Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Sofosbuvir/velpatasvir

Proprietary Product Name: Epclusa

Sponsor: Gilead Sciences Pty Ltd

August 2021

TGA Health Safety Regulation

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About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ARTG	Australian Register of Therapeutic Goods
CI	Confidence interval
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration (United States of America)
HCV	Hepatitis C virus
PI	Product Information
RMP	Risk management plan
SD	Standard deviation
SmPC	Summary of Product Characteristics (European Union)
SVR	Sustained virologic response
SVR12	Sustained virologic response 12 weeks after cessation of treatment
SVR24	Sustained virologic response 24 weeks after cessation of treatment
SVR4	Sustained virologic response 4 weeks after cessation of treatment
US(A)	United States (of America)

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Product name:	Epclusa
Active ingredients:	Sofosbuvir/velpatasvir
Decision:	Approved
Date of decision:	9 April 2021
Date of entry onto ARTG:	13 April 2021
ARTG number:	266823
, *Black Triangle Scheme:*[1]	No
Sponsor's name and address:	Gilead Sciences Pty Ltd Level 6, 417 St Kilda Road Melbourne, VIC, 3004
Dose form:	Film-coated tablet
Strength:	Fixed dose combination: 400 mg sofosbuvir, 100 mg velpatasvir
Container:	Bottle
Pack size:	28 tablets
Approved therapeutic use:	*Epclusa is indicated for the treatment of chronic hepatitis C virus (HCV) infection (genotype 1, 2, 3, 4, 5 or 6) in adults and paediatric patients ≥ 12 years of age and weighing ≥ 30 kg. (see 4.2 Dose and method of administration section for the recommended regimens for different patient subgroups).*
Route of administration:	Oral
Dosage:	The recommended dose of Epclusa in adults is one tablet, taken orally, once daily with or without food. In patients without cirrhosis and patients with compensated cirrhosis, the recommended course for Epclusa is 12 weeks. In patients with decompensated cirrhosis, the recommended course of Epclusa is 12 weeks, in combination with ribavirin for

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

12 weeks. In patients with decompensated cirrhosis, the ribavirin starting dose should be 600mg daily, with dose adjustment according to tolerance.

In paediatric patients ≥ 12 years of age and weighing ≥ 30 kg, the recommended dosage of Epclusa is one tablet taken orally once daily with or without food for 12 weeks. Epclusa is not indicated for use in paediatric patients < 12 years of age or weighing < 30 kg.

In elderly patients, no dose adjustment is warranted.

In patients with renal impairment, no dose adjustment of Epclusa is required for patients with renal impairment, including end stage renal disease (ESRD) requiring dialysis (see 5.2 Pharmacokinetic properties: Special Populations). Safety data are limited in patients with severe renal impairment (estimated glomerular filtration rate < 30 mL/min/1.73 m^2) and ESRD who are not receiving haemodialysis.

In patients with hepatic impairment, no dose adjustment of Epclusa is required for patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C) (see 5.2 Pharmacokinetic properties: Special Populations). Safety and efficacy of Epclusa have been established in adult patients with decompensated cirrhosis (see 4.8 Adverse Effects (Undesirable effects) and 5.1 Pharmacodynamic properties, Clinical Trials).

For further information regarding dosage, refer to the Product Information.

Pregnancy category: B1

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals have not shown evidence of an increased occurrence of fetal damage.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by Gilead Sciences Pty Ltd (the sponsor) to register Epclusa (sofosbuvir/velpatasvir) fixed dose combination oral tablets, with each tablet

containing 400 mg sofosbuvir and 100 mg velpatasvir for the following proposed extension of indications:

> *Epclusa is indicated for the treatment of chronic hepatitis C virus (HCV) infection (genotype 1, 2, 3, 4, 5 or 6) in adults and paediatric patients ≥ 12 years of age or weighing ≥ 35 kg.*

The proposed indication sought to expand the indicated population to include the treatment of paediatric patients ≥ 12 years of and over, and weighting ≥ 35 kg. The approved indication at the time of submission was as follows:

> *Epclusa (sofosbuvir/velpatasvir fixed-dose combination) is indicated for the treatment of chronic hepatitis C virus (HCV) infection (genotype 1, 2, 3, 4, 5 or 6) in adults.*

Additionally, the sponsor sought to update data from the previous approved submission, to include efficacy and safety data from Study GS-US-342-4062, in adult patients with hepatitis C virus (HCV) infection and severe renal impairment or end-stage renal disease; and to make updates to the Epclusa Product Information (PI).

Hepatitis C virus infection

Hepatitis C virus (HCV) infection has an estimated global prevalence of 1%, with a total of 71 million individuals worldwide chronically infected with HCV. The disease burden of HCV infection is due to progression of chronic liver disease, which can lead to cirrhosis, liver failure, hepatocellular carcinoma, and death. Globally, 27% of all cirrhosis and 25% of all hepatocellular carcinoma is attributable to HCV infection. In addition to having a higher incidence of hepatocellular carcinoma, patients with chronic HCV infection may develop extrahepatic HCV manifestations, such as cryoglobulinaemia, renal disease, and porphyria cutanea tarda. The global prevalence of HCV infection in children aged 1 to 19 years has been estimated to be 0.15%, or 3.5 million people.[2] In Australia, it has been estimated that approximately 200,000 people lived with chronic HCV and that 10,000 new HCV infections occurred each year.[3]

The HCV has significant genetic (RNA sequence) variability. Eight major genotypes have been identified: genotypes 1 and 3 are the most prevalent globally (46% and 30%, respectively) while genotypes 2, 4, and 6 represent approximately 23% of cases, genotypes 5 and 7 comprise < 1%, and genotype 8 has only recently been identified in 4 patients.

