Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Ledipasvir / Sofosbuvir

Proprietary Product Name: Harvoni

Sponsor: Gilead Sciences Pty Ltd

October 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website < https://www.tga.gov.au> .

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.

Contents

Common abbreviations

Abbreviation	Meaning
ACSOM	Advisory committee for the safety of medicines
AE	Adverse event
ALT	alanine aminotransferase
BMI	Body Mass Index
CHC	Chronic hepatitis C virus infection
CI	Confidence interval
CMI	Consumer Medicine Information
CPT	Child-Pugh Turcotte score
CYP	cytochrome P450 enzymes
DAA	Direct Acting Antiviral
DDI	Drug-drug interaction
DILI	Drug-Induced Liver Injury
DTG	dolutegravir
EASL	European Association for the Study of the Liver
EFV	efavirenz
eGFR	estimated glomerular filtration rate
eGFRCG	estimated glomerular filtration rate Cockgroft Gault
EMA or EMEA	European Medicines Agency
EOT	End Of Therapy
EVG	elvitegravir
EU	European Union
FDA	US Food and Drug Administration
FDC	Fixed dose combination
FTC	emtricitabine
GS-331007	A metabolite of SOF

Abbreviation	Meaning
GT	genotype
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV	human immunodeficiency virus
hr	hour
ICH	International Conference on Harmonisation
IFN	interferon
ITT	Intent to treat
LDV	ledipasvir
LL	lower limit
LLOQ	Lower limit of quantification
LTFUP	lost to follow up
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
NI	nucleoside inhibitor
NS5B	nonstructural protein5B
PCR	polymerase chain reaction
PEG-IFN	PEGylated interferon
P-gp	P-glycoprotein
PI	Product Information
PK	Pharmacokinetics
PO	per oral (taken orally)
PP	Per protocol
RAL	raltegravir
RAP	Resistance associated polymorphism

Abbreviation	Meaning
RAV	Resistance associated variant
RBV	ribavirin
RT-PCR	Reverse transcription polymerase chain reaction
RTV	ritonavir
SAE	Serious adverse event
SAS	Safety Analysis Set
SOF	Sofosbuvir
SVR	sustained virological response
SVR4	sustained virological response 4 weeks after EOT
SVR12	sustained virological response 12 weeks after EOT = cure
SVR24	sustained virological response 24 weeks after EOT
TAF	Tenofovir Alafenamide
TDF/FTC	Truvada = FDC of tenofovir Disoproxil Fumarate+ emtricitabine
TDF/FTC/EFV	Atripla - the FDC of tenofovir Disoproxil Fumarate, emtricitabine and efavirenz
TEV	treatment-emergent variant
TGA	Therapeutic Goods Administration
t½	apparent plasma half-life
TR	treatment related
US	United States

I. Introduction to product submission

Submission details

Type of submission:	Major variation; extension of indications
Decision:	Approved
Date of decision:	14 November 2016
Date of entry onto ARTG	16 November 2016
Active ingredients:	Ledipasvir / Sofosbuvir
Product name:	Harvoni
Sponsor's name and address:	Gilead Sciences Pty Ltd Level 6/ 417 Saint Kilda Road Melbourne Vic 3004
Dose form:	Tablet, film coated
Strength:	95.9 mg ledipasvir acetone solvate (90 mg equivalent ledipasvir)/400mg sofosbuvir
Container:	Bottle
Pack size:	26 tablets
Approved therapeutic use:	*Harvoni (ledipasvir/sofosbuvir fixed-dose combination) is indicated for the treatment of chronic hepatitis C (CHC) infection in adults.* *(see precautions and clinical trials sections for information on the available data for HCV patients of each genotype, see dosage and administration section for recommended regimens and treatment durations for different patient subgroups).*
Route of administration:	Oral
Dosage:	The recommended dose of Harvoni tablets is one tablet, taken orally, once daily with or without food. For full details of dosage and duration of treatment please see the Product Information.
ARTG number:	222848

Product background

This AusPAR describes the application by Gilead Sciences Pty Ltd (the sponsor) to register Harvoni ledipasvir / sofosbuvir 90 mg/ 400 mg tablet for the following indication:

> *Harvoni (ledipasvir/sofosbuvir fixed-dose combination) is indicated for the treatment of chronic hepatitis C (CHC) infection in adults.*

At the time of this submission Harvoni was approved for the indication:

> *Harvoni (ledipasvir/sofosbuvir fixed-dose combination) is indicated for the treatment of chronic hepatitis C (CHC) genotype I infection in adults.*

The current application is seeking to extend the indication to all hepatitis C virus (HCV) genotypes.

The sponsor also proposes to update the pharmacokinetics (PK), drug-drug interaction (DDI), clinical trials sections of the Product Information (PI) based on submitted pharmacokinetics and clinical studies and an update of the carcinogenicity statement.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 13 May 2015.

At the time the TGA considered this application, a similar application had been approved in (country, date); USA, 12 November 2015; European Union (EU) (centralised process), 28 October 2015 and New Zealand, 26 May 2016 and was under consideration in Canada.

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. Quality findings

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

III. Nonclinical findings

Introduction

Gilead Sciences Pty Ltd has applied to extend the indication and update the PI for Harvoni tablets. Harvoni (ledipasvir /sofosbuvir fixed dose combination) is currently approved in Australia for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults. This application proposes to extend the indication, for treatment of chronic hepatitis C (CHC) infection in adults, including patients with HCV/HIV co-infection, patients who have previously failed a sofosbuvir/ribavirin/ PEGylated interferon (PEG-IFN) regimen, patients with chronic genotype 2, 3, 4, 5 or 6 HCV infection, patients with HCV infection post-transplantation with compensated liver disease, and patients with decompensated liver disease post-transplantation, and is based on data generated from clinical studies. No new module 4 data were provided to support this extension of indication.

However, proposed changes to the Precautions – Carcinogenicity section of the PI require nonclinical comment. In support of the proposed changes, the sponsor submitted a 26 week carcinogenicity study of ledipasvir in mice.

Nonclinical summary and conclusions

The carcinogenic potential of ledipasvir by the oral route was assessed in transgenic mice following daily doses for 26 weeks. Group sizes of 25 per sex and 26 week dosing were appropriate for this species[1]. The choice of a transgenic model is considered acceptable. A concurrent positive control (N-methyl-N-nitrosourea) was included and tumours expected from administration of this mutagen were observed, confirming the validity of this study.

No ledipasvir related effect on survival, changes in food consumption or neoplastic findings were observed in any of the treated groups. A small non adverse weight gain was observed in both males and females administered ledipasvir at the three concentrations 20, 60 and 300 mg/kg/day. However, the weight increase was not regarded to be toxicological relevant as it was only statistically significant in females ($p \leq 0.05$) and not in males, did not correlate with increased food consumption, increase with increased dosing or have any impact on survivability or carcinogenicity. Dose levels were selected based on results of a 4 week oral gavage toxicity and toxicokinetic study in Model 001178-W (wild type) mice (previously evaluated in submission PM-2014-00469-1-2). In this 4 week study, the no-observable-adverse-effect level (NOAEL) was the highest dose level of 300mg/kg/day which is equivalent to approximately 26 times the recommended human dose indicated for human use, calculated based on AUC and was acceptable.

Therefore, based on this study, ledipasvir is not expected to pose a carcinogenic risk during clinical use. The sponsor has indicated a 2 year rat carcinogenicity study is currently in progress, which should confirm the findings in this study.

Table 1: Relative exposure in the carcinogenicity study

Species	Dose (mg/kg/day PO)	$AUC_{0-\tau}$ (µg·h/mL)	Exposure ratio#
Mice (001178W (wild type))	20	38.7	5
	60	95.3	11
	300	225	26
Human[a] (healthy volunteers)	400/90 mg	8.525	

= animal:human plasma AUC0–24 h; [a] data obtained from PM-2014-00469-1-2 PO = per oral

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

[1] MacDonald, J. et al. (2004) The utility of genetically modified mouse assays for identifying human carcinogens: a basic understanding and path forward. *Toxicol. Sci.* 77**:** 188–194.
[1] Morton, D. et al. (2002) The Tg rasH2 mouse in cancer hazard identification. *Toxicol. Pathol.* 30: 139–146.

Introduction

Clinical rationale

HCV is a global health challenge and untreated, can lead to liver cirrhosis, decompensated liver disease, hepatocellular carcinoma (HCC) and death. Currently, approximately 170 million individuals worldwide are chronically infected with HCV. [2] In the US, > 3 million are estimated to be chronically infected with HCV,[3] with > 800,000 estimated to have cirrhosis and > 100,000 of these estimated with decompensated cirrhosis.[4]

In a systematic review, the rate of transition from compensated cirrhosis (Child-Pugh Turcotte score (CPT) CPT A) to decompensated cirrhosis (CPT B or CPT C) was 5% to 7% per year. Once decompensated, the 1 year mortality for CPT B decompensated cirrhosis is approximately 20%, while the 1 year mortality for CPT C decompensated cirrhosis is > 50%.[5] In the US, there are currently no approved therapies for the treatment of HCV patients with decompensated liver disease. The poor adverse event (AE) profile of interferon (IFN) based regimens has limited their use in this sick patient population to specialised centres and clinical trials. Instead, the mainstay of treatment in the US for patients with decompensated liver disease due to HCV has been liver transplantation.

Accordingly, liver failure and HCC secondary to HCV infection are the most common indications for liver transplantation in the US, accounting for > 30% of liver transplants.[6] Unfortunately, of the > 100,000 with decompensated liver disease due to HCV, only approximately 4,500 are listed in a given year for transplantation, and only approximately 1,500 liver transplantations for HCV are performed annually. Furthermore, the odds of being transplanted once on the waiting list (1:3) are similar to those of dying/becoming too sick to undergo transplantation (1:5).[7]

Need for medical treatment and the long-term benefits of achieving sustained virological response (SVR) = HCV cure in cirrhotics and those with decompensated liver disease.

The large number with decompensated disease due to HCV, the small number able to obtain a liver transplant, and limited prognosis even in those who receive a transplant, highlight the need for safe and efficacious HCV therapy for decompensated disease as well as those with recurrent HCV post liver transplantation. IFN free treatment regimens have created an opportunity to address this unmet medical need. The purpose of SOLAR-1 and SOLAR-2 is

a. to assess the efficacy of ledipasvir/sofosbuvir (LDV/SOF) FDC[8]+ ribavirin (RBV) in post transplantation subjects with compensated liver disease as well as those with decompensated liver disease, regardless of transplantation status; and

b. demonstrate the safety of LDV/SOF+RBV in a population with very high morbidity and mortality.

Treatment of genotypes other than GT 1

The most common HCV GT in the US, Australia and EU is GT 1;[9] GT 2 and 3 HCV represent the majority of the remaining cases of chronic HCV infection in the US and EU.[10] GT 4, 5,

[2] http://www.who.int/csr/disease/hepatitis/whocdscsrlyo2003
[3] Kershenobich D, et al. Applying a system approach to forecast the total hepatitis C virus-infected population size: model validation using US data. *Liver Int* 2011; 31 Suppl 2:4-17.
[4] Davis GL, et al. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. *Gastroenterology* 2010; 138: 513-521.
[5] D'Amico G, et al. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J Hepatol* 2006; 44:217-231.
[6] Brown RS, Jr. Hepatitis C and liver transplantation. *Nature* 2005; 436 :973-978.
[7] Kim WR, et al. OPTN/SRTR 2013 Annual Data Report: liver. *Am J Transplant* 2013; 15 Suppl 2: 1-28
[8] FDC = fixed dose combination

and 6 HCV infections are most prevalent in the Middle East, South Africa, and Southeast Asia, respectively.[11] While SOF+RBV for 12 weeks is approved for GT 2 a RBV free treatment regimen would likely be less toxic and allow treatment of those in whom RBV is contraindicated. A currently approved regimen for treatment naive GT 3 is SOF+RBV for 24 weeks; a shorter treatment duration would be of benefit. There is currently no approved all oral, IFN and RBV free therapy for patients with GT 4, 5, or 6 HCV. For patients with GT 4, 5 and 6 HCV, SOF+Peg-IFN+RBV for 12 weeks is an option. Thus, there is an unmet medical need for IFN free treatment regimens in these groups.

Treatment; if HIV/HCV co-infection

There are currently 2 approved regimens for this group.

Sovaldi (SOF) is approved for patients with GT 1, 4, 5 and 6 HCV infection (SOF +PEG+ RBV for 12 weeks), and patients with GT 2 or 3 HCV infection (SOF+RBV for 12 or 24 weeks, respectively) (Sovaldi SPC).

Viekira Pak (ombitasvir, paritaprevir, and ritonavir (RTV) tablets; dasabuvir tablets) is also approved in the US for patients with GT 1 HCV (Viekira ± RBV for 12 or 24 weeks for patients ± cirrhosis) (Viekira Pak SPC). Efficacy ranged from 76% to 92%, based on small numbers of subjects. Additionally, due in part to the inclusion of the potent cytochrome P450 enzymes (CYP) CYP3A4 inhibitor, RTV, in Viekira Pak, this regimen has the potential for numerous DDI that may require alteration of the patient's antiretroviral (ARV) regimen which not always be feasible or desirable.

Prior SOF failures

There is currently no approved therapy for patients with HCV infection who have previously failed a SOF+RBV±PEG regimen. Although SOF-based regimens are efficacious, the extensive number of patients being treated with these regimens has resulted in a pool of patients who have nevertheless failed these regimens. Thus, there is an unmet medical need for regimens that are effective in patients who have failed a prior SOF+RBV±PEG regimen.

