug-drug interactions							
α-receptor antagonists			✘ Alfuzosin contraindicated				
Analeptics				✘ Modafinil			
Antianginal			✘ Ranolazine contraindicated				
Antiarrhythmics	✘ Amiodarone not recommended; digoxin with caution	✘ Amiodarone not recommended	✘ Amiodarone, quinidine, dronedarone contraindicated	✘ Not recommended when co- administered with another DAA	✘ Caution with amiodarone, digoxin, diltiazem, verapamil		
Antibacterials			✘ Fusidic acid contraindicated		Caution with clarithromycin, erythromycin		
Anticonvulsants	✘		✘ Contraindicated	✘	✘ Contraindicated	✘ Phenytoin, carbamazepine	
Antigout medications			✘ Colchicine contraindicated in renal/hepatic impairment				
Antihistamines			✘ Astemizole, terfenadine				

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Characteristic establishing distinct populations	Regimen						
			contraindicated				
Antihyperlipidaemic			✘ Gemfibrozil contraindicated				
Antimycobacterials	✘	✘ Rifampicin	✘ Contraindicated	✘ Rifampicin, rifabutin, rifapentine	✘ Contraindicated	✘ Rifampin	
Antipsychotic			✘ Lurasidone contraindicated				
Antiretrovirals	✘ Efavirenz not recommended; TDF with caution	✘ Caution with TDF	✘ Efavirenz contraindicated	✘ Tipranavir/ritonavir ✓ Darunavir/ritonavir, emtricitabine, efavirenz, raltegravir, rilpivirine, TDF	Requires dose reduction with protease inhibitors and/or cobicistat and dose increase with efavirenz, etravirine, nevirapine ✓ Darunavir/ritonavir, dolutegravir, lopinavir/ritonavir, tenofovir	✘ Contraindicated with efavirenz, atazanavir, darunavir, lopinavir, saquinavir, tipranavir	✘ Contraindicated with didanosine
β receptor agonists			✘ Salmeterol contraindicated				
Cancer chemotherapies			✘ Mitotane, enzalutamide contraindicated				
Immunosuppressants				✓ Cyclosporin, tacrolimus	✓ Cyclosporin, tacrolimus	✘ Contraindicated with cyclosporin	Caution with azathioprine
Dexamethasone					✘ Contraindicated		
Ergot derivatives			✘ Contraindicated				
Ethinylestradiol	✓		✘ Contraindicated	✓	✓ also		

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Characteristic establishing distinct populations	Regimen						
					levonorgestrel, norethisterone		
Famotidine					✓		
GI motility agents			✗ Cisapride contraindicated				
HMGCoA reductase inhibitors			✗ Contraindicated		Caution with rosuvastatin		
Methadone				✓	✓ also buprenorphine, naloxone		
Neuroleptics			✗ Pimozide contraindicated				
Omeprazole					✓		
PDE5 inhibitors			✗ Sildenafil contraindicated for PAH				
Platelet aggregators			✗ Ticagrelor contraindicated				
Sedatives			✗ Triazolam, midazolam contraindicated		✓ midazolam		
St Johns Wort	✗	✗	✗ Contraindicated	✗	✗ Contraindicated	✗ Contraindicated	
P-gp inducers	✗ Not recommended	✗ Caution	✗ Caution	✗ Caution			
BCRP inducers				✗ Caution			
CYP450 enzyme inducers	✗ Not recommended		✗ Contraindicated		✗ Contraindicated	✗ Contraindicated with strong inducers, not recommended with moderate inducers	

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Characteristic establishing distinct populations	Regimen						
	CYP450 enzyme inhibitors or other substrates			✘ Contraindicated		Dose reduction with boceprevir, telaprevir, ketoconazole, itraconazole, posaconazole, voriconazole ✓ simeprevir	✘ Not recommended with strong inhibitors
OATP1B1/3 inhibitors						✘ Contraindicated	
Potential clinically relevant metabolic drug-drug interactions with inducers/inhibitors/substrates of:							
CYP450	✓ inhibitors only		✘		✘	✘	
OATP1B1, OATP1B3, OATP2B1	✘		✘		✘	✘	
UGT1A1			✘				
P-gp	✓ inhibitors only	✘	✘	✓ inhibitors, substrates only	Caution if narrow therapeutic index e.g. dabigatran	✘	
BCRP	✓ inhibitors only	✘	✘	✓ inhibitors, substrates only	Caution if narrow therapeutic index	✘	
OCT-1					Caution if narrow therapeutic index		

✓ = may be used; ✘ = should not be used
Source: Table 1, pp 8-11 of the submission

- 4.5 The sponsor claimed that, due to differences in the safety profiles of the DAA regimens for CHC infection, patient outcomes at either the individual or population level are different, and that as such the PBAC advice that sofosbuvir with velpatasvir should be treated as interchangeable on an individual patient basis with other DAA regimens is not supported by the evidence base.

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.

6 PBAC Outcome

- 6.1 The PBAC confirmed its previous advice for sofosbuvir with velpatasvir with regards to interchangeability on an individual patient basis under Section 101(3BA) of the *National Health Act 1953*, with the following:
- ledipasvir with sofosbuvir, and paritaprevir with ritonavir with ombitasvir and dasabuvir +/- RBV for genotype 1 (GT1) CHC;
 - sofosbuvir in combination with RBV for genotypes 2 (GT2) and 3 (GT3) CHC;
 - daclatasvir and sofosbuvir for GT3 CHC; and
 - grazoprevir with elbasvir +/- RBV for genotype 4 (GT4) CHC.
- 6.2 The PBAC also recalled that at its July 2016 meeting it advised 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.
- 6.3 The PBAC considered that, for the purposes of providing advice under Section 101(3BA) of the Act, therapies with comparative health outcomes at the population level do not need to be identical with regards to patient-specific considerations, as these factors are a clinical practice decision taken into account when selecting the appropriate treatment for an individual patient. The PBAC considered that it was likely that, for some patients, sofosbuvir with velpatasvir would be the preferred treatment because of a particular combination of patient genotype, intolerance to other therapies, potential drug interactions, contraindications and patient baseline characteristics such as decompensated liver disease or renal function, however these factors were considered on a patient-by-patient basis, rather than at the broader

CHC population level.

Outcome:

Rejected

7 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.

8 Sponsor's Comment

The submission sought to understand on what evidence the PBAC made the original determination and to request that the determination be reconsidered based on information provided in the minor submission. Gilead remains unclear as to the evidentiary basis and criteria on which this determination was been made. Gilead maintains that the determination is not supportable on all the evidence.