Current treatment options

The goal of HCV treatment in both paediatric and adult populations is virus eradication, thereby preventing progressive hepatic inflammation, hepatic fibrosis, cirrhosis, and liver failure that results in the need for liver transplantation. In recent years, HCV treatment in adult patients has been transformed by the development and approval of direct-acting antiviral agents that target viral proteins and cellular processes essential to HCV replication, such as those that contain sofosbuvir, a HCV NS5B polymerase inhibitor. Since the introduction of single-agent sofosbuvir (tradename: Sovaldi), several sofosbuvir-containing regimens have been introduced as fixed dose combinations, such as Harvoni (a combination of sofosbuvir and ledipasvir, a HCV NS5A inhibitor), and Epclusa, a fixed dose combination of sofosbuvir and velpatasvir.

[2] Schmelzer J, Dugan E, Blach S, Coleman S, Cai Z, DePaola M, et al. Global prevalence of hepatitis C virus in children in 2018: A modelling study. *Lancet Gastroenterol Hepatol* 2020: 1-19.
[3] Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia: annual surveillance report 2018. Sydney: Kirby Institute, UNSW Sydney; 2018.

With regards to treatment of paediatric patients with HCV, Sovaldi (single-agent sofosbuvir) and Harvoni (sofosbuvir/ledipasvir) have been approved for the treatment of patients between 3 to 18 years of age in both the United States of America (USA) and in the European Union (EU).

Clinical rationale

According to the sponsor, the availability of the first oral direct-acting antiviral agent therapies for HCV-infected paediatric patients represents a major therapeutic advance by eliminating the need for weekly pegylated interferon injections and the consequent systemic side effects associated with its use. However, sofosbuvir is given in combination with ribavirin, which is associated with significant toxicities, such as haematologic, constitutional and teratogenic side effects. In addition, treatment duration with either sofosbuvir alone, or sofosbuvir/ledipasvir is dependent on HCV genotype and cirrhosis status, and this may be a limiting factor for some paediatric patients.

Therefore, the sponsor is of the opinion that treatment options that do not include ribavirinn, have a fixed duration regardless of HCV genotype, and are effective across all HCV genotypes, would be beneficial in the HCV paediatric setting by avoiding the adverse reactions associated with ribavirin and thus decreasing the frequency of monitoring and blood tests, and by increasing patient adherence. The availability of a pan-genotypic regimen (for example, Epclusa) is also anticipated to be beneficial in areas where HCV genotype diversity is high and where genotyping may not be readily available or routinely performed. Epclusa provides a 12-week treatment option for HCV-infected adult patients, regardless of HCV genotype, demographics, and disease characteristics. Therefore, the availability of Epclusa as a single, pan-genotypic regimen for paediatric patients with HCV infection is anticipated to expand paediatric access to treatment.

With regards to expanding the treatment population to include patients with end stage renal disease, the sponsor noted that chronic HCV infection has a significant negative impact on morbidity and mortality in end stage renal disease patients on dialysis. Patients infected with HCV and with chronic kidney disease Stages 1 to 4 have an accelerated rate of loss of kidney function, increased risk of progression to end stage renal disease (chronic kidney disease, Stage 5), and increased risk of all-cause mortality in persons on dialysis. HCV treatments approved for use in patients with HCV infection and chronic kidney disease (Stages 1 to 5) include Viekira Pak (paritaprevir, ritonavir, ombitasvir, dasabuvir), Zepatier (elbasvir/ grazoprevir) and Maviret (glecaprevir/ pibrentasvir). However, these approved treatments for HCV in patients with chronic kidney disease have limitations. For example, the use of Viekira Pak is limited due to the required addition of ribavirin for optimal efficacy in many populations, and ribavirin-induced toxicities are exacerbated in subjects with renal impairment. The use of Zepatier is limited by the requirement for baseline resistance testing for subjects with genotype 1a HCV infection and, similar to Viekira Pak, requires use with ribavirin for optimal efficacy in some populations. Furthermore, all 3 treatment options involve the use of a protease inhibitor, which carries the risk of alanine aminotransferase elevations and/or hepatotoxicity, especially in patients with hepatic decompensation, resulting in an inability to use these drugs in patients with hepatic decompensation. Additional risk includes drug-drug interactions with other drugs including immunosuppressive medications, which is of clinical relevance to the kidney dialysis population. The sponsor is therefore of the opinion that Epclusa could address a medical need for effective treatment, based on a simple once-daily dosing regimen, for HCV-infected patients with severe renal impairment or end stage renal disease.

Regulatory status

This product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 19 December 2016 for the following indication:

> *Epclusa (sofosbuvir/velpatasvir fixed-dose combination) is indicated for the treatment of chronic hepatitis C virus (HCV) infection (genotype 1, 2, 3, 4, 5 or 6) in adults.*

At the time the TGA considered this application, similar extension of indications applications to include paediatric populations had been approved in the USA and the EU, as are detailed below. Note, the paediatric population age and weight ranges applied for by the sponsor for in both regions are different to those applied for in Australia.

In the USA, an application (submitted on 19 September 2019) was approved on 19 March 2020 for the following extension of indications:

> *Epclusa is indicated for the treatment of adults and pediatric patients 6 years of age and older or weighing at least 17 kg with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5, or 6 infection:*
>
> § *without cirrhosis or with compensated cirrhosis*
>
> § *with decompensated cirrhosis for use in combination with ribavirin.*

In the EU, an application (submitted on 13 October 2019) was approved on 25 August 2020 for the following extension of indications:

> *Epclusa is indicated for the treatment of chronic hepatitis C virus (HCV) infection in patients aged 6 years and older and weighing at least 17 kg.*

Applications to expand the use of Epclusa to include patients with end stage renal disease had been approved in both the USA (as of 15 November 2019) and the EU (as of 21 October 2019).