Contents of the clinical dossier

Nine clinical studies were provided in support of Gilead's application to extend the indication:

- GS-US-337-0102 (ION-1): A Phase III, multi-centre, randomized, open label study to investigate the efficacy and safety of sofosbuvir/GS-5885 fixed dose combination ± ribavirin for 12 and 24 weeks in treatment naïve subjects with chronic Genotype 1 HCV infection.
- GS-US-337-0115 (ION-4): A Phase III, multi-centre, open label study to investigate the efficacy and safety of sofosbuvir/ledipasvir fixed dose combination for 12 weeks in subjects with chronic Genotype 1 or 4 Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV)-1 co-infection
- GS-US-337-0121 (SIRIUS): A Phase II, multi-centre, randomized, double blind, placebo controlled study to investigate the efficacy and safety of sofosbuvir/ledipasvir fixed dose combination for 12 weeks with ribavirin or for 24 weeks without ribavirin in treatment experienced cirrhotic subjects with chronic Genotype 1 HCV infection.

[9] Backus LI, et al. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. *Clin Gastroenterol Hepatol* 2011; 9: 509-516.
[10] Fattovich G, et al. Hepatitis C virus genotypes: distribution and clinical significance in patients with cirrhosis type C seen at tertiary referral centres in *Europe. J Viral Hepat* 2001; 8: 206-216
[11] Nguyen MH, Keeffe EB. Prevalence and treatment of hepatitis C virus genotypes 4, 5, and 6. *Clin Gastroenterol Hepatol* 2005; 3:S97-S101.

- GS-US-337-0122 (ELECTRON 2): A Phase II, multi-centre, open label study to assess the efficacy and safety of sofosbuvir containing regimens for the treatment of chronic HCV infection
- GS-US-337-1118 (RETREATMENT): An Open label, multi-centre study to evaluate the efficacy and safety of sofosbuvir/ledipasvir fixed dose combination ± ribavirin for 12 or 24 weeks in chronic Genotype 1 HCV infected subjects who participated in a prior Gilead sponsored HCV treatment study
- GS-US-337-1119: A Phase II, multi-centre, open label study to investigate the efficacy and safety of sofosbuvir/ledipasvir fixed dose combination in treatment naïve and treatment experienced subjects with chronic Genotype 4 or 5 HCV infection
- GS-US-337-1468 (LEPTON): A Phase II, multi-centre, open label study to assess the efficacy and safety of oral regimens for the treatment of chronic HCV infection
- GS-US-337-0123 (SOLAR-1): A Phase II, multi-centre, open label study to investigate the safety and efficacy of sofosbuvir/ledipasvir fixed dose combination + ribavirin administered in subjects infected with chronic HCV who have advanced liver disease or are post-liver transplant.
- GS-US337-0124 (SOLAR-2): A Phase II, multi-centre, open label study to investigate the safety and efficacy of sofosbuvir/ledipasvir fixed dose combination + ribavirin administered in subjects infected with chronic HCV who have advanced liver disease or are post-liver transplant.

Studies providing further supporting data but not key to this application

- CO-US-337-0117 (SYNERGY): A pilot study to evaluate the safety and efficacy of multiple anti-HCV combination therapy; supports retreatment; genotype 4.

Integrated summaries:

- PC-337-2006
- PC-337-2007

Extrinsic Factor PK Study Reports (n = 4)

- GS-US-334-1344: A Phase I Study in healthy volunteers to evaluate transporter-mediated drug-drug interactions between rifampin (RIF) and sofosbuvir (SOF)
- GS-US-337-1306: A Phase I Study to evaluate pharmacokinetic drug-drug interaction potential between sofosbuvir/ledipasvir (SOF/LDV) fixed dose combination (FDC) tablet and HIV antiretroviral regimens ritonavir-boosted atazanavir (ATV plus RTV) plus emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) or ritonavir-boosted darunavir (DRV plus RTV) plus FTC/TDF or elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF)
- GS-US-337-1501: A Phase I Study to evaluate pharmacokinetic drug-drug interaction potential between ledipasvir/sofosbuvir (LDV/SOF) fixed dose combination (FDC) tablet and HIV antiretroviral regimen dolutegravir (DTG) plus emtricitabine/tenofovir df (FTC/TDF)
- GS-US-337-1624: A Phase I Study to evaluate pharmacokinetic drug-drug interaction potential between ledipasvir/sofosbuvir (LDV/SOF) fixed dose combination (FDC) tablet with HIV antiretroviral regimen elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) FDC tablet.

Integrated summaries of virology, efficacy, and safety.

Population PK Study reports;

- Population PK report - GS-US-337-0115 (ION4)
- Population PK Report - GS-US-337-0123 & GS-US-337-0124

Clinical overview, summary of clinical efficacy, summary of clinical safety and literature references.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

All included studies were conducted in accordance with good International Conference on Harmonisation (ICH) Clinical Practice Guidelines (ICH-GCP), considerations for the ethical treatment of human subjects were in place at the time the trials were performed and informed consent was obtained from all trial participants.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 2 shows the studies relating to each PK topic. This application included 4 extrinsic PK studies exploring DDI between Harvoni -rifampicin; and new ARVs and Harvoni. Population PK was provided from 2 studies in the target population.

Table 2: Submitted PK studies

PK topic	Subtopic	Study ID
PK interactions	interaction with rifampicin	GS-US-334-1344
	interaction with Elvitegravir/Cobicistat/Emtricitabine/TDF	GS-US-337-1306
	interaction with dolutegravir and Truvada (TRU)	GS-US-337-1501
	Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide	GS-US-337-1624
Population PK analyses	Target population	Population PK

Evaluator's conclusions on pharmacokinetics

The application explored DDI between LDV/SOF-ARV regimens (ATV+RTV, DRV+RTV or DTG plus FTC/TDF, or E/C/F/TAF); Harvoni-rifampicin in healthy volunteers.

Rifampicin cannot be administered with Harvoni. Importantly, results of this rifampicin DDI study inform on DDI with other P-glycoprotein (P-gp) inducers for example carbamazepine, rifabutin, St. John's wort. Like rifampicin, other P-gp inducers are expected to decrease LDV and SOF exposure and have limited or no impact on

GS-331007[12] concentrations. In terms of ARVs, higher tenofovir exposures observed, unclear what the clinical consequences might be, no dose adjustment needed but should have closer monitoring of renal function during co-administration. There is no data on bone health during co-administration of TDF-Harvoni. In exploring the effects of liver dysfunction on LDV/SOF PK, SOF AUC_{tau} was increased approximately 2 fold in post-transplantation subjects ± compensated liver disease and in subjects with decompensated liver disease regardless of transplantation status. This increase is not likely to have safety consequences and no dose adjustment is recommended in this setting.

Pharmacodynamics

Studies providing pharmacodynamic data

SOLAR-1 and SOLAR-2:

Relative to the LDV/SOF new drug application (NDA) Population, SOF and its metabolite GS-331007, and LDV exposures were only modestly altered in SOLAR-1 and SOLAR-2 in subjects ± compensated liver disease and in subjects with decompensated liver disease regardless of transplantation status. Given the high sustained virological response 12 weeks after EOT = cure (SVR12) rate and relatively small number of relapsers, an analysis of LDV/SOF exposure in relapsers versus those achieving SVR12 should be interpreted with caution.

Evaluator's conclusions on pharmacodynamics

Not Applicable. All new clinical studies have been reviewed in the efficacy section.

Dosage selection for the pivotal studies

As currently approved that is FDC containing 90 mg LDV/400 mg SOF taken orally once daily ± food.

Efficacy

Pivotal studies for SOF in the treatment of HCV infection

- Studies providing efficacy data
- Study GS-US-337-0102 (ION-1)
- Study GS-US-337-0115 (ION-4)
- Study GS-US-337-0121 (SIRIUS)
- Study GS-US-337-0122 (ELECTRON 2)
- Study GS-US-337-1118 (RETREATMENT)
- Study GS-US-337-1119
- Study GS-US-337-1468 (LEPTON)
- Study GS-US-337-0123 (SOLAR-1)
- Study GS-US337-0124 (SOLAR-2)

[12] GS-331007 is a metabolite of SOF

Other efficacy studies

- Study CO-US-337-0117 (SYNERGY)

Analyses performed across trials (pooled analyses and meta-analyses)

- Study PC-337-2006
- Study PC-337-2007

For the full evaluation of the above studies please see Attachment 2, extract from the clinical evaluation report.

Evaluator's conclusions on efficacy

In Australia, Harvoni is approved for the treatment of hepatitis C virus (HCV) GT 1 infection. This application proposes to extend the indication to: Harvoni for the treatment of CHC infection in adults to include patients with HCV infection who are post liver transplantation with compensated liver disease as well as those with decompensated liver disease, regardless of transplantation status; patients with chronic GT 2, 3, 4, 5 or 6 HCV infection as there is currently no approved all oral, IFN and RBV free therapy for these genotypes; HCV/HIV co-infection; and those who have previously failed a SOF+RBV±PEG regimen as there is currently no approved therapy for those who have previously failed a SOF containing regimen. The sponsor has provided a comprehensive swathe of Phase II and III studies and 4 PK studies in support of this extension of indication request. Overall, in all settings, this FDC is highly efficacious and safe, with no new safety signal of concern revealed even in the very sick populations of patients enrolled in SOLAR-1 and SOLAR-2.

The extension of indication seeks to meet unmet medical need. Overall the data supports the extension of indication with the caveat that there is a paucity of data for retreatment with Harvoni ± RBV for non-Genotype 1 patients who have previously failed sofosbuvir. The data from ELECTRON-2, suggests that adjunctive ribavirin may important to achieve high rates of SVR12 when using 12 week courses of Harvoni for Genotype 3, especially in treatment experienced patients where even with ribavirin, SVR12 was 82%. In addition SOLAR-1 and SOLAR-2 did not include patients with genotypes other than 1 and 4, so there is very little data about the efficacy and safety of Harvoni with these other genotypes in those with varying degrees of liver impairment including pre and post liver transplantation. All studies enrolled a majority of male subjects (most especially true of ION-4), and in most, the majority ethnicity was White and this was even the case in GS-US-337-1119 which enrolled GT 4 and GT 5 subjects.

Safety

Studies providing safety data

Studies considered in the evaluation of safety included the two Phase II clinical studies that included LDV/SOF, with RBV, in subjects with HCV infection who were post-transplantation with compensated liver disease as well as those with decompensated liver disease, regardless of transplantation status (SOLAR-1 and SOLAR-2). Three of the pivotal studies are highlighted because of their particular populations:

- Treatment experienced with Cirrhosis (GS-US-337-0121 [SIRIUS])
- HCV/HIV Co-infection (GS-US-337-0115 [ION-4])
- SOLAR-1 and SOLAR -2 (pooled data).

Patient exposure

Some 987 subjects have received ≥ 1 dose of LDV/SOF FDC in the studies supporting this extension of indications application

- 335 in a Phase III study
- 496 in Phase II studies
- 156 in Phase I.

Patient exposure in the following specific populations was:

a. SIRIUS. Of 155 randomised, 155 (100.0%) received ≥ 1 dose and were included in the Safety Analysis Set (SAS)

b. ION-4. 335 enrolled and received ≥ 1 dose of study drug

c. SOLAR-1 and SOLAR-2: of 673 randomised, 670 received ≥ 1 dose of LDV/SOF+RBV and were included in the SAS.

Mean exposure 11.6 to 12.2 weeks (12 week Group) and 21.3 to 24.1 weeks (24 Week Group).

For the full details of the clinical evaluation of safety please see Attachment 2

Evaluator's conclusions on safety

The data presented in this application demonstrate that Harvoni has an overall highly acceptable safety profile.

This application provides clinical trial (many open label and several un-randomised, single arm) data in a number of different populations that is treatment experienced subjects with cirrhosis, HCV/HIV co-infection, prior treatment failures with a SOF containing regimen, and chronic HCV infection with Genotypes other than GT 1 (Harvoni is already approved in GT 1 CHC).

The safety profile of LDV/SOF for 12 or 24 weeks and LDV/SOF+RBV for 12 weeks was consistent with that observed for LDV/SOF±RBV in previous Phase III studies (Studies GS-US-337-0102 [ION-1], GS-US-337-0109 [ION-2], and GS-US-337-0108.

Overall, the safety profile of LDV/SOF+RBV treatment was similar to the expected safety profile of RBV. The safety profile of LDV/SOF for 12 weeks in HCV/HIV-1 co-infected subjects stable on ARVs and with suppressed plasma HIV RNA was consistent with the safety profile of LDV/SOF in the HCV mono-infected population. There was no negative impact on surrogate markers of ARV efficacy that is HIV viral load and CD4 T-cell count during treatment with Harvoni.

The elevated levels of TFV with TDF-containing regimens are of uncertain significance, especially as co-administration of these drugs will be relatively short. However, this DDI merits closer renal monitoring especially in patients with some degree of renal impairment and probably some attention to bone health (see summary comments).

Another special population with data presented in this application for extension of indications are liver transplant (for HCV) recipients where HCV recrudescence is universal and associated with poorer graft and patient survival compared with non-HCV related liver transplants. SOLAR-1 and SOLAR-2 evaluated LDV/SOF+RBV for 12 or 24 weeks across the spectrum of patients who are pre and post-liver transplantation including those without cirrhosis, and those with compensated and decompensated cirrhosis. This is a varying sick population of patients with overall high morbidity and mortality especially those with decompensated cirrhosis. Other all oral regimens are available in some countries but AbbVie's Viekira Pak ('3D' regimen), whilst of proven efficacy and well

tolerated, including in cirrhotic patients with GT 1, contains ritonavir as a PK booster for the component direct acting antiviral (DAAs). Unfortunately, ritonavir is a drug fraught with the potential for multiple DDI. This might be challenging in some of these patients with end-stage liver disease who are frequently on multiple medications with the potential for DDI (for example beta-blockers). That said, Harvoni is not free of DDI and cannot be co-administered with potent P-gp inducers like rifampicin.