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 1: Timeline for Submission PM-2020-00171-1-2

Description	Date
Submission dossier accepted and first round evaluation commenced	2 March 2020
First round evaluation completed	31 July 2020
Sponsor provides responses on questions raised in first round evaluation	29 September 2020

Description	Date
Second round evaluation completed	29 October 2020
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	7 January 2021
Sponsor's pre-Advisory Committee response	21 January 2021
Advisory Committee meeting	4 to 5 February 2021
Registration decision (Outcome)	9 April 2021
Completion of administrative activities and registration on the ARTG	13 April 2021
Number of working days from submission dossier acceptance to registration decision*	208

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

Updated results from a two year carcinogenicity study of velpatasvir (Study TX-281-2030) in Sprague-Dawley rats were included in this submission.

There were no nonclinical objections to the findings and conclusions of the carcinogenicity study. The nonclinical evaluator recommended changes to the Epclusa PI following the first round evaluation in regards to the exposure ratio for a mouse carcinogenicity study (Study TX-281-2043) which was evaluated during a previous submission.[4]

The sponsor provided a response and proposed a mouse: human exposure ratio of 74, based on pharmacokinetic data after a single dose of velpatasvir in wild type Tg-rasH2 (001178-W), and the CD 1 strains of mice at 1000 mg/kg and saturation of absorption at ≥ 1000 mg/kg. The sponsor's justification of the exposure ratio was deemed acceptable and the statement in the PI was also acceptable.

[4] Australian Public Assessment Report for Vosevi sofosbuvir/velpatasvir /voxilaprevir Gilead Sciences Pty Ltd Submission: PM-2016-04442-1-2. Approved: 13 March 2018. AusPAR date: 4 March 2019. Available at: https://www.tga.gov.au/auspar/auspar-sofosbuvir-velpatasvir-voxilaprevir

Clinical

The following information was provided in support of the proposed changes to the Epclusa PI:

- One pivotal efficacy/safety study (Study GS-US-342-1143; supporting extension of indication to include paediatric population).
- One supportive efficacy/safety study (Study GS-US-342-4062; supporting the use of Epclusa in HCV patients with end stage renal disease).
- One clinical pharmacology study (Study GS-US-334-2130; supporting changes to the drug-drug interactions section of the PI) that examined the effects of cytochrome P450 and drug transporter inducers on sofosbuvir pharmacokinetics in healthy subjects
- Two population pharmacokinetic analyses were provided, which examined sofosbuvir and velpatasvir pharmacokinetics and associated covariates in populations of end stage renal disease patients with HCV (Study QP-2018-1029) and in paediatric subjects with HCV, respectively (Study CTRA-2019-1038).
- A quantitative analysis was submitted which further examined the relationship between cytochrome P450s and drug transporters.

The clinical evaluator commented that the clinical summary of efficacy and clinical overview in this submission both reference data from interim report 2 of the paediatric Study GS-US-342-1143 which contains data on subjects aged 6 to < 12 years old. This interim report 2 was not provided by the sponsor in the clinical dossier as it is not relevant to the Australian proposed indication.

In response, the Delegate states that the sponsor is requested to provide the interim report 2 of the paediatric Study GS-US-342-1143 which contains efficacy and safety data on subjects aged 6 to < 12 years old.

Pharmacology

Pharmacokinetics

The pharmacokinetics of sofosbuvir and velpatasvir, and the metabolites of sofosbuvir (metabolites GS-331007 and GS-566500) in patients with impaired renal function and paediatric patients were summarised in the clinical evaluation report. A summary of this information is provided below.

- Absorption, distribution, metabolism and excretion:
  - Epclusa is a film-coated tablet, which is to be taken orally, one-daily with or without food. Following a single dose of 400 mg sofosbuvir under fasted conditions to healthy subjects, the median time to maximum concentration values ranged from 0.5 to 1.0 hour.
  - For a typical, adult patient with HCV infection and end stage renal disease on dialysis, the sofosbuvir absorption rate, apparent volume of distribution, elimination half-life and apparent clearance were estimated to be 1.01 h^{-1}, 116 L, 0.54 h and 150 L/h, respectively. For velpatasvir, the estimated absorption rate, apparent volume of distribution, apparent peripheral volume, elimination half-life and apparent clearance values were 0.98 h^{-1}, 743 L, 424 L, 64.0 h and 44.6 L/h, respectively.
  - For a typical paediatric patient with HCV patient (that is, 42 kg female aged 12 years) receiving sofosbuvir/velpatasvir, the estimated absorption rate, apparent volume of distribution, elimination half-life and apparent clearance values for sofosbuvir were 1.25 h^{-1}, 62 L, 0.57 h and 127 L/h, respectively. For

velpatasvir, the estimated absorption rate, apparent volume of distribution, apparent peripheral volume, elimination half-life and apparent clearance values were 0.116 h^{-1}, 25.3 L, 577 L, 6.26 h and 23.5 L/h, respectively.