As discussed in Section 8, anaemia was the predominant treatment related safety finding in the post-transplant subjects, which is associated with RBV and likely exacerbated by the relatively low estimated glomerular filtration rate Cockgroft Gault (eGFRCG) in some of these subjects. Most patients were successfully managed with dose reduction, and haemoglobin recovered quickly after end of treatment. Paradoxically, and reflecting efficacy against HCV, dose adjustment (frequency of dosing) for some immunosuppressants as liver function improved.

Decompensated cirrhosis

Consistent with the underlying severity of the liver disease in these subjects AEs, including serious adverse event (SAEs), occurred more frequently compared with the rates observed in subjects in previous Phase III studies that excluded decompensated subjects. However, the AEs were consistent with decompensated liver disease or the known toxicity profile of RBV, including anaemia. Decreases in haemoglobin to < 10.0 g/dL and < 8.5 g/dL during treatment occurred in just over 1/3 and 1/10 of subjects, respectively. Most episodes were successfully managed with RBV dose reduction, although just fewer than 20% had to discontinue RBV. Reassuringly, haemoglobin declines reversed rapidly after completion of treatment.

The Independent Adjudication Committee after formal review of hepatic safety including the impact of longer exposure to Harvoni, determined that LDV/SOF+RBV was safe and well tolerated, with a low potential for causing drug-induced liver injury (DILI). However, the IAC and sponsor propose that for patients treated with LDV/SOF+RBV, monthly liver tests, including direct bilirubin, be performed. The latter would align with standard-of-care monitoring for this patient population.

In summary, the data provided in this extension shows Harvoni is safe (and effective) in the populations providing clinical trial data included in this extension application without any new and/or concerning safety signal.

First Round Benefit-Risk Assessment

First round assessment of benefits

The benefits of Harvoni in the extended usage are:

- High rates of SVR12 that is cure in all genotypes, in patients who had previously failed a SOF containing regimen (GT 1) and in those with severe compensated and decompensated liver disease with/without liver transplant and (the evaluator) agrees many of these scenarios are areas of 'unmet medical need'
- Safe and well tolerated, no new safety signal of concern revealed
- Low risk for drug-drug interactions
- Safe and well tolerated at the proposed therapeutic dose
- Much of the data suggests treatment without ribavirin can be used, a great advantage in terms of certain populations where RBV is absolutely/relatively contraindicated.

First round assessment of risks

The risks of Harvoni in the proposed usage are:

- It will not protect against re-infection (same for all the DAA, and not unique to this FDC), and this is not clearly stated in the PI or Consumer Medicine Information (CMI)
- This is not a risk per se but the evaluator noted that there were frequent transcription errors in this application that is *'LDV/SOF was administered to all subjects orally at a dose of 400 mg/90 mg (1 tablet once daily)'.* This is not correct; it should read LDV/SOF (90/400 mg). Please ensure consistency.
- There is still a relative paucity of data from those with Genotype 4, although the data provided does not suggest that the SVR12 or safety profile differs substantially from GT 1
- Lower SVR12 for GT 3 when not partnered with RBV and given for short course (12 weeks) true for both treatment naïve and treatment experienced (refer to ELECTRON-2)
- Very little data on non-GT 1 cirrhotics, and no data on non GT 1 pre and post liver transplant subjects
- Paucity of data from populations other than those of White ethnicity
- Relative paucity of women enrolled in these studies, all studies are majority male (especially true of ION-4 the study in HIV/HCV co-infection), this may reflect the demographics of HCV in some countries or may reflect the almost universal difficulties in enrolling women into studies (a similar issue is known in many of the licensing studies for ARVs) or enrolment restrictions placed around pregnancy/breast-feeding
- Paucity of data presented on retreatment of genotypes other than GT 1 in patients previously treated with SOF-containing regimens; further data from LEPTON and ELECTRON-2 may be informative
- Paucity of data from patients with cirrhosis CPT C category
- High rates of SVR12 in most subjects irrespective of baseline resistance associated polymorphism (RAP) and Resistance associated variants (RAVs). The predictors of virological failure are not currently completely understood; some trends in some settings (related to high body mass index (BMI) for example). Even though suggested otherwise in this application, clinicians are likely to conduct expensive and largely pointless genotypic (and even phenotypic) resistance tests before/after use of Harvoni.

First round assessment of benefit-risk balance

Favourable.

First Round Recommendation Regarding Authorisation

Recommend authorisation with one caveat. The clinical evaluator did not think there is enough data (yet) to recommend the use of Harvoni for retreatment of patients with HCV genotypes other than GT 1 and who have been previously treated with sofosbuvir. The evaluator had particular concerns with respect to Genotype 3.

Clinical Questions

There were no clinical questions.

Second Round Evaluation of clinical data submitted in response to questions

For details of the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second Round Benefit-Risk Assessment

Second round assessment of benefits

No new clinical information was submitted in response to questions. Accordingly, the benefits of Harvoni are unchanged from those identified in the first round assessment of benefits.

Second round assessment of risks

No new clinical information was submitted in response to questions. Accordingly, the risks of Harvoni are unchanged from those identified in first round assessment of risks.

Second round assessment of benefit-risk balance

The benefit-risk balance of Harvoni, given the proposed usage, is favourable.

Second round recommendation regarding authorisation

Recommend authorisation.

The clinical evaluator no longer had any caveats as the evaluator did following the Round 1 evaluation. This is because Gilead Sciences have now clarified their intentions with respect to the evaluator's particular concerns regarding retreatment of patients with HCV genotypes other than Genotype 1, who have received sofosbuvir previously. The evaluator's concerns extended particularly to Genotype 3. The reasons the evaluator's concerns have been allayed is that Gilead in their response dated 24-May-2016 have provided the following clarifications:

'Gilead wishes to clarify that it was never the intent to recommend use of Harvoni with ribavirin for the treatment of treatment experienced patients with Genotype 3. As stated (in the submission), the totality of evidence suggests that LDV/SOF+RBV for 12 weeks has comparable efficacy with SOF+RBV for 24 weeks. Nevertheless, Gilead acknowledges that in treatment experienced, Genotype 3 patients, the duration of LDV/SOF+RBV for 12 weeks is not optimal. Gilead, therefore, proposes that LDV/SOF+RBV for 12 weeks be indicated for use only in patients with Genotype 3 HCV infection who are treatment naïve.

The proposed PI has been revised to clarify that treatment with Harvoni and ribavirin is recommended for Genotype 3 patients that are treatment naïve only. This revision will remove the ambiguity around the product's use in previously treated Genotype 3 patients, including patients previously treated with sofosbuvir. The PI has been modified.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan EU-RMP Version 1.1 (dated 23 June 2015, DLP 31 May 2015) and Australian Specific Annex Version 1.1 (dated September 2015) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 3.

Table 3: Sponsor's summary of ongoing safety concerns

Summary of ongoing safety concerns	
Important Identified Risks	Severe bradycardia and heart block when used with concomitant amiodarone (LDV, SOF)
Important Potential Risks	Drug-drug interaction with potent P-gp inducers (LDV, SOF)
	Administration of proton pump inhibitors (LDV)
	Drug-drug interaction with TDF + PK enhancer (LDV)
	Drug-drug interaction with rosuvastatin (LDV) Drug-drug interaction with digoxin (LDV)
Missing Information	Safety in children
	Safety in pregnant or breastfeeding women
	Safety in patients with HCV/HIV co-infection Safety in patients with HCV/HBV co-infection
	Safety in patients with severe renal impairment or end-stage renal disease
	Development of resistance

Pharmacovigilance plan

The sponsor proposes routine and additional pharmacovigilance activities (as stated above). The additional pharmacovigilance activities are provided and include the following studies as shown in Table 4.

Table 4: Ongoing studies proposed or in progress

Study	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of Interim of Final reports (planned or actual)
GS-US-337-1115	To evaluate the relative bioavailability and safety of an age-appropriate paediatric SOF formulation in	safety of age appropriate paediatric SOF formulation	planned	April 2016

Study	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of Interim of Final reports (planned or actual)
	healthy adult volunteers			
GS-US-337-1116	To evaluate the PK efficacy and safety of LDV/SOF for 12 weeks in adolescents and children	safety in children	planned	final study report 2019
GS-US-334-0154	To evaluate the safety, efficacy and PKs of treatment with SOF + RBV for 24 weeks in subjects with chronic genotype 1 or 3 HCV infection and severe renal impairment	safety in patients with severe renal impairment or end stage renal disease	started	final study report July 2017
GS-US-337-0115	To evaluate the safety and efficacy of treatment with LDV/SOF ± RBV in subjects with HCV/HIV co-infection	safety in patients with HCV/HIV co-infection	started	March 2017
GS-US-337-0122	To evaluate the safety and efficacy of combination therapy with SOF-containing regimens for the treatment of chronic HCV infection	one cohort will provide safety information in patients with HCV/HBV co-infection	started	June 2016
GS-US-337-1118	To determine the efficacy of SOF/LDV ± RBV and to evaluate the emergence of viral	safety efficacy and development of resistance	started	January 2017

Study	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of Interim of Final reports (planned or actual)
	resistance to LDV and SOF during and after treatment discontinuation			
GS-XX-XXX-XXXX	To assess the effect of LDV on a CYP3A probe drug	drug interaction	planned	to be determined
BP-US-337-1117	To evaluate growth, development and viral relapse in adolescents and children who received LDV/SOF in study GS-US-337-1116	growth, long term safety	planned	March 2024
GS-US-248-0123	To evaluate HCV viral sequences and the persistence or evolution of treatment-emergent viral mutations in subjects who fail to achieve SVR after treatment with a Gilead oral antiviral containing regimen in a previous Gilead sponsored hepatitis C study	development of resistance	started	July 2020
GS-EU-337-1820	To characterise the frequency of post-marketing co-use of LDV/SOF +TDF + PK enhancer	HCV/HIV co-infection	planned	To be determined

Study	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of Interim of Final reports (planned or actual)
	in adult HCV/HIV co-infected patients and the rates of renal ADRs			
GS-XX-XXX-XXXX	To be determined	Safety in patients using concomitant amiodarone	planned	To be determined

Risk minimisation activities

The sponsor is proposing additional risk minimisation activities in the EU-RMP, but not in the corresponding ASA.

Reconciliation of issues outlined in the RMP report

The section below summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.

TGA recommendation 1

Safety considerations may be raised by the nonclinical and clinical evaluators in the consolidated request for information. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.

Sponsor's response:

Gilead confirms that there were no safety considerations raised by the nonclinical and clinical evaluators through the consolidated section 31 request and/or the Nonclinical and Clinical Evaluation Reports that impact the Risk Management Plan.

The clinical evaluator stated please keep your terminology aligned, the header states 'Harvoni (Sofosbuvir/Ledipasvir Fixed Dose Combination Tablets) EU Risk Management Plan', in the document you refer to Harvoni – Ledipasvir/sofosbuvir FDC. An updated ASA to correct the terminology is provided.

RMP Evaluator comment:

This is acceptable regarding no need to change the RMP on the basis of the clinical and non-clinical evaluation. The updated ASA in response to the clinical evaluator is noted and is adequate.

TGA recommendation 2

The sponsor should provide the overseas approval status of the indication sought in this submission, that is,: HCV/HIV co-infection; SOF+RBV±Peg IFN regimen failure; genotype 2, 3, 4, 5, or 6; post-transplantation with compensated liver disease; decompensated liver disease of transplantation status.

Sponsor's response:

An updated overseas approval status is provided.

RMP Evaluator comment:

The status table provided is comprehensive and is acceptable.

TGA recommendation 3

The sponsor should conduct relevant and meaningful pharmacovigilance activities that address the safety concern 'Development of resistance' for all genotypes for which approval is sought. Ideally, these activities should also be conducted in Australia. The sponsor should provide a proposal for such activities in the response.

Sponsor's response:

Gilead acknowledges the safety concern 'Development of resistance' as 'Missing information' in the Harvoni EU-RMP and its accompanying ASA. Two studies are ongoing to collect data on the development of resistance:

- Study GS-US-337-1118: An Open label, Multi-centre Study To Evaluate The Efficacy And Safety Of Sofosbuvir/Ledipasvir Fixed-Dose Combination ± Ribavirin For 12 or 24 Weeks In Chronic Genotype 1 HCV Infected Subjects Who Participated In A Prior Gilead-Sponsored HCV Treatment Study
- Study GS-US-248-0123: A Long Term Follow-up Registry Study of Subjects Who Did Not Achieve Sustained Virologic Response in Gilead-Sponsored Trials in Subjects with Chronic Hepatitis C Infection

Study GS-US-337-1118:

This study is an open label study to investigate the safety, tolerability and antiviral efficacy of LDV/SOF ± RBV for 12 or 24 weeks in chronic genotype 1 HCV infected subjects who failed prior treatment in a previous Gilead-sponsored HCV treatment study. This study includes subjects who failed a prior LDV/SOF ± RBV regimen and provides information on the retreatment of patients with LDV/SOF once daily for 24 weeks. The study is ongoing and includes Australian patients as indicated in the ASA and acknowledged by the clinical evaluator.

Study GS-US-248-0123:

This study is an observational registry study which has the primary objective to evaluate HCV viral sequences and the persistence or evolution of treatment-emergent viral mutations in subjects who fail to achieve a sustained virologic response (SVR) after receiving at least one Gilead oral antiviral (OAV) containing regimen in a previous Gilead-sponsored hepatitis C study. The Registry is enrolling subjects across all genotypes and includes subjects whose HCV RNA:

- Failed to drop below the Lower Limit of Quantification (LLoQ) on treatment;
- Dropped below the LLoQ and then had a confirmed value above the LLoQ during treatment (breakthrough);
- Dropped below the LLoQ and then had a confirmed value above the LLoQ during the post-treatment follow up period (relapse).

The primary analysis will be performed after all enrolled subjects in a treatment regimen have been followed for 144 weeks or discontinued from the study. Presently, the study is being conducted in a number of sites globally, including Australian sites.

An updated ASA including this study in the list of studies referenced in the Pharmacovigilance Plan and conducted in Australia is provided.

RMP Evaluator comment:

The information collected from studies described is intended to address the issue of missing information regarding viral resistance, and in addition to routine pharmacovigilance activities are considered adequate to address this recommendation. The updated ASA satisfactorily addresses the concern that these activities should be conducted in Australia.

TGA recommendation 4

The survey planned to measure the effectiveness of the Direct Healthcare Professional Communication (DHPC) should be extended to Australia.

Sponsor's response:

Gilead does not consider a Direct Healthcare Professional Communication (DHPC) letter as necessary given that Harvoni was not registered in Australia at the time this safety concern was identified. The Harvoni PI has included the safety text related to amiodarone since the product's registration. As such, a survey to measure the effectiveness of the DHCP communication is not considered applicable.

Please refer to Gilead's response to question 1.7 below for further details.

An updated ASA with an explanation for this discrepancy between the risk minimisation activities in Australia and Europe is provided.

RMP Evaluator comment:

The survey referred to in the EU-RMP was in response to a safety concern identified prior to registration of Harvoni in Australia; the evaluator agrees this is not relevant to Australia. Further discussion regarding risk minimisation is included below.

TGA recommendation 5

The sponsor should provide a summary of medication errors in the post-market environment.

Sponsor's response:

Gilead captures medication errors in the post-market environment through routine pharmacovigilance activities. In addition to the medication errors provided in the EU-RMP and included in the RMP evaluation report, there are data available on medication errors for the reporting period 10 April 2015 to 09 April 2016. As per the condition of registration outlined in the Harvoni TGA approval letter dated 8 May 2015, Gilead will provide complete Periodic Safety Update Reports (PSURs) to the TGA annually until the period covered by such reports is not less than three years from the date of this approval letter in accordance with the PSUR submission process. A summary of the medication errors from marketing experience in the reporting period 10 April 2015 to 09 April 2016 is provided.

A total of 352 cases of medication errors leading to accidental overdose involving LDV/SOF were received during the reporting period 10 April 2015 to 09 April 2016. The majority of overdose cases describe patients who took double doses of LDV/SOF. A total of 142 cases of general medication errors were also received during the reporting period. Marketing experience included cases reported from market research, patient support programs, and compassionate use cases. The majority of cases were not associated with Adverse Events (AEs). Those that were associated with AEs were typically associated with non-serious AEs.

A summary of medication errors during the PSUR reporting period 10 April 2015 to 09 October 2015 is provided (in table format). A summary of medication errors for the reporting period 10 October 2015 to 09 April 2016 is provided.

No new safety issues were identified from review of the cases of medication errors received during the period of this safety update.

RMP Evaluator comment:

The tables provided are very comprehensive and are considered adequate.

The data included in these tables, is consistent with the information provided in the EU-RMP from the PSUR reporting period for the period 10 October 2015 to 09 April 2016. On the basis of the adverse events reported arising from medication error leading to overdose, the evaluator agrees that there are no new safety concerns.

However, it is unclear what proportion of the total medication use the reported medication errors comprise, that is, for the 6 months reported (10 October 2015 to09 April 2016) are the 135 cases of overdose a significant number of the total number of total use or a only small percentage of the total use? The sponsor should provide this information.

The sponsor should also provide information regarding how many medication errors occurred when Harvoni was taken in conjunction with ribavirin, and whether this combination treatment resulted in increased medication error.

If there is evidence that patients taking Harvoni in conjunction with ribavirin are overdosing on Harvoni, it is recommended that the sponsor considers methods to address this risk, for example a dosing reminder or dosing chart for the patient, a sticker alert on the Harvoni bottle, a flag for pharmacists if the prescription is filled earlier than expected.

TGA recommendation 6

The sponsor should provide mock-ups of the proposed packaging materials to assess whether those could lead to a dosing error. A weekday designation on the blister pack may sufficiently minimise medication errors.

Sponsor's response:

The Harvoni carton and container label meet the requirements of Therapeutic Goods Order No. 69 General requirements for labels for medicines and were provided to the TGA in the original Category 1 application for Harvoni, approved on 8 May 2015. For ease of review, the current approved Harvoni labels are provided.

Gilead appreciates the evaluator's suggestion to include a weekday designation to minimise medication errors. As Harvoni is provided in bottles, a weekday designation of the blister pack is not feasible. The Australia PI and Consumer Medicine Information (CMI) include detailed instructions on the dose and route of administration. Gilead believes these documents provide adequate information on the recommended dosing and administration and that no additional preventative measures are necessary. Medication errors will continue to be monitored as part of routine pharmacovigilance activities. Should data emerge indicating a safety issue relating to medication errors, the Australian PI, CMI, packaging and/or RMP will be updated through the submission of an appropriate application to the TGA.

RMP Evaluator comment:

The evaluator acknowledges the mock-ups provided and that they meet the requirements of the TGO 69. The suggestion of including a weekday designation on a blister pack is in relation to the ongoing occurrence of medication error resulting in overdose. Before determining if the routine risk minimisation of including the relevant information in the PI and CMI together with product packaging is adequate for addressing the risk of overdose, the sponsor should provide the information regarding the total use of Harvoni, as discussed for recommendation 5.

TGA recommendation 7

The sponsor should conduct the same additional risk minimisation activity as in the EU, that is, a Direct Healthcare Professional Communication (DHPC) for the risk 'Severe bradycardia and heart block when used with concomitant amiodarone'. The ASA should be updated accordingly.

Sponsor's response:

Gilead acknowledges that there is a discrepancy in the additional risk minimisation activities outlined in the EU-RMP and the ASA. The Harvoni marketing authorisation application was approved in Europe on 17 November 2014, prior to registration in Australia on 13 May 2015.

As the safety concern relating to amiodarone was identified prior to approval in Australia, Gilead updated the Australian PI during TGA evaluation and therefore the PI with the amiodarone text was approved as part of the initial Category 1 application. Given Harvoni was not registered at the time of this PI change, a DHPC letter alerting healthcare professionals to changes in the Australian PI was not warranted. This approach was discussed with the TGA at the time and was considered acceptable.

An updated ASA clarifying the discrepancy between the risk minimisation activities in Australia and Europe is provided.

RMP Evaluator comment:

Given the timing of the EU safety alert and registration in Australia, together with the inclusion in the PI of the risk of bradycardia and heart block when used with concomitant amiodarone, the sponsor's response is considered adequate. In addition, the increased number of products containing sofosbuvir will also contribute to awareness of this risk, therefore additional risk minimisation activities for Harvoni are not considered necessary.

Summary of recommendations

Outstanding issues

The sponsor is asked to provide additional information regarding medication errors, in particular:

- The total number of patients taking Harvoni
- If the medication errors resulting in overdose occurred when Harvoni was taken in combination with ribavirin.

This information will be used to determine if the risk minimisation activities for medication errors, especially those relating in overdose, are sufficient.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

Implement RMP (version 1.1, 23 June 2015, DLP 31 May 2015) with Australian Specific Annex (version 1.2, June 2016) and any future updates as a condition of registration.

VI. Overall conclusion 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

Gilead proposes to add the following statement under Carcinogenicity section of the PI:

> *'LDV was not carcinogenic in the 6-month rasH2 transgenic mouse study at exposures up to 26-fold higher than human exposure. A carcinogenicity study in rats is ongoing.'*

A 26 week carcinogenicity study of ledipasvir in mice was submitted. The evaluator has proposed the following as an alternative for consistency with recommended text for sofosbuvir:

> *'Carcinogenicity studies in mice do not indicate any carcinogenicity potential of ledipasvir administered at doses up to 300mg/kg/day in male and female, transgenic mice. Exposure to ledipasvir in these studies was up to 26 x higher than the clinical exposure at 90 mg ledipasvir. A carcinogenicity study in rats is ongoing.*
>
> *Carcinogenicity studies in mice and rats do not indicate any carcinogenicity potential of sofosbuvir administered at doses up to 200 mg/kg/day in male mice and 600 mg/kg/day in female mice, and 750 mg/kg/day in rats. Exposure to GS-331007 in these studies in mice was up to 7 x (male) and 30 x (female), and in rats up to 13 x (male) and 17 x (female) higher than the clinical exposure at 400 mg sofosbuvir.'*

Clinical

The following pharmacokinetic (PK) studies were included in this submission.

Table 5: Submitted Pharmacokinetic (PK) studies

PK topic	Subtopic	Study ID
PK interactions	interaction with rifampicin	GS-US-334-1344
	Interaction with Elvitegravir/Cobicistat/Emtricitabine/TDF	GS-US-337-1306
	interaction with dolutegravir and Truvada (TRU)	GS-US-337-1501
	Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide	GS-US-337-1624

The following clinical studies, as shown in Table 6, were included in this submission.

Table 6: Submitted pharmacokinetic studies

Study populations	Study ID number
Treatment-experienced subjects with cirrhosis	GS-US-337-0121(SIRIUS) Genotype 1 patients
HCV/HIV co-infection	GS-US-337-0115 (ION-4) Genotype 1 or 4
Prior SOF failures	GS-US-337-1118 (RETREATMENT in Genotype 1 patients) GS-US-337-0122 (ELECTRON 2, different genotypes) GS-US-337-0115 (ION-4) GT1 or GT4 CO-US-337-0117 (SYNERGY)
Non-GT1 HCV infection	Genotype 2: GS-US-337-1468 (LEPTON) Genotype 3: GS-US-337-0122 (ELECTRON 2, Cohort 2, Groups 3,4, 6) Genotype 4: GS-US-337-1119 (GT4 subset) GS-US-337-0115 (ION-4, GT4 subset) CO-US-337-0117 (SYNERGY, Group E=GT4) Genotype 5: GS-US-337-1119 (GT5 subset) Genotype 6: GS-US-337-0122 (ELECTRON 2, Cohort 2, Group 5)
Patients with pre/post liver transplantation	GS-US-337-0123 (SOLAR-1) and GS-US-337-0124 (SOLAR-2)
Additional study updates	GS-US-337-0102 (ION-1)

Pharmacokinetics

This submission included four extrinsic PK studies exploring drug-drug interaction (DDI) between Harvoni -rifampicin; and new ARVs and Harvoni. Population PK was provided from 2 studies in the target population. Table 5 above summarised the studies relating to each PK topic.

The four extrinsic factor PK studies were discussed in the CER (see Attachment 2) and is briefly mentioned here:

2. GS-US-334-1344: A Phase I Study in Healthy Volunteers to Evaluate Transporter-Mediated Drug-Drug Interactions between Rifampin (RIF) and Sofosbuvir (SOF)
3. GS-US-337-1306: A Phase I Study to Evaluate Pharmacokinetic Drug-Drug Interaction Potential between Sofosbuvir/Ledipasvir (SOF/LDV) Fixed Dose Combination (FDC) Tablet and HIV Antiretroviral Regimens Ritonavir-boosted Atazanavir (ATV plus RTV) plus Emtricitabine/Tenofovir Disoproxil Fumarate (FTC/TDF) or Ritonavir-boosted Darunavir (DRV plus RTV) plus FTC/TDF or Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate (EVG/COBI/FTC/TDF)
4. GS-US-337-1501: A Phase I Study to Evaluate Pharmacokinetic Drug-Drug Interaction Potential between Ledipasvir/Sofosbuvir (LDV/SOF) Fixed-Dose Combination (FDC) Tablet and HIV Antiretroviral Regimen Dolutegravir (DTG) plus Emtricitabine/Tenofovir DF (FTC/TDF)
5. GS-US-337-1624: A Phase I Study to Evaluate Pharmacokinetic Drug-Drug Interaction Potential between Ledipasvir/Sofosbuvir (LDV/SOF) Fixed-Dose Combination (FDC) Tablet with HIV Antiretroviral Regimen Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) FDC Tablet.

The DDIs between LDV/SOF and antiretroviral regimens (ATV+RTV, DRV+RTV or DTG plus FTC/TDF, or E/C/F/TAF), and Harvoni-rifampicin in healthy volunteers have been explore in these studies. The results showed that rifampicin cannot be administered with

Harvoni. Importantly, results of this rifampicin DDI study also inform on DDI with other P-gp inducers for example, carbamazepine, rifabutin, St. John's wort. Like rifampicin, other P-gp inducers are expected to decrease LDV and SOF exposure. In terms of ARVs, higher tenofovir exposures were observed; it is unclear what the clinical consequences might be. No dose adjustment is needed but should have closer monitoring of renal function during co-administration. There is no data on bone health during co-administration of TDF and Harvoni. In exploring the effects of liver dysfunction on LDV/SOF PK, SOF AUC_{tau} was increased around 2 fold in post-transplantation subjects ± compensated liver disease and in subjects with decompensated liver disease regardless of transplantation status. This increase is not likely to have safety consequences and no dose adjustment is recommended in this setting.

Clinical Efficacy

Detailed evaluation of these clinical studies was discussed in the Clinical Evaluation Report (CER) (please see Attachment 2). The results of these studies are briefly summarised below.

GS-US-337-0121 (SIRIUS)

This is a Phase II, randomised, double blind, placebo controlled, multicentre study, and the study assessed the efficacy and safety of LDV/SOF for 12 weeks with RBV or 24 weeks without RBV in treatment experienced cirrhotic subjects infected with HCV GT 1. The study enrolled adults GT 1 patients; they were HCV treatment experienced (that is, prior virologic failure after treatment with Peg-IFN, RBV, and a protease inhibitor following documented prior virologic failure after treatment with a Peg-IFN+RBV regimen). The primary endpoint is SVR12.