- Intra- and inter-individual variability:
  - For adult subjects with HCV and with end stage renal disease on dialysis, the population pharmacokinetic estimates for the intra- and inter-individual variability on sofosbuvir apparent clearance and apparent volume of distrubution were 35.8 % and 124%, respectively and the residual error was 107%. For velpatasvir, the corresponding values were 60.7%, 79.7% and 60.7%, respectively.
  - For paediatric patients with HCV, the population pharmacokinetic estimates for the intra- and inter-individual variability on sofosbuvir apparent clearance and apparent volume of distrubution were 80.0% and 224%, respectively and the proportional error values was 93.0%. For velpatasvir, the corresponding values were 52%, 83% and 79%, respectively.
- Special populations
  - A cross-study comparison indicated that adult patients infected with HCV, with severe renal impairment, showed increased sofosbuvir and the metabolite GS-331007 exposure by 103% and 501%, respectively compared to those with normal renal function and these increases were consistent with the results of the dedicated sofosbuvir Phase I renal impairment study in non-HCV-infected subjects. By contrast, the differences in steady-state velpatasvir plasma exposure between patients infected with HCV with severe renal impairment and normal renal function are unlikely to be clinically relevant.
  - A second cross-study comparison indicated that adult patients infected with HCV, with end stage renal disease requiring dialysis who were administered sofosbuvir/velpatasvir showed increased sofosbuvir and the metabolite GS-331007 exposure by 81% and 1719%, respectively compared to those without renal impairment and these increases were consistent with the results of the dedicated sofosbuvir Phase I study undertaken in HCV-negative subjects with end stage renal disease on chronic dialysis. By contrast, the differences in velpatasvir plasma exposure between HCV-infected patients with end stage renal disease and normal renal function are unlikely to be clinically relevant.
  - In both the HCV-infected adult population who have end stage renal disease and are receiving dialysis and the paediatric HCV-infected population, gender had a minimal impact on exposure to sofosbuvir, its' metabolite GS-331007, and velpatasvir.
  - A cross-study comparison indicated that sofosbuvir, its' metabolite GS-331007, and velpatasvir exposures in the paediatric population were similar to exposures shown to be safe and effective in HCV-infected adult subjects from the Phase II/III studies. Moreover, age was not identified as a statistically significant covariate for either sofosbuvir or velpatasvir pharmacokinetics.
  - In paediatric patients with HCV infection, bodyweight was identified as the most influential covariate on sofosbuvir and velpatasvir pharmacokinetics, with percentage changes in sofosbuvir and velpatasvir exposures ranging from −42.2% to +119% and −41.7% to +81.1%, respectively (relative to the median exposures) for subjects with extreme covariate values. However, the changes in exposure related to bodyweight are not considered clinically significant, as sustain virologic response rates remain high, the active pharmaceutical ingredients have favourable clinical safety profiles and there is a lack of association between exposure and

adverse events across the range of exposures observed in adult and subjects aged 6 to < 18 years old.

Drug-drug interactions

Study GS-US-334-2130 examined the effects of cytochrome P450 and drug transporter inducers on sofosbuvir and probe drug pharmacokinetics in healthy subjects.

Following administration of rifabutin or carbamazepine, which are moderate-to-strong inducers of P-glycoprotein, sofosbuvir exposure (area under the concentration versus time cure, from dosing to infinity) was decreased by 24% and 48%, respectively. Decreases in the exposure of metabolite GS-566500 were similar or to a lesser extent than those observed for sofosbuvir when co-administered with rifabutin or carbamazepine, whereas the pharmacokinetics of metabolite GS-331007 was unchanged by rifabutin or carbamazepine co-administration.

This study also examined the effects of 2 mg, 10 mg, 75 mg and 600 mg doses of rifampin on the pharmacokinetics of probe drugs for transporters including P-glycoprotein, organic-anion-transporting polypeptides, and breast cancer resistance protein, and cytochrome P450 enzymes (CYP3A, CYP2C9 and CYP1A2).[5] The results indicated that the exposure of all probe drugs decreased in a rifampin dose dependent manner when co-administered with rifampin.

Population pharmacokinetics

Analysis report QP-2018-1029 in end-stage renal disease

The evaluator concluded that the population pharmacokinetic analyses based on data obtained from HCV-infected adult subjects who have end stage renal disease and are receiving dialysis indicated that sofosbuvir plasma concentrations could be described by a one-compartment model with first order absorption, first order elimination and absorption lag time, whereas, velpatasvir pharmacokinetics were best described by a two-compartment model with first order absorption, first order elimination from the central compartment, absorption lag time and included clearance during dialysis.

The Delegate commented that the information in the proposed PI for this patient population is based on the clinical studies not the population pharmacokinetic data.

Analysis report CTRA-2019-1038 in paediatric patients

The dataset for the analysis included the results from three Phase II studies (Studies GS-US-334-1112, GS-US-337-1116 and GS-US-342-1143), which were undertaken in paediatric subjects (aged 3 to < 18 years old) with chronic HCV infection. The population pharmacokinetic data included 105 subjects from Study GS-US-334-1112, 226 subjects from Study GS-US-337-1116, and 173 subjects from Study GS-US-342-1143.

Bodyweight was identified as the most influential covariate on sofosbuvir and velpatasvir pharmacokinetics, with percent changes in sofosbuvir and velpatasvir exposures ranging from −42.2% to +119% and −41.7% to +81.1%, respectively (relative to the median exposures) for subjects with extreme covariate values. The changes in exposure related to

[5] **Cytochrome P450** (CYP) enzymes: CYPs are the major enzymes involved in drug metabolism, accounting for large part of the total metabolism. Most drugs undergo deactivation by CYPs, either directly or by facilitated excretion from the body. Also, many substances are bioactivated by CYPs to form their active compounds. Many drugs may increase or decrease the activity of various CYP isozymes either by inducing the biosynthesis of an isozyme (enzyme induction) or by directly inhibiting the activity of the CYP (enzyme inhibition). This is a major source of adverse drug interactions, since changes in CYP enzyme activity may affect the metabolism and clearance of various drugs. Such drug interactions are especially important to take into account when using drugs of vital importance to the patient, drugs with important side-effects and drugs with small therapeutic windows, but any drug may be subject to an altered plasma concentration due to altered drug metabolism.

weight were not considered clinically significant, as sustain viral response rates remain high, the active pharmaceutical ingredients have favourable clinical safety profiles and there was a lack of association between exposure and adverse events across the range of exposures observed in adult and subjects aged 6 to < 18 years old.