The enrolled 155 subjects were randomised (1:1 ratio) and stratified by genotype (1a or 1b; mixed or other GT 1) and prior response to HCV therapy (never achieved HCV RNA < LLOQ or achieved HCV RNA < LLOQ). Study treatment assignment and on treatment HCV RNA results were double blinded. Majority subjects were male (73.5%), White (97.4%), and not Hispanic or Latino (97.4%), mean age of 56 years. 93.5% had non-CC (CT or TT) IL28B alleles. All subjects met the protocol defined definition of cirrhosis, with the exception of one.

Group 1(LDV/SOF 24 week group): received LDV/SOF + matched placebo RBV 24 weeks.

Group 2 (LDV/SOF+RBV 12 week): received matched LDV/SOF placebo + matched RBV placebo for 12 weeks followed by LDV/SOF+RBV 12 weeks.

Table 7: Results of SVR12 (GS-US-337-0121, SIRIUS study)

	LDV/SOF + Placebo RBV 24 Weeks (N = 77)	Placebo 12 Weeks Followed by LDV/SOF+RBV 12 Weeks (N = 77)
SVR12	75/77 (97.4%)	74/77 (96.1%)
95% CI	90.9% to 99.7%	89.0% to 99.2%
LDV/SOF 24 Weeks vs. LDV/SOF+RBV 12 Weeks		
p-value	0.63	
Prop Diff (95% CI)	1.4% (−5.9% to 8.6%)	

HCV RNA analyzed using Roche TaqMan V 2.0 assay for use with High Pure system with limit of quantitation 25 IU/mL.
SVR12 was sustained virologic response (HCV RNA < LLOQ) 12 weeks after stopping study treatment.
A missing SVR12 value was imputed as a success if it was bracketed by values that were termed successes (ie, '< LLOQ TND' or '< LLOQ detected'); otherwise, the missing SVR12 value was imputed as a failure. TND = target not detected.
The exact 95% CI for the proportion within treatment group was based on the Clopper-Pearson method.
Source: Section 15.1, Table 8

- 97.4% subjects in the LDV/SOF 24 week group and 96.1% in the LDV/SOF+RBV 12 week group achieved SVR12. The difference in SVR12 between the two groups was not statistically significant (p = 0.63). All 5 subjects who did not achieve SVR12 relapsed.
- All subjects in the FAS completed study treatment and no subject in either group had on-treatment virologic failure (that is, breakthrough, rebound, or nonresponse).
- Sustained virological response 4 weeks after EOT (SVR4) = SVR12 with exception of 1 who achieved SVR4 but relapsed at post therapy Week 12.
- All subjects who achieved SVR12 also achieved sustained virological response 24 weeks after EOT (SVR24).

LDV/SOF for 24 weeks is currently approved regimen for treatment experienced GT 1 patients with compensated cirrhosis. The study results indicate that a 12 week treatment of LDV/SOF+RBV results in similar efficacy as the currently approved 24 week treatment with LDV/SOF in this group of 'hard to cure' patients (all patients had cirrhosis and are treatment experienced with prior treatment failure). Thus, 12 weeks of triple therapy with LDV/SOF+RBV is an equally effective and shorter duration therapeutic option for treatment experienced GT 1 patients with cirrhosis.

GS-US-337-0115 (ION-4): HCV/HIV co-infection

This is a Phase III, open label, non-randomised, multicentre study, and the study assessed the efficacy and safety of 12 weeks of LDV/SOF in treatment naïve and treatment experienced subjects with HCV GT 1 or GT 4 who are co-infected with HIV-1. The primary objective was to assess the proportion of subjects with SVR12, treatment safety and tolerability. All enrolled subjects were 335 subjects (only 8 GT 4 subjects). About 55% subjects had prior hepatitis C therapy, most of whom had a prior non-response or null-response to that therapy.

The overall SVR12 rate was 95.8% (95% confidence interval (CI): 93.1% to 97.7%). Of the 14 who did not achieve SVR12, 10 relapsed, 2 had on treatment virologic failure (both non-compliance), one died (sepsis), and one was lost to follow up (LTFUP). SVR4 = SVR12 results with the exception of 3 subjects: two achieved SVR4 but did not achieve SVR12 (relapsed), and one achieved SVR4 but was then LTFUP. High SVR12 rates were observed in most subgroups, including treatment experienced (96.8%, 179 of 185), treatment experienced with cirrhosis (97.9%). High and similar SVR12 rates observed irrespective of ARV regimen. However, black subjects and those with IL28B TT allele (had lower SVR12). In multivariate analysis, only black race was associated with increased relapse.

There were 13 treatment experienced GT 1 subjects enrolled who had failed a SOF+RBV regimen. All 13 of these subjects achieved SVR12. Of the only 8 subjects with GT 4 all achieved an SVR12. HCV RNA levels ($\log_{10}$ IU/mL) declined rapidly irrespective of ARV regimen. After 1 week of treatment, mean (SD) $\log_{10}$ IU/mL change from baseline was −4.68 $\log_{10}$ IU/mL.

Virologic resistance

A total of 83 of 325 subjects (25.5%) with GT 1 infection and with available sequencing data had NS5A RAPs at pre-treatment. Seventy-eight of the 83 subjects with pre-treatment NS5A RAPs achieved SVR12 (94.0%), and 235 of 242 (97.1%) subjects without pre-treatment NS5A RAPs achieved SVR12. All subjects with GT 4 infection had NS5A RAPs and achieved SVR12. Two subjects who experienced on-treatment virologic failure developed NS5A resistance associated variants (RAVs) at the time of virologic failure. Seven of the 10 (70%) who experienced virologic relapse had pre-treatment NS5A RAPs, 4 of the 10 had pre-treatment NS5A RAVs, and 8 of the 10 who relapsed had post treatment NS5A RAVs. No NS5A RAVs were detected at pre and post treatment in 2 of the 10 subjects who relapsed. The 3 (0.9%) with the SOF treatment emergent variant (TEV) L159F at

pre-treatment achieved SVR12. The SOF RAV S282T and SOF TEVs L320F and V321A were not detected by deep sequencing in any subjects' pre-treatment. Only 1 had L159F (9.86%) at the time of relapse, observed together with the nonstructural protein5B (NS5B) RAV Y93N (> 99%).

GS-US-337-0122 (ELECTRON 2)

This was an ongoing Phase II multicentre, open label study that evaluated the safety and efficacy of SOF-containing regimens administered for up to 24 weeks in CHC patients. This study was conducted in a number of cohorts and groups of subjects, and the details were discussed in the CER (see Attachment 2). This study was not designed to evaluate formal statistical hypotheses. Primary efficacy endpoint was SVR12 in Full Analysis Set (FAS). The study involved various numbers of subjects infected with different genotypes (GT 1, 2, 3, 4, 5, and 6). For the current application, the main aim of this study appears to be providing data for the use of Harvoni +/- RBV in subjects infected with HCV GT 3 and GT 6. The SVR results in subjects with GT 3 and GT 6 subjects are presented in Table 8 below.

Table 8: SVR12 in subjects with HCV genotype 3 and 6 in GS-US-337-0122 (ELECTRON 2)

Study Number[a]	Study Description[b]	SVR12 (n/N, %)[c]	
		Overall	Subjects with Cirrhosis
Genotype 3 HCV Infection, N = 101			
GS-US-337-0122 (ELECTRON-2; Cohort 2, Groups 3, 4, and 6)	Treatment-naive subjects with genotype 3 HCV infection, with or without cirrhosis, received LDV/SOF for 12 weeks or LDV/SOF+RBV for 12 weeks. Treatment-experienced subjects with genotype 3 HCV infection, with or without cirrhosis, received LDV/SOF+RBV for 12 weeks.	Treatment-Naive LDV/SOF 12 Weeks: 16/25 (64.0%) Treatment-Naive LDV/SOF+RBV 12 Weeks: 26/26 (100.0%) Treatment-Experienced LDV/SOF+RBV 12 Weeks: 41/50 (82.0%)	Treatment-Naive LDV/SOF 12 Weeks: 1/4 (25.0%) Treatment-Naive LDV/SOF+RBV 12 Weeks: 6/6 (100.0%) Treatment-Experienced LDV/SOF+RBV 12 Weeks: 16/22 (72.7%)
Genotype 6 HCV Infection (N = 25)			
GS-US-337-0122 (ELECTRON-2; Cohort 2, Group 5)	Treatment-naive and treatment-experienced subjects with genotype 6 HCV infection, with or without cirrhosis, received LDV/SOF for 12 weeks.	24/25 (96.0%)	2/2 (100.0%)

SVR 12 results in Cohort 2 (Groups 3 to 6, GT 3)

- In treatment naïve GT 3 patients, 12 weeks of LDV/SOF+RBV → SVR12 = 100.0% (26/26), whereas treatment with LDV/SOF resulted in a SVR12 of 64.0%, suggesting an advantage to add RBV to LDV/SOF when treating treatment naïve GT 3 subjects.
- 12 weeks of LDV/SOF+RBV for treatment experienced GT 3 subjects → SVR12 = 82.0%. One subject experienced on-treatment breakthrough.
- 12 weeks of LDV/SOF in subjects with GT 6 infection → SVR12 = 96.0%; all subjects who completed study drug achieved SVR12.
- Of all the GT 3 subjects who relapsed, NS5A RAPs and NS5B S282T were detected in 7 of 17 and 1 of 17 subjects, respectively. The on treatment breakthrough in 1 subject was associated with the emergence of low levels of NS5B L159F only.
- NS5B S282T emerged in 1 subject with GT 6 HCV infection who completed 8 weeks of treatment and relapsed.

It is noted the number of GT 3 subjects in this study is limited: 26 treatment naïve GT 3 patients were treated with 12 weeks of LDV/SOF+RBV. It is also noted that there was a lower SVR12 (64%, 25% for cirrhotic) for treatment naïve GT 3 when Harvoni was not partnered with RBV and was given for short course (12 weeks). In treatment experienced GT 3 patients who were treated with Harvoni +RBV, SVR12 rate was only 82%.

GS-US-337-1118 (RETREATMENT in GT 1 patients)

This is a non-randomised open label study, and the study assessed the safety and efficacy of LDV/SOF with or without RBV for 12 or 24 weeks in GT 1 HCV subjects who failed prior treatment in a previous Gilead sponsored study. Eligible subjects were adult CHC patients with GT 1 infection, who had screening HCV RNA levels > LLOQ, were HCV treatment experienced, and had participated in a previous Gilead sponsored HCV study. Primary efficacy endpoint was SVR12. There were three treatment groups below:

- Group 1: LDV/SOF+RBV 12 Weeks: subjects who failed a prior SOF+RBV±PEG regimen
- Group 2: LDV/SOF 24 Week: subjects who failed a prior LDV/SOF±RBV regimen
- Group 3: LDV/SOF+RBV 24 Weeks: subjects with advanced compensated or decompensated cirrhosis who failed a prior SOF+RBV regimen.

The interim report only has result for Group 1. In Group 1, a total of 51 subjects were included in the FAS. Majority were male (60.8%), White (84.3%), non-Hispanic/Latino (92.2%), mean age of 54 years. 27.5% of subjects had cirrhosis. In terms of prior treatment:

- 25 patients previously received SOF+PEG+RBV
- 20 patients previously received SOF+RBV, and
- 6 patients previously received therapy without SOF.

92.2% had experienced virologic failure, 1 discontinued treatment due to an AE, and 3 (5.9%) had an outcome categorised as 'other'.

SVR12 results for Group 1

Fifty (98.0%) completed treatment. One subject discontinued treatment after Week 10 due to an AE (worsening of bipolar disorder). 98.0% achieved SVR12. The 1 subject not achieving SVR12 relapsed at post-treatment week 4 after completing treatment. This patient had been misclassified as GT 1 when in fact they had GT 3a. In summary, retreatment of prior SOF failures with LDV/SOF+RBV resulted in a high SVR12 (Table 9, below). All who achieved SVR12 also achieved SVR24.

Table 9: Proportion of subjects (Group1) with SVR12 and virologic outcomes (FAS)

	LDV/SOF+RBV 12 Weeks (Group 1) (N = 51)
SVR12	50/51 (98.0%)
95% CI	89.6% to 100.0%
Overall Virologic Failure	1/51 (2.0%)
Relapse	1/51 (2.0%)
Completed Study Treatment	1/50 (2.0%)
Discontinued Study Treatment	0/1
On-Treatment Virologic Failure	0/51
Other	0/51

Among the 44 subjects in Group 1 who had previously failed a treatment with SOF+RBV+Peg-IFN or with SOF+RBV, the SVR was 100% (44/44) following 12 weeks treatment with LDV/SOF+RBV.

Resistance

All GT 1 with NS5A RAVs (n = 6) or NS5B L159F (n = 2) at baseline achieved SVR12.

Study-GS-US-337-1119 (GT 4 and GT 5)

This was a non-randomised, Phase II, multicentre, open label study, and the study assessed the efficacy and safety of 12 weeks LDV/SOF in treatment naïve and treatment experienced subjects with GT 4 or 5 HCV Infection. SVR12 was the primary efficacy endpoint. A total of 85 subjects (44 GT 4, 41 GT 5) were included in the FAS and SAS. The proportion achieving SVR12 by genotype and prior HCV treatment status was estimated.

GT 4

81.8% White and 95.5% not Hispanic or Latino; 68.2% of European descent, 18.2% of Egyptian descent. Mean age 51 years (range: 21 to 69), 63.6% male. 6.8% had GT 4a subtype; 81.8% non-CC IL28B allele. Mean (SD) HCV RNA 6.2 (0.47) $\log_{10}$ IU/mL. 22.7% cirrhosis.