Proposed changes at the second round of evaluation

The sponsor proposed a new weight-band dosing regimen of 400 mg sofosbuvir/100 mg velpatasvir for patients weighing > 30 kg; and 200 mg sofosbuvir/50 mg velpatasvir for patients weighing 17 to < 30 kg as this would decrease the proportion of the subjects (in the 30 to 40 kg weight band) with minimum drug concentration values falling below the fifth percentile of adult values from 12% to 4%. Conversely, this increases the proportion of subjects with maximum drug concentrations and exposure (area under the concentration time curve) above the 95th percentile of adult values. Given the safety profile and lack of observed efficacy-safety relationship, this may not be significant.

The population pharmacokinetic evaluator expressed concern that the population pharmacokinetic results do not support an age cut-off of 12 years. It was highlighted that mean the body weight in the study for Group 1 was 60.6 kg (range: 21.5 to 146.5 kg). On that basis, there could be some patients in the ≥ 12 years of age group that weigh less than 30 kg, thus leading to higher exposures. The mean body weight in the study for Group 2 (6 to < 12 years) was 29.7 kg (range: 18.4 to 77.9 kg) which closely resembles the weight cut-off approved for 6 kg and above (17 to less than 30 kg) by the US Food and Drug Administration (FDA) and the European Medicine Agency (EMA).

Efficacy

Study GS-US-342-1143, extension of indication to paediatric population

Study GS-US-342-1143 was a Phase II, open-label, multicentre, multi-cohort study to investigate the safety and efficacy of sofosbuvir/velpatasvir in adolescents and children with chronic HCV Infection.

It was an *ongoing* study evaluating the pharmacokinetics, safety, and antiviral activity of sofosbuvir/velpatasvir in paediatric subjects aged 3 to < 18 years with chronic HCV infection. Subjects of three age groups were enrolled in a sequential fashion: 12 to < 18 years old, followed by 6 to < 12 years old, and 3 to < 6 years old. The study consisted of a pharmacokinetic lead-in phase (pharmacokinetic cohorts 1, 2, and 3) and a treatment phase (groups 1 and 2) within each age group. The pharmacokinetic cohorts 1, 2 and 3 included subjects of age groups 12 to < 18 years old, 6 to < 12 years old, and 3 to < 6 years old, respectively.

Treatment phase group 1 (including pharmacokinetic cohort 1) comprised adolescent subjects 12 to < 18 years old; group 2 (including pharmacokinetic cohorts 2 and 3) comprised paediatric subjects 6 to < 12 years old and paediatric subjects 3 to < 6 years old.

The sponsor provided an interim clinical study report containing data for adolescent subjects aged 12 to < 18 years (group 1). The study design, statistical analyses, and results for subjects aged 3 to < 12 years (group 2) were not included in the interim clinical study report.

The pharmacokinetic lead-in phase evaluated and confirmed the age-appropriate sofosbuvir/velpatasvir dose for each age group by analysing the pharmacokinetics, safety, and antiviral activity of sofosbuvir/velpatasvir 400 mg/100 mg through 7 days of dosing. At least 17 subjects were planned to be enrolled into cohort 1 (12 to < 18 years old) to receive a sofosbuvir/velpatasvir fixed dose combination 400 mg/100 mg adult tablet or 2 x 200 mg/50 mg tablets (if determined necessary based on sofosbuvir/velpatasvir swallowability assessment) once a day for 7 days. If unable to swallow the tablet

formulations, the subjects were to receive sofosbuvir/velpatasvir fixed dose combination of 400 mg/100 mg oral granules (8 x 50 mg/12.5 mg packets). Subjects underwent an intensive pharmacokinetic evaluation on Day 7. Subjects who completed the pharmacokinetic lead-in phase were immediately enrolled into the treatment phase with no interruption of study drug administration until the appropriateness of the dose had been confirmed by pharmacokinetic and safety results from the pharmacokinetic lead-in phase.

Approximately 100 subjects, including subjects from cohort 1 of the pharmacokinetic lead-in phase, were planned to be enrolled into treatment phase group 1 (that is, ages 12 to < 18 years old). Subjects received a sofosbuvir/velpatasvir fixed dose combination of 400 mg/100 mg (total daily dose) orally once daily for 12 weeks. If a subject (in Cohort 2) was unable to swallow the tablet formulations, they were assigned a sofosbuvir/velpatasvir fixed dose combination oral granules formulation.

Primary objective

The primary objective was to evaluate the safety and tolerability of a sofosbuvir/velpatasvir fixed dose combination for 12 weeks in paediatric subjects with chronic HCV.

Secondary objectives

To determine the efficacy of sofosbuvir/velpatasvir fixed dose combination for 12 weeks in paediatric subjects with chronic HCV infection, as assessed by the by the proportion of subjects with sustained virologic response (SVR) 12 weeks after cessation of treatment (SVR12); to determine the proportion of subjects with SVR at 4 and 24 weeks after cessation of treatment (SVR4 and SVR24, respectively); to evaluate the proportion of subjects with virologic failure, including breakthrough/non-response and relapse.

Results

102 subjects were enrolled for Group 1. All 102 enrolled subjects received at least 1 dose of study drug and were included in both the safety analysis set and full analysis set. All but 1 subject completed study treatment (99.0%, 101 subjects).