GT 5

All White and not Hispanic/Latino; 95.1% of European descent. Mean age 63 years (range: 40 to 79), 51.2% male. Mean (SD) baseline BMI of 25.4 (4.11) kg/m2. All subtype 5a, except 1 subject with undetermined subtype; 53.7% non-CC IL28B allele. Mean (SD) HCV RNA 6.4 (0.47) $\log_{10}$ IU/mL. 22.0% had cirrhosis; mean (SD) alanine aminotransferase (ALT) 61 (43.6) U/L.

Table 10 below presents the SVR12 results.

Table 10: GS-US-337-1119: SVR12 (FAS)

	Group 1 GT 4 TN (N = 22)	Group 2 GT 4 TE (N = 22)	Total GT 4 (N = 44)	Group 3 GT 5 TN (N = 21)	Group 4 GT 5 TE (N = 20)	Total GT 5 (N = 41)
SVR12	21/22 (95.5%)	20/22 (90.9%)	41/44 (93.2%)	19/21 (90.5%)	19/20 (95.0%)	38/41 (92.7%)
95% CI	77.2% to 99.9%	70.8% to 98.9%	81.3% to 98.6%	69.6% to 98.8%	75.1% to 99.9%	80.1% to 98.5%

GT = genotype; TN = treatment naive; TE = treatment experienced
HCV RNA was analyzed using the COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0. The LLOQ of the assay was 15 IU/mL.
SVR12 = sustained virologic response (HCV RNA < LLOQ) 12 weeks after stopping study treatment.
A missing SVR12 value was imputed as a success if it was bracketed by values that were termed successes (ie, '<LLOQ TND' or '<LLOQ detected'); otherwise, the missing SVR12 value was imputed as a failure. TND = target not detected.
The exact 95% CI for the proportion within treatment group was based on the Clopper-Pearson method.
Source: Section 15.1, Table 7

- SVR12 rate was 93.2% (41 of 44) for GT 4 and 92.7% (38 of 41) for GT 5.
- SVR12 was similar in treatment naive and -experienced. For GT 4, 95.5% treatment naive and 90.9% treatment experienced achieved SVR12. For GT 5, 90.5% treatment naive and 95.0% treatment experienced subjects achieved SVR12.
- No on-treatment virologic failure. Each of the 3 GT 4 subjects not achieving SVR12 relapsed. Two of the three GT 5s not achieving SVR12 relapsed. One GT 5 subject not achieving SVR12 had HCV RNA < LLOQ at last on-treatment visit; however, the subject was then lost to follow up (LTFUP).
- No apparent differences in SVR12 rates for subgroups. 100% GT 4 subjects with cirrhosis achieved SVR12; 88.9% GT 5 cirrhotic achieved SVR12.
- Rapid suppression of HCV RNA observed in all groups. All with SVR4 also achieved SVR12.

Resistance

Of the 5 with virologic relapse, NS5B S282T emerged at virologic relapse for 1 with GT 4r and 1 with GT 5a. At relapse, post treatment NS5B sequencing showed that the NS5B V321I RAP was retained or enriched in 2 with GT 4 infection, and the M289I RAP emerged in one GT 5a subject with post treatment NS5B sequencing data. High SVR were achieved despite the presence of NS5A RAPs. Virologic relapse associated with retained NS5A and NS5B RAPs and emergence of NS5A Y93C (n = 1), NS5B S282T (n = 2) or M289I (n = 1).

GS-US-337-1468 (LEPTON)

This is a Phase II, multicentre, non-randomised, open label study, and the study assessed the efficacy and safety of oral HCV regimens for adult subjects. Up to 40% of subjects were HCV treatment experienced, and up to 25% have cirrhosis. The treatment was LDV/SOF FDC for various treatment durations. SVR12 was the primary efficacy endpoint. The interim report for Group 1 subjects (GT 2) were discussed in the CER (see Attachment 2). The treatment duration was 12 weeks. A total of 26 GT 2 subjects were enrolled into Cohort 2, Group 1. All of the enrolled subjects received at least 1 dose of study drug and were included in the Safety Analysis Set and the Full Analysis Set. Twenty-five of the enrolled subjects (96.2%) completed 12 weeks of treatment with LDV/SOF; 1 subject withdrew consent and prematurely discontinued from the study after receiving 1 dose of study drug.

In Group 1 of Cohort 2, majority of the subjects were male (65.4%) and White (92.3%), none Hispanic or Latino. Mean age was 53 years. Mean (SD) HCV RNA was 6.1 (0.66) $\log_{10}$ IU/mL; 57.7% had HCV RNA ≥ 800,000 IU/mL. All were GT 2 HCV with 61.5% subtype 2b (subtype 2b was most common, 15/26 (58%), 8/26 had subtype 2a or 2c). 61.5% had non-CC IL28B alleles and IL28 CC genotype (most favourable for chance to cure) was seen in 10/26 (35%) of patients. There were only 2 subjects with cirrhotic; 80.8% naive to prior HCV treatment and 5/21 patients had experienced prior treatment failure (this concerned prior relapse in 3/5).

SVR12 results for Group 1 of Cohort 2

Twenty-five of 26 subjects (96.2%) achieved SVR12 following 12 weeks of treatment with LDV/SOF (see Table 11 below). No subjects had on-treatment virologic failure or virologic relapse. The only subject who did not achieve SVR12 withdrew consent and prematurely discontinued from the study after receiving a single dose of LDV/SOF.

Table 11: Proportion of subjects (Group 1 of Cohort 2) who achieved SVR12

	Cohort 2, Group 1 LDV/SOF 12 Weeks (N = 26)
Number (%) of Subjects with HCV RNA < LLOQ 12 Weeks Posttreatment	
SVR12	25/26 (96.2%)
95% CI	80.4% to 99.9%

Study Number[a]	Study Description[b]	SVR12 (n/N, %)[c]	
		Overall	Subjects with Cirrhosis
Genotype 2 HCV Infection, N = 26			
GS-US-337-1468 (LEPTON; Cohort 2, Group 1)	Treatment-naive and treatment-experienced subjects with genotype 2 HCV infection, with or without cirrhosis, received LDV/SOF for 12 weeks.	25/26 (96.2%)	2/2 (100%)

Resistance

Deep sequencing results obtained for 26/26 and 25/26 for NS5A and NS5B, respectively. Of the 26, 11 were GT 2a, and 15 were GT 2b. Pre-treatment NS5A RAPs (T24A, F28L, K30R, or L31M) detected in all 11 GT 2a subjects, with L31M present in 10 of 11 GT 2a. Pre-treatment NS5A RAPs (L28F, L31M) detected in 5/15 with HCV GT 2b. The NS5B RAPs (M289I/V) detected in 2 GT 2a and 2 GT 2b subjects. High SVR rates despite NS5A and NS5B RAPs.

CO-US-337-0117 (SYNERGY)

The SYNERGY study was a National Institute of Allergy and Infectious Diseases (NIAID) sponsored Phase II study and was included in this application to provide supporting data. It is an exploratory study with an open label design; the study was to assess the safety and efficacy of multiple combination therapy (interferon-sparing therapy) in adult CHC patients. This is a multipart study, containing 8 groups (A-H). The study involved both treatment naïve and interferon treatment experienced patients. Many groups were patients infected with GT 1 while Group E was patients infected with GT 4. In 2 of the groups (Groups A and E), the LDV/SOF FDC tablet was used alone in GT 1 treatment naïve subjects and GT 4 treatment naïve or treatment experienced subjects; in groups B and C, the LDV/SOF FDC tablet was taken along with other oral antiviral agents (either GS-9669 or GS-9451) for 6 weeks in HCV GT 1 treatment naïve subjects with early liver disease.

The focus of this study report is on Group E (GT 4). In Group E, a total of 21 GT 4 patients were treated with LDV/SOF for 12 weeks. Twenty out of 21 (20/21; 95%CI: 76 to 100%) achieved SVR12. The 1 failure was non-adherent. In a further analysis from this study, a small amount of retreatment data was provided for GT 1 subjects who failed previous treatment with 24 weeks of SOF+RBV. There were small data on the use of LDV/SOF in combination with other oral antiviral agents. These are not related to the current submission and will not be discussed further here.

GS-US-337-0123 (SOLAR-1) and GS-US-337-0124 (SOLAR-2

These were two Phase II open label, randomised, multicentre studies, and the studies evaluated the efficacy and safety of LDV/SOF+RBV in GT 1 or GT 4 CHC patients with advanced liver disease and/or who had undergone liver transplantation. The purpose of the two studies were to assess the efficacy of LDV/SOF +RBV in pre or post-liver transplantation subjects with compensated liver disease as well as those with decompensated liver disease, regardless of transplantation status, and to assess the safety of LDV/SOF+RBV in a population with very high morbidity and mortality. Subjects were enrolled into Cohort A or B according to their transplantation status and into 1 of the 7 groups based on severity of liver impairment. Of the 670 treated patients, 455 were post-liver transplant and 329 were with decompensated cirrhosis. Detailed description and analysis are included in the CER (see Attachment 2). The results of SVR12 in GT 1 and GT 4 subjects are briefly discussed below.

SVR12 in Genotype 1 subjects

The SVR12 in post-transplant subjects without cirrhosis (F0-F3 fibrosis) and in those with compensated cirrhosis (CPT A) were high at 95% and 98% respectively with 12 weeks of LDV/SOF + RBV treatment. Extending treatment from 12 to 24 weeks did not meaningfully impact SVR12 rates.

Table 12: SVR12 for post-transplant subjects without cirrhosis and in those with compensated cirrhosis (SOLAR 1 and 2)

Liver Disease Status (Group)	Duration of Treatment	Genotype 1	
		SVR12 (n/N [%])	95% CI
Stage F0-F3 Fibrosis (Group 3)	12 Weeks	94/99 (94.9%)	88.6% to 98.3%
	24 Weeks	99/100 (99.0%)	94.6% to 100.0%
CPT A Cirrhosis (Group 4)	12 Weeks	55/56 (98.2%)	90.4% to 100.0%
	24 Weeks	51/53 (96.2%)	87.0% to 99.5%

Subjects with decompensated liver disease, regardless of liver transplantation status, achieved SVR12 rates ranged from 89% and 57% with 12 weeks of LDV/SOF + RBV. Extending treatment from 12 to 24 weeks did not meaningfully impact SVR12 rates.

Table 13: SVR12 for subjects with decompensated cirrhosis Regardless of liver transplantation status (SOLAR 1 and 2)

	Liver Disease Status (Group)	Duration of Treatment	Genotype 1	
			SVR12 (n/N [%])	95% CI
Pretransplantation	CPT B Cirrhosis (Group 1)	12 Weeks	45/52 (86.5%)	74.2% to 94.4%
		24 Weeks	46/50 (92.0%)	80.8% to 97.8%
	CPT C Cirrhosis (Group 2)	12 Weeks	35/40 (87.5%)	73.2% to 95.8%
		24 Weeks	38/46 (82.6%)	68.6% to 92.2%
Posttransplantat	CPT B Cirrhosis (Group 5)	12 Weeks	41/46 (89.1%)	76.4% to 96.4%
		24 Weeks	43/45 (95.6%)	84.9% to 99.5%
	CPT C Cirrhosis (Group 6)	12 Weeks	4/7 (57.1%)	18.4% to 90.1%
		24 Weeks	7/9 (77.8%)	40.0% to 97.2%

SVR12 in Genotype 4 subjects

A total of 40 GT 4 subjects were evaluated, and 82.5% (33/40) achieved SVR12.

- Among post-liver transplantation subjects with GT 4 infection and compensated liver disease, high SVR12 rates were observed (95.5%, 21/22). No subjects relapsed. Extending therapy to 24 weeks did not meaningfully impact SVR12 rates.
- Among GT 4 subjects with decompensated cirrhosis, regardless of transplantation status, only 18 subjects were evaluated (SVR12 rates of 60.0% and 75.0% after 12 or 24 weeks of treatment, respectively). Of these subjects, 3 relapsed; therefore, insufficient data are available to determine the optimal treatment duration for GT 4 subjects with decompensated liver disease.

GS-US-337-0102 (ION-1)

This Phase III, randomised, open label study was submitted at the initial registration application, and the study assessed the efficacy and safety of 12 or 24 weeks of LDV/SOF±RBV in treatment naive subjects with GT 1 HCV infection. The SVR 12 results are presented in Table 14. Please refer to the CER (see Attachment 2) for detail of the study analysis.

Table 14: GS-US-337-0102 (ION-1): SVR12 (FAS)

	LDV/SOF 12 Weeks (N = 214)	LDV/SOF+RBV 12 Weeks (N = 217)	LDV/SOF 24 Weeks (N = 217)	LDV/SOF+RBV 24 Weeks (N = 217)
SVR12	211/214 (98.6%)	211/217 (97.2%)	213/217 (98.2%)	215/217 (99.1%)
95% CI	96.0% to 99.7%	94.1% to 99.0%	95.3% to 99.5%	96.7% to 99.9%
P-value (compared to 60%)	< 0.001	< 0.001	< 0.001	< 0.001

Integrated virology report for SOF/LDV-containing regimens for the treatment of HCV

A full description of the resistance analysis methodologies is summarised in the virology analysis plan. Baseline deep sequencing of the full-length HCV NS3, NS5A, and NS5B coding region was performed using reverse transcription polymerase chain reaction (RT-PCR) and then deep sequencing using the Illumina MiSeq deep sequencing platform. The NS3, NS5A, and NS5B sequence was utilised to confirm the results of genotyping/subtyping performed at screening. Sequencing only attempted if HCV RNA ≥ 1000 IU/mL. Data for this integrated report is derived from the LDV/SOF Phase II or III studies:

GS-US-337-0115 (ION 4), GS-US-337-0121 (SIRIUS), GS-US-337-1118 (Group 1), GS-US-337- 0122 (ELECTRON 2; Cohort 1, Group 1; Cohort 2, Groups 3, 4, 5, and 6), GS-US- 337-1468 (LEPTON; Cohort 2, Group 1), and GS-US-337-1119.

In summary:

- high SVR rates in subjects with HCV GT 1, 2, 3, 4, 5, and 6
- high SVR12 achieved in the presence of baseline NS5A or NS5B nucleoside inhibitor (NI) RAVs, irrespective of patient population or GT. This is similar to the findings from the previous LDV/SOF Phase III studies (ION-1, ION-2 and ION-3) conducted in GT 1 HCV.
- The lack of a high predictive value between baseline viral sequence and treatment outcome also appears to preclude the clinical utility of baseline HCV sequencing.
- Of the limited number who experienced virologic failure, NS5A RAVs observed in the majority. With regard to NS5B NI RAVs, S282T emerged in 1 subject each for GT 4, 5, and 6, whereas S282T was not observed in any GT 1 HCV-infected subject with relapse.

Integrated virology study report from SOLAR-1 and SOLAR-2 Studies

Full description of the resistance analysis and virological analysis plan methodologies are found in the analysis plan PC-337-2004. Overall results are as follows:

- when pooling all GT 1 subjects irrespective of group or duration, high SVR12 rates in the presence of baseline NS5A RAPs or RAVs: 143 of 148 (96.6%) with NS5A RAPs (15% cut-off) achieved SVR12 versus 424 of 439 (96.6%) with no NS5A RAPs; and 96 of 101 (95.0%) with NS5A RAVs (1% cut-off) achieved SVR12 versus 471 of 486 (96.9%) with no NS5A RAVs
- When subjects were analysed according to their group and treatment duration, except for subjects in group 2 (CPT C), no clear differences in SVR12 observed by the presence or absence of NS5A RAPs or RAVs. For the small number of CPT C subjects who received LDV/SOF+RBV for 12 weeks: 7 of 9 subjects (77.8%) and 6 of 8 (75.0%) with RAPs (15% cut-off) and NS5A RAVs (1% cut-off), respectively, achieved SVR12

versus subjects who received LDV/SOF+RBV for 24 weeks: 9 of 9 (100%) and 10 of 10 (100%) subjects with no NS5A RAPs or RAVs, respectively

- When pooling subjects by stage of liver disease, in GT 1, NS5A RAP did not have a meaningful impact on outcome; conversely, a statistically significant difference was observed for the subset with decompensated disease with NS5A RAVs known to confer > 100 fold resistance to LDV in vitro: SVR12 rates were 75% (12/16) and 100% (18/18), respectively, for those treated with SOF/LDV+RBV for 12 weeks versus for 24 weeks (p value: 0.039; 2-sided Fisher's Exact test). However, all four subjects with a pre-treatment NS5A RAV that confers > 100 fold shift in EC_{50} who relapsed, also had BMI > 30. Subsequent logistic regression analyses demonstrated that, when accounting for BMI, presence of NS5A RAVs conferring > 100 fold shift in EC_{50} was **not** associated with relapse. No effect on SVR12 with pre-treatment NS5B NI RAVs. For GT 4, no subjects without RAPs (n = 11) or RAVs at 1% cut-off (n = 10) relapsed. Of those with NS5A RAPs (n = 24) or RAVs (n = 25), 3 relapsed; all 3 had decompensated disease and were treated for 12 weeks. No GT 4 subjects with NS5A RAPs or RAVs who were not decompensated relapsed. No subjects treated for 24 weeks relapsed, irrespective of the presence or absence of NS5A RAPs or RAVs. No effect on SVR12 rate observed with NS5B NI RAVs at pre-treatment. Virologic failure associated with single class LDV resistance in the majority of subjects. The NS5B NI RAVs S282T, L159F and V321A, not detected in any at virologic failure. E237G, a conserved site substitution in NS5B, was detected in 3 GT 1a subjects and 1 GT 4d subject at time of relapse. E237G showed a small reduction in susceptibility to SOF (1.3-fold change) in a GT 1a replicon assay. The clinical significance of E237G is unknown.

Clinical Safety

The clinical evaluator has considered all the studies defined as 'pivotal' in efficacy section of the CER, as pivotal in Safety section of the CER (see Attachment 2). The clinical evaluator is of the view that the data presented in this Application demonstrate that Harvoni has an overall highly acceptable safety profile. This Application provides clinical trial (many open label and several un-randomised, single arm) data in a number of different populations that is, treatment experienced subjects with cirrhosis, HCV/HIV co-infection, prior treatment failures with a SOF containing regimen, and chronic HCV infection with Genotypes other than GT 1. The safety profile of LDV/SOF for 12 or 24 weeks and LDV/SOF+RBV for 12 weeks was consistent with that observed for LDV/SOF±RBV in previous Phase III studies (Studies GS-US-337-0102 [ION-1], GS-US-337-0109 [ION-2], and GS-US-337-0108. Overall, the safety profile of LDV/SOF+RBV treatment was similar to the expected safety profile of RBV. The safety profile of LDV/SOF for 12 weeks in HCV/HIV-1 co-infected subjects stable on ARVs and with suppressed plasma HIV RNA, was consistent with the safety profile of LDV/SOF in the HCV-mono-infected population. There was no negative impact on surrogate markers of ARV efficacy that is, HIV viral load and CD4 T-cell count during treatment with Harvoni. The elevated levels of TFV with TDF-containing regimens are of uncertain significance, especially as co-administration of these drugs will be relatively short. However, this drug-drug interaction merits closer renal monitoring especially in patients with some degree of renal impairment and probably some attention to bone health.

Harvoni cannot be co-administered with potent P-gp inducers like rifampicin. Anaemia was the predominant treatment related safety finding in the post-transplant subjects, which is associated with RBV and likely exacerbated by the relatively low eGFRCG in some of these subjects. Most patients were successfully managed with dose reduction, and haemoglobin recovered quickly after the end of treatment. The interactions between LDV/SOF and HIV ARV regimens (ritonavir boosted ATV or DRV plus FTC/TDF, DTG plus

FTC/TDF and E/C/F/TAF) have been evaluated. No dose adjustment is necessary for any of these drugs or regimens.

For special population of liver transplant (for HCV) recipients where HCV recrudescence is universal and associated with poorer graft and patient survival compared with non-HCV related liver transplants. SOLAR-1 and SOLAR-2 evaluated LDV/SOF+RBV for 12 or 24 weeks across the spectrum of patients who are pre and post-liver transplantation including those without cirrhosis, and those with compensated and decompensated cirrhosis. This is a varying sick population of patients with overall high morbidity and mortality especially those with decompensated cirrhosis. In terms of safety, for all groups of subjects evaluated in SOLAR-1 and SOLAR-2, LDV/SOF+RBV for 24 weeks was not associated with an overall increased safety burden compared with LDV/SOF+RBV treatment for 12 weeks. One subject was determined to have experienced an increase in direct bilirubin for which Drug Induced Liver Injury (DILI) could not be excluded. This subject's increase in direct bilirubin occurred at Week 20 of LDV/SOF+RBV treatment. No deaths or transplantation events were the result of DILI. Given this single occurrence, it is suggested that clinicians should be made aware and direct bilirubin be measured during LDV/SOF+RBV therapy in patients with advanced liver disease.

Consistent with the underlying severity of the liver disease in subjects with decompensated cirrhosis, AEs, including SAEs, occurred more frequently compared with the rates observed in subjects in previous Phase III studies that excluded decompensated subjects. However, the AEs were consistent with decompensated liver disease or the known toxicity profile of RBV, including anaemia. Decreases in haemoglobin to < 10.0 g/dL and < 8.5 g/dL during treatment occurred in just over 1/3 and 1/10 of subjects, respectively. Most episodes were successfully managed with RBV dose reduction although just < 20% had to discontinue RBV. Reassuringly, haemoglobin declines reversed rapidly after completion of treatment. The Independent Adjudication Committee (IAC) after formal review of hepatic safety including the impact of longer exposure to Harvoni, determined that LDV/SOF+RBV was safe and well tolerated, with a low potential for causing DILI. However, the IAC and Sponsor propose that for patients treated with LDV/SOF+RBV, monthly liver tests, including direct bilirubin, be performed. The latter would align with standard-of-care monitoring for this patient population.

Post-marketing experience with Harvoni

A few cases of symptomatic bradycardia, including 1 fatal cardiac arrest and 1 requiring pacemaker insertion, have been reported in patients taking amiodarone and LDV/SOF. Bradycardia was observed within hours to days of starting LDV/SOF. Co-administration of amiodarone with LDV/SOF is not recommended. TGA was notified and updated LDV/SOF labelling submitted on 23 Mar 2015.

Overall, the data provided in this submission shows Harvoni is safe in the proposed populations without any new and/or concerning safety signal.

Risk management plan

ACSOM advice was not sought for this submission. The RMP evaluator recommends to the Delegate that the updated RMP version is implemented. Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise. Suggested wording for conditions of registration:

- Implement RMP (version 1.1, 23 June 2015, DLP 31 May 2015) with Australian Specific Annex (version 1.2, June 2016) and any future updates as a condition of registration.

Risk-benefit analysis

GT 1 patients with cirrhosis and prior treatment failure

SIRIUS study in GT 1 patients indicate that a 12 week of LDV/SOF+RBV results in similar efficacy as the currently approved 24 week therapy with LDV/SOF in the 'hard to cure' patients population (cirrhosis and prior treatment failure). Thus, 12 weeks of LDV/SOF+RBV is an equally effective and shorter duration therapeutic option for treatment experienced CHC patients with cirrhosis.

It is noted that CHMP considers that both regimens (12 weeks of LDV/SOF+RBV and 24 weeks of LDV/SOF) yielded the same good results and should be regarded as equal.

Patients with HCV/HIV-1 co-infection (GT 1 and GT 4)

Study ION-4 evaluated the 12 weeks of LDV/SOF in 335 treatment naive or treatment experienced subjects with HCV/HIV co-infection, 96% of the subjects achieved SVR12. Those treatment experienced subjects with cirrhosis also achieved a SVR12 of 98% (46/47). The efficacy results are consistent with the results from other Phase III studies in HCV-mono-infected subjects. The use of LDV/SOF in HCV/HIV co-infected subjects was well tolerated.

It is noted that in Study ION-4, the subjects with HCV/HIV co-infection were GT 1 or GT 4 HCV infected. Co-infected HCV patients with other HCV genotypes were not included.

GT 1 patients who have previously failed a SOF-containing regimen

There is currently no approved therapy for CHC patients who have previously failed a SOF+RBV±Peg-IFN regimen. The totality of virologic evidence suggests that the primary mode of resistance to SOF is the development of the S282T mutation. This mutation develops rarely, and is rapidly overgrown by wild-type virus. This suggests that the patients who have failed SOF could be retreated with a SOF containing regimen.

The results from four independent studies (Studies GS-US-337-1118, GS-US-337-0122, GS-US-337-0115, and CO-US-337-0117) showed that SOF/LDV, with and without RBV, is efficacious in treatment experienced GT 1 patients who have failed a prior SOF containing regimen. The 90 GT 1 patients who had previously failed a SOF containing regimen have achieved SVR12 following treatment with 12 weeks of LDV/SOF±RBV. Safety in these 4 studies was consistent with that observed for LDV/SOF±RBV in the Phase III studies from the initial application for LDV/SOF.

Table 15: Retreatment with 12 weeks SOF/LBV+/-RBV in GT 1 patients who are prior SOF failures

Study/ Population studied	Re-treatment regimen	SVR12, n/N	
		Overall	Cirrhotics
GS-US-337-1118 (Group 1) *Patients who had failed a prior SOF+RBV +/- peg-IFN regimen.*	SOF/LDV + RBV 12 weeks	44/44	12/12
GS-US-337-0122 (ELECTRON-2, cohort 1, group 1) *Patients who had failed a prior SOF-containing regimen.*	SOF/LDV + RBV 12 weeks	19/19	1/1
GS-US-337-0115 (ION-4; prior SOF-failures) *HIV co-infected patients; the subset of patients included ion ION-4 who had a prior failure to SOF + RBV.*	SOF/LDV 12 weeks	13/13	1/1
GS-US-337-0117 (SYNERGY, group D) *Patients who had failed therapy with SOF + RBV*	SOF/LDV 12 weeks	14/14	-

Gilead proposes that the dosage and administration of LDV/SOF be modified to include prior SOF+RBV±Peg-IFN failures in the category of treatment experienced patients. It is noted that the number of GT 1 patients assessed in these studies are limited and there appears to be no data in non-GT 1 patients who have previously failed a SOF containing regimen.

CHC patients with non-GT 1 HCV infection

Genotype 2

In Study GS-US-337-1468 (LEPTON; Cohort 2, Group 1), 25 out of 26 GT 2 patients (96%) achieved SVR12 after 12 weeks of LDV/SOF, one subject withdrew consent and prematurely discontinued. Gilead proposes that patients with GT 2 infection be eligible to receive LDV/SOF for 12 weeks, it is of concern that the data in GT 2 subjects is limited to only 26 patients who belong to 'easy to cure' category. Only 2 of the 26 patients had cirrhosis. The proportion of treatment experienced patients is also low and mainly concerned cases of prior relapse. The CHMP questions whether a high point estimate for cure (96% SVR12: 25/26) in 26 patients with generally favourable baseline characteristics is a sufficient basis for a formal treatment recommendation for GT 2 patients. CHMP is of the view that a larger study would be needed to support this recommendation.