Baseline demographics

The majority of subjects were female (51.0%) and White (72.5%). The mean age was 15 years (standard deviation (SD) = 1.9 years) years. The mean (SD) body mass index was 22.7 (6.34) kg/m^2.

The majority of subjects had been infected through vertical transmission (89.2%), had genotype 1 HCV infection (73.5%) or genotype 3 HCV infection (11.8%), and were treatment naive (78.4%).

Results for primary efficacy outcome

The proportion of adolescent subjects who achieved SVR12 was 95.1% (95% confidence interval (CI): 88.9% to 98.4%; 97/102 subjects). The SVR12 rates were 93.4% (71/76 subjects) in subjects with genotype 1 HCV infection and 100.0% in subjects with genotype 2 (6/6), 3 (12/12), 4 (2/2) and 6 (6/6) HCV infection.

Results for other efficacy outcomes

Subgroup analyses of SVR12 rates by demographic subgroups and baseline disease characteristics for adolescent subjects 12 to < 18 years old showed consistent results to the overall primary analysis.

The proportion of adolescent subjects who achieved SVR4 was 96.1% (95% CI: 90.3% to 98.9%; 98/102 subjects). All but 1 subject who achieved SVR4 achieved SVR12. Results were consistent across genotypes.

No subject had on-treatment virologic failure (that is, breakthrough, rebound, or non-response). A total of 5 of 102 subjects (4.9%) did not achieve SVR12. Of these, 1 subject relapsed following discontinuation of study drug due to pregnancy, and 4 subjects were categorised as 'Other'. Of these 4 subjects 3 subjects were lost to follow-up and did not have post-treatment Week 12 assessments. One subject was pending a post-treatment Week 12 visit at the time of analysis.

Evaluator conclusions on clinical efficacy (extension of indications for the paediatric population)

The study design, inclusion and exclusion criteria, and study endpoints of the pivotal efficacy study on paediatric HCV patients (Study GS-US-342-1143) were appropriate.

The adolescent study population evaluated did not have cirrhosis. The efficacy/safety of Epclusa has not been evaluated in HCV-infected adolescents with HIV co-infection.

Efficacy results were generally supportive of a positive effect of Epclusa in the treatment of chronic HCV in adolescent patients (12 to < 18 years old). The proportion of adolescent subjects who achieved HCV RNA < lower limit of quantitation (< 15 IU/mL) at 12 weeks after discontinuation of the study drug was 95.1% (95% CI: 88.9% to 98.4%). This is comparable to the proportion of adult HCV patients achieving a sustained virologic response (SVR) after 12 weeks (SVR12) of Epclusa in the clinical studies (the ASTRAL 1, ASTRAL 2, ASTRAL 3, ASTRAL 4 and ASTRAL 5 trials) presented in the currently approved PI (SVR12 rates of 83% to 99% across these studies).

The clinical evaluator was satisfied with the proposed updates to the product information, based on these data.

Study GS-US-342-4062, use in patients with end stage renal disease

Study GS-US-342-4062 was a Phase II, multicentre, open-label study to evaluate the efficacy and safety of sofosbuvir/velpatasvir for 12 weeks in adult subjects with chronic HCV infection who are on dialysis for end stage renal disease.

Primary objectives

To evaluate the antiviral efficacy of treatment with sofosbuvir/velpatasvir for 12 weeks as measured by the proportion of subjects with sustained viral response 12 weeks after cessation of treatment (SVR12); and to evaluate the safety and tolerability of the treatment regimen.

Secondary objectives

To determine the proportion of subjects who attained sustained virologic response (SVR) at 4 and 24 weeks after cessation of the study treatment regimen (SVR4 and SVR24, respectively); to evaluate the proportion of subjects with virologic failure; to evaluate the kinetics of circulating hepatitis C virus (HCV) RNA during treatment and after cessation of treatment.

Results

59 subjects were enrolled and all enrolled subjects received at least one dose of study drug All but 1 subject completed study treatment (98.3%).

Most subjects were currently undergoing haemodialysis (91.5%), with the remainder receiving peritoneal dialysis. The mean (range) duration that subjects were on dialysis was 7.3 (0 to 40) years. A prior history of kidney transplantation was reported for 32.2% of subjects.

94.9% (95%CI: 85.9% to 98.9%) of subjects (56 of 59) achieved SVR12. The SVR12 rates were 92.0% (23/25 subjects) in subjects with genotype 1 HCV infection, 100.0% in

subjects with genotype 2 (7/7), 4 (4/4) and 6 (2/2) HCV infection, and 93.8% (15/16) in subjects with genotype 3 infection.

Virologic outcomes were presented in the clinical evaluation report. No subject had on-treatment virologic failure (that is, breakthrough, rebound, or non-response). A total of 3 of 59 subjects (5.1%) did not achieve SVR12. Of these, 1 subject relapsed, 1 subject relapsed following discontinuation of study drug due to noncompliance and 1 subject was categorised as 'Other'.

Evaluator conclusions (use in patients with end stage renal disease)

Results of study GS-US-342-4062 were supportive of the efficacy of Epclusa in patients with end stage renal disease. Efficacy sections of the proposed PI were evaluated and deemed to be appropriate.

Safety

The safety data to support the extension of indication to include adolescent patients was derived from Study GS-US-342-1143. Study GS-US-342-4062 provided safety data to support the proposed use of Epclusa in patients with end stage renal disease.

The evaluator concluded that the safety profile of Epclusa in adolescent patients and in end stage renal disease patients was consistent with the known adverse effects of Epclusa in adult HCV patients and did not raise any major safety concerns.

The most commonly reported adverse drug reactions in adult HCV patients receiving 12 weeks of treatment with Epclusa (as described in the currently approved PI) were headache (29%), fatigue (21%) and nausea (13%).

In Study GS-US-342-1143, the most commonly reported treatment-related adverse events with Epclusa in adolescent HCV patients were headache (17.6%), fatigue (15.7%), and nausea (14.7%). All of these treatment-related adverse events were of mild (Grade 1) or moderate (Grade 2) severity. The incidence of serious adverse events was low (2.0%; 2/102) and none of the serious adverse events were considered to be treatment-related.

In Study GS-US-342-4062, the most commonly reported treatment-related adverse events with Epclusa in end stage renal disease patients were nausea (6.8%), headache (5.1%), and vomiting (5.1%). All of these treatment-related adverse events were of mild (Grade 1) or moderate (Grade 2) severity. The percentage of patients with any serious adverse events was 18.6%. No serious adverse event was reported for > 1 subject and none of the serious adverse events were considered to be treatment-related.

Study GS-US-334-2130, which examined the pharmacokinetics and safety of sofosbuvir in the presence and absence of rifabutin or carbamazepine in healthy subjects, indicated that there was a higher incidence of adverse events when sofosbuvir was co-administered with rifabutin or carbamazepine compared to when sofosbuvir was administered alone.

Evaluator conclusions on safety

The evaluator was of the opinion that the safety sections of the proposed PI adequately describe the submitted safety data.

Specific to the issue of the removal of a footnote in the dosage instruction of the PI, in regards to addition of ribavirin for genotype 3 infected patients with compensated cirrhosis; following the first round of evaluation, the clinical evaluator was of the opinion that removal of this footnote in regards to addition of ribavirin in genotype 3 infected HCV patients with compensated cirrhosis was acceptable based on the literature submitted by the sponsor. The US PI has been similarly updated, while the EU Summary of Product Characteristics (SmPC) has retained the footnote.

The Delegate comments that advice from the Advisory Committee on Medicines (ACM) is sought, given this footnote has been retained in the EU SmPC.

Risk management plan

There was no requirement for a risk management plan (RMP) evaluation for a submission of this type.[6]

The Delegate has since confirmed with the RMP evaluator that an RMP is not required, should this application be extended to paediatric patients ages 6 years and older.

Risk-benefit analysis

Delegate's considerations

Data submitted in support of the proposed changes to the Epclusa PI are generally acceptable. The main concern relates to the paediatric extension and proposal to limit the approval to adolescents aged 12 years and over, as this is not supported by the population pharmacokinetic data and is inconsistent with the approval by the FDA and EMA.

The same supporting data in relation to safety and efficacy were submitted to Australia, although the interim report 2 of the paediatric Study GS-US-342-1143 which contains efficacy and safety data on subjects aged 6 to < 12 years old was not included in this submission.

While the prevalence of hepatitis C in children in Australia is rare, an estimated 780 cases in children aged 7 to 11 years in Australia;[7] therefore, this represents a considerable number of children who may benefit from treatment.

The TGA would like to reach an agreement with the sponsor in including the indication from 6 years and above and weighing at least 17 kg and registering the lower strength tablet. Approval of a pangenotypic direct acting antiviral in children is an important step forward for paediatric patients with hepatitis C in Australia.

Summary of issues

The sponsor is proposing to update the PI for Epclusa with five changes:

1. Extension of the indication to include paediatric patients aged ≥ 12 years of age or weighing ≥ 35 kg based on efficacy and safety data from Study GS-US-342-1143.
2. Inclusion of safety and efficacy data from Study GS-US-342-4062, HCV-infected adult patients with severe renal impairment or end-stage renal disease.
3. Updates to the drug interactions for Epclusa, based on Study GS-US-334-2130, and reclassification of inducers.
4. Update to include results from nonclinical Study TX-281-2030 (A 2-year oral carcinogenicity study of velpatasvir in Sprague-Dawley rats).
5. Removal of footnote: 'Addition of ribavirin may be considered for genotype 3 infected patients with compensated cirrhosis' in a table of the PI concerned recommended treatment regimen regardless of HCV genotype.

[6] The sponsor must still comply with routine product vigilance and risk minimisation requirements.
[7] Schmelzer J, Dugan E, Blach S, Coleman S, Cai Z, DePaola M, et al. Global prevalence of hepatitis C virus in children in 2018: A modelling study. *Lancet Gastroenterol Hepatol* 2020:1-19.

The Delegate is seeking ACM advice in regards to Issue 1, above: extension of indication to include paediatric patients aged ≥ 12 years of age or weighing ≥ 35 kg based on efficacy and safety data from Study GS-US-342-1143, given that the submitted population pharmacokinetic data do not support the proposed age restriction to age 12 years and above.

Following the second round of evaluation, the Epclusa PI was updated to lower the weight cut-off to ≥ 30kg, with a revised indication proposed by the sponsor:

> *Epclusa is indicated for the treatment of chronic hepatitis C virus (HCV) infection (genotype 1, 2, 3, 4, 5 or 6) in adults and paediatric patients ≥ 12 years of age or weighing ≥30 kg. (see 4.2 Dose and method of administration section for the recommended regimens for different patient subgroups).*

Comment is also sought regarding Issue 5, removing the footnote.

The other proposed changes to the PI (that is, points raised as Issues 2 to 4, above) are deemed acceptable.

Proposed action

The Delegate had no reason to say, at the time, that the application for Epclusa should not be approved for registration.

Registration is recommended for the Delegate's amended indication:

> *Epclusa is indicated for the treatment of chronic hepatitis C virus (HCV) infection (genotype 1, 2, 3, 4, 5 or 6) in adults and paediatric patients aged 6 years and older and weighing at least 17 kg.*

Questions for the sponsor

The sponsor provided the following response to questions from the Delegate.

1. ***Please provide an update of the overseas regulatory status for each of the five proposed changes to the product information.***

The current overseas regulatory status for the proposed variations related to the extension of indication for each of the five proposed changes to Epclusa is provided in [a sponsor-attached document titled] Foreign Regulatory Status.[8]

2. ***Please provide the interim report 2 of the paediatric study GS-US-342-1143 which contains efficacy and safety data on subjects aged 6 to < 12 years old as part of the pre-ACM response.***

As requested, the sponsor has provided the interim report 2 for the paediatric Study GS-US-342-1143 containing efficacy and safety data in subjects aged 6 to < 12 years old.

3. ***Please submit data to register the lower strength tablet for evaluation by pharmaceutical chemistry as a new submission. Alternatively, a mutual stop-clock post-ACM could be considered to allow time for evaluation of the lower strength tablet.***

[Information reacted].

[8] Relevant contents for the overseas regulatory status are available in the Regulatory Status section, towards the beginning of this AusPAR.

Advisory Committee considerations[9]

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

The ACM advised the following in response to the Delegate's specific request for advice:

1. ***The Delegate's proposal to approve the indication from 6 years of age and from 17 kg:***

   Epclusa is indicated for the treatment of chronic hepatitis C virus (HCV) infection (genotype 1, 2, 3, 4, 5 or 6) in adults and paediatric patients ≥ 6 years of age or weighing ≥ 17 kg. (see 4.2 Dose and method of administration section for the recommended regimens for different patient subgroups).

   Please comment.

The ACM agreed with the Delegate's proposed indication for approval, as there is a positive efficacy and safety profile in the 6 to 12 year age group. The ACM advised that extending the paediatric indication to 6 years of age and over would benefit the intended treatment population, allowing for better treatment regimes.

If the product is only approved in patients 12 years of age and older, the ACM advised that trial data from the 6- to 12-year age group should be included in the Product Information.

2. ***The Delegate is also proposing that the lower strength tablet (200 mg/50 mg) be registered as part of this submission, even if the sponsor does not propose to supply it at present. Please comment.***

The ACM advised that the lower strength tablet would be particularly beneficial in the younger aged patients and noted that this would greatly improve treatment outcomes. The ACM noted the younger population frequently has difficulty with ingesting larger tablets. The ACM expressed concerns regarding the possibility of confusion in a clinical setting if the lower strength tablet was registered but not marketed in Australia.

3. ***Related to Question 1 (above), the committee is asked to consider the sponsor's response to Milestone 5 outlining the reasoning for restricting the indication to patients aged 12 years and above and the intention to only supply the currently registered 400/100 mg tablet in Australia.***

The ACM were of a strong opinion that excluding the 6 to 12 year paediatric population based on a company decision was not appropriate. The ACM noted that a global prevalence study from 2018 does not reflect the current needs, is irrelevant and that they could see real world clinical improvement in this population if made available in Australia.

4. ***Please comment on the current clinical need for hepatitis C direct acting-antivirals in paediatric patients in Australia, particularly the 6 to 12 year age group. The Delegate is of the opinion that registering the lower age group will***

[9] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

lead to improved access and funding for the paediatric population with Hepatitis C in Australia.

The ACM agreed and supported the need for an indication of over 12 years of age, and they further noted there would be more clinical significance to register and supply the product with the over 6 year old indication.

5. Does the committee agree with the removal of the footnote in the table of dosing regimens, in relation to the addition of ribavirin for genotype 3 infected patients with compensated cirrhosis?

The ACM agreed with the Delegate that this footnote should be removed, noting that ribavirin is no longer recommended as adjuvant treatment. The ACM further noted that a second footnote should also be reviewed and amended as follows:

> 'In patients with decompensated cirrhosis, the ribavirin starting dose should be 600 mg daily, with dose adjustment according to tolerance.'

6. The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

The ACM noted that there is limited information in the PI in regards to treatment of HCV in patients with severe renal failure. The ACM strongly encouraged the inclusion of further information relating to the dosage/precautions section of the PI in regards to pharmacokinetics in chronic kidney disease Stages 3b, 4 and 5-non dialysis patients. The ACM noted that chronic kidney disease Stages 3b, 4 and 5-non dialysis patients were excluded from clinical trials and data is limited. The ACM advised that further guidance relating to this in the PI is required to provide more clarity around the unknown effects on safety and tolerability of the GS-331007 metabolite, as its excretion is markedly impaired in patients with chronic kidney disease and kidney failure. The ACM agreed with the Delegate that the EU Summary of Product Characteristics (SmPC) was more detailed and recommended adoption of Table 20 from the EU SmPC in the PI.

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

> *Epclusa is indicated for the treatment of chronic hepatitis C virus (HCV) infection (genotype 1, 2, 3, 4, 5 or 6) in adults and paediatric patients aged 6 years and older and weighing at least 17 kg.*

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Epclusa (sofosbuvir/velpatasvir) fixed dose combination oral tablets containing 400 mg sofosbuvir and 100 mg velpatasvir for the following extension of indications:

> *Epclusa is indicated for the treatment of chronic hepatitis C virus (HCV) infection (genotype 1, 2, 3, 4, 5 or 6) in adults and paediatric patients ≥ 12 years of age and weighing ≥ 30 kg. (see 4.2 Dose and method of administration section for the recommended regimens for different patient subgroups).*

As such, these were the full indications at this time.

Specific conditions of registration applying to these goods

- This approval does not impose any requirement for the submission of Periodic Safety Update reports. Sponsor should note that it is a requirement that all existing

requirements for the submission of PSURs as a consequence of the initial registration or subsequent changes must be completed.

Attachment 1. Product Information

The PI for Epclusa approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

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