Genotype 3

The currently approved regimen for treatment naive patients with GT 3 infection is SOF+RBV for 16 to 24 weeks. ELECTRON-2 was provided to support the dose recommendation for GT 3 subjects. It is noted that in ELECTRON 2, for the treatment naïve GT 3 patients, the SVR12 was low (64%) when Harvoni was not partnered with RBV and was given for shorter duration of 12 weeks. In treatment experience GT 3 patients who treated with Harvoni +RBV, SVR12 rate was only 82%.

Table 16: SVR12 in subjects with HCV GT 3 and 6 patients (ELECTRON-2)

Study Number[a]	Study Description[b]	SVR12 (n/N, %)[c]	
		Overall	Subjects with Cirrhosis
Genotype 3 HCV Infection, N = 101			
GS-US-337-0122 (ELECTRON-2; Cohort 2, Groups 3, 4, and 6)	Treatment-naive subjects with genotype 3 HCV infection, with or without cirrhosis, received LDV/SOF for 12 weeks or LDV/SOF+RBV for 12 weeks. Treatment-experienced subjects with genotype 3 HCV infection, with or without cirrhosis, received LDV/SOF+RBV for 12 weeks.	Treatment-Naive LDV/SOF 12 Weeks: 16/25 (64.0%) Treatment-Naive LDV/SOF+RBV 12 Weeks: 26/26 (100.0%) Treatment-Experienced LDV/SOF+RBV 12 Weeks: 41/50 (82.0%)	Treatment-Naive LDV/SOF 12 Weeks: 1/4 (25.0%) Treatment-Naive LDV/SOF+RBV 12 Weeks: 6/6 (100.0%) Treatment-Experienced LDV/SOF+RBV 12 Weeks: 16/22 (72.7%)

Gilead acknowledges that 12 weeks of LDV/SOF+RBV in treatment experienced GT 3 patients is not optimal, and they do not intend to recommend the use of 12 weeks LDV/SOF +RBV for treatment experienced GT 3 patients. Gilead proposes that LDV/SOF+RBV for 12weeks for use only in GT 3 patients who are treatment naïve, with and without cirrhosis. However, the Delegate noted that the number of treatment naïve GT 3 subjects treated with 12 weeks of LDV/SOF+RBV was only 26 patients in ELECTRON-2.

Genotypes 4, 5, and 6

For patients with genotypes 4, 5 and 6 HCV infection, SOF+Peg-IFN+RBV for 12 weeks is a treatment option. For those who have failed prior treatment, options are limited. In Studies GS-US-337-1119, GS-US-337-0115, GS-US-337-0122, and CO-US-337-0117, SVR12 rates of 95%, 93%, and 96% have been observed in subjects with GT 4, 5, and 6 HCV infection, respectively, after LDV/SOF therapy for 12 weeks. Based on these data, Gilead proposes that the dosage of LDV/SOF for patients with GT 4, 5, and 6 HCV infections mirror the dosage of LDV/SOF for patients with genotype 1 HCV infection, including those with HCV/HIV co-infection.

Patients with liver transplantation and decompensated cirrhosis

As discussed previously, SOLAR 1 and SOLAR 2 studies have provided good results regarding the efficacy and safety of 12 weeks of SOF/LDV+ RBV for the treatment of CHC patients with liver transplantation (GT 1 and GT 4) and decompensated cirrhosis (GT 1). However, SOLAR-1 and -2 did not include patients with genotypes other than 1 and 4; there are very little data about the efficacy and safety of Harvoni with these patients other genotypes and with varying degrees of liver impairment including pre and post liver transplantation.

For GT 4 subjects with decompensated cirrhosis, regardless of transplantation status, only 18 subjects were evaluated (SVR12 rates of 60.0% and 75.0% after 12 or 24 weeks of treatment, respectively). Of these subjects, 3 relapsed; therefore, insufficient data are available to determine the optimal treatment duration for GT 4 subjects with decompensated liver disease.

Overall, Harvoni is efficacious and safe in certain CHC patient populations as discussed in this Overview. However, the data are still limited in the following settings:

- non-GT 1 patients who previously failed SOF containing regimens
- non-GT 1 cirrhotic patients/non-GT 1 pre and post liver transplant subjects

- non-GT 1 patients with decompensated cirrhosis (cirrhosis CPT C category)
- HIV/HCV co-infected patient other than GT 1 and GT 4 (Study ION-4)
- Relative paucity of women enrolled in these studies, all studies are majority male (especially true of ION-4 the study in HIV/HCV co-infection)
- Paucity of data from populations other than those of White ethnicity.

It is obvious that RBV free and shorter duration therapy is better tolerated, however, in some settings, addition of ribavirin and longer treatment duration is required to achieve higher viral clearance. The addition of ribavirin to 12 weeks of Harvoni is required for treatment experienced patients (GT 1) with compensated cirrhosis who are at high risk of clinical disease progression, for treatment naïve GT 3 infected patients with or without cirrhosis, and GT 1 infected patients who have decompensated cirrhosis irrespective of transplantation status, and GT 1 or 4 infected patients who are liver transplant recipients.

In the proposed Australian PI, the information regarding the ribavirin (when it is required in addition to Harvoni) is presented as a text format and is located under Table 17 (the dose instruction table). The Delegate considers this is not a clear and optimal way to present the dose recommendation. The Delegate is of the view that the dose instruction table in the FDA approved Prescribing Information is clearer and is reflecting accurately the available evidence. Table 17 in the proposed Australian PI should be revised to that effect.

Delegate's considerations

The submitted data are limited in the following settings:

- non-GT 1 patients who previously failed SOF-containing regimens
- non-GT 1 cirrhotic patients/non-GT 1 pre and post liver transplant subjects
- non-GT 1 patients with decompensated cirrhosis
- HIV/HCV co-infected patient other than GT 1 and GT 4
- Relative paucity of women enrolled in these studies, all studies are majority male and paucity of data from populations other than those of White ethnicity.

Proposed action

The Delegate had no reason to say, at this time, that the application should not be approved. However a modified recommendation for dosage and duration may be required pending ACPM discussion.

Condition of registration should include the followings:

- Implement RMP (version 1.1, 23 June 2015, DLP 31 May 2015) with Australian Specific Annex (version 1.2, June 2016) and any future updates as a condition of registration.

The final approval is subject to satisfactory resolutions of any issues relating to the PI and the RMP/ASA.

Request for advisory committee for prescription medicines (ACPM) advice

The committee is requested to provide advice on the following specific issues:

1. Does ACPM consider the submitted data in GT 2 CHC patients adequate to support the approval and proposed dose recommendation for GT 2 CHC patients?

2. Does ACPM consider the submitted data adequate to support the proposed 12 weeks of Harvoni +ribavirin (RBV) for re-treatment of non-GT 1 patients who have previously failed SOF-containing regimens?
3. Does ACPM consider the submitted data in HIV-HCV co-infected GT 1 and GT 4 patients would support the dose recommendation for co-infected subjects of all 6 genotypes?
4. Does ACPM consider the submitted data are adequate to support the proposed 12 weeks of LDV/SOF+RBV for GT 3 patients who are treatment naïve, with and without cirrhosis?
5. Does ACPM support the proposed indication: Harvoni is indicated for the treatment of chronic hepatitis C infection in adults?
6. Does ACPM consider Table 17 in the proposed PI requires amendments?

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.

Response from Sponsor

Summary

Gilead considers that the goal of hepatitis C virus (HCV) drug development is to maximise the sustained virologic response rates at week 12 (SVR12) and provide a cure for HCV infection for all patient populations with a safe and well tolerated regimen. The Harvoni ± ribavirin (RBV) treatment regimens proposed in this application have consistently demonstrated high efficacy and a favourable safety profile in patients with non-genotype 1 HCV infection, patients who have previously failed a sofosbuvir (SOF) -containing regimen, patients with HCV/HIV co-infection, liver transplant recipients with compensated liver disease and in patients with genotype 1 decompensated liver disease. Although there are limited data in some HCV patient subpopulations, available data are consistent across populations and with the established efficacy and safety profile of Harvoni. Based on the totality of data, it is reasonable to suggest that in the various patient subpopulations where limited data are available, treatment with Harvoni will be consistent in achieving high SVR12 rates and that a lack of efficacy would be extremely unlikely. Thus, Harvoni ± RBV addresses an important unmet medical need and provides an opportunity to cure a range of patients with HCV infection who currently have limited or no treatment options.

Background

Harvoni is currently approved for the treatment of patients with chronic genotype 1 HCV infection, including treatment naive and treatment experienced patients, with and without cirrhosis. Gilead has submitted this application to extend the Harvoni indication to patients with non-genotype 1 HCV infection and expand the dosage recommendations to include subpopulations with limited treatment options that are currently excluded from the Harvoni PI.

The data provided within this application demonstrate that treatment with Harvoni ± RBV for 12 weeks is highly efficacious across all genotypes and achieves SVR12 rates comparable to those observed in patients with genotype 1 HCV infection. In patients with genotype 1 HCV infection who have previously failed a SOF-containing regimen, treatment with Harvoni ± RBV for 12 weeks was highly efficacious and comparable to treatment of patients who have previously failed treatment with Peg-IFN + RBV ± PI. In HCV/HIV co-infected patients with genotype 1 and 4 HCV infection, high SVR12 rates comparable to those seen in HCV mono-infected patients were observed following treatment with Harvoni for 12 weeks, irrespective of prior treatment status or the presence or absence of cirrhosis. In liver transplant recipients with genotype 1 and 4 HCV infection and

compensated liver disease, treatment with Harvoni + RBV for 12 and 24 weeks also achieved high SVR12 rates with no significant difference between treatment durations. Patients with genotype 1 HCV infection and decompensated liver disease, regardless of liver transplantation status, also achieved high SVR12 rates following 12 and 24 weeks of treatment with no significant difference between treatment durations. Finally, in treatment experienced patients with genotype 1 HCV infection and cirrhosis, reducing treatment from the currently approved 24 weeks to 12 weeks through the addition of RBV did not meaningfully impact SVR12 rates. Overall, treatment with Harvoni ± RBV achieved consistently high SVR12 rates across patient populations and displayed a safety profile consistent with that known for Harvoni and RBV.

Gilead considers that the established efficacy and safety profile for Harvoni supports extension of the Harvoni indication and expansion of the dosage recommendations to include a range of patient populations with HCV infection. The proposed Harvoni indication is as follows:

> *Harvoni (ledipasvir/sofosbuvir fixed-dose combination) is indicated for the treatment of chronic hepatitis C (CHC) infection in adults (see DOSAGE AND ADMINISTRATION and CLINICAL TRIALS).*

ACPM advice sought by the TGA Delegate

1. *Does ACPM consider the submitted data in GT 2 CHC patients adequate to support the approval and proposed dose recommendation for GT 2 CHC patients?*

Gilead acknowledges the number of patients with GT 2 HCV infection in the study GS-US-337-1468 (LEPTON) was limited however when the totality of data are considered, Gilead believes the available data support the proposed regimen of Harvoni for 12 weeks in patients with GT 2 HCV infection with or without cirrhosis.

The efficacy results achieved in the study GS-US-337-1468 (LEPTON) following treatment with Harvoni for 12 weeks in genotype 2 patients were comparable to those achieved in patients with other HCV genotypes, including genotype 1, where there is a large body of data available. In this study, no patients had on-treatment virologic failure or virologic relapse. The only patient who did not achieve SVR12 withdrew consent and prematurely discontinued from the study after receiving a single dose of Harvoni. All patients with pre-treatment NS5A and NS5B resistance associated variants (RAVs; defined as those specific amino acid substitutions known to cause a phenotypic shift in EC_{50} in vitro) and resistance associated polymorphisms (RAPs; defined as any amino acid change (polymorphism) from genotype-specific reference at positions known to be associated with resistance) achieved SVR12. These virologic observations are consistent with those known for Harvoni and seen in patients with other genotypes. Harvoni was well tolerated in these patients with low rates of serious adverse events (SAEs) and laboratory abnormalities, and no discontinuations due to adverse events (AEs), pregnancies, or death.

The only approved regimen for the treatment of patients with genotype 2 HCV infection in Australia is SOF + RBV for 12 weeks. The SVR12 rates observed following treatment with Harvoni for 12 weeks are comparable to those observed with SOF + RBV (FISSION study: 97% (68/70 patients); POSITRON study: 93% (101/109 patients); FUSION study: 86%; 31/36 patients). The established efficacy profile of SOF, one of the components of Harvoni, provides further reassurance of the efficacy of Harvoni in genotype 2 patients.

Gilead notes that the SVR12 rate achieved in patients with genotype 2 HCV infection following treatment with Harvoni for 12 weeks is one of the highest achieved to date for this population. Available data, although limited, suggests that treatment with Harvoni will be consistent in achieving high SVR12 rates in these patients and that a lack of efficacy would be extremely unlikely. Gilead believes Harvoni offers a safe, tolerable, efficacious

RBV-free regimen and is an important advance for genotype 2 patients who currently have limited or no treatment options.

2. *Does ACPM consider the submitted data adequate to support the proposed 12 weeks of Harvoni +ribavirin (RBV) for re-treatment of non-GT 1 patients who have previously failed SOF-containing regimens?*

Although treatment with SOF + RBV ± Peg-IFN regimens is efficacious, the extensive number of patients being treated with these regimens has resulted in a pool of patients who have, nevertheless, failed these regimens. There are currently limited options for these patients and given the unmet medical need, Gilead believes that Harvoni provides an important treatment option.

Virologic evidence suggests that the primary mode of resistance to SOF is the development of the S282T mutation. This mutation develops rarely and is rapidly overgrown by wild-type virus, suggesting that patients who have failed SOF can be retreated with a SOF containing regimen. The retreatment studies submitted within this application are concordant with this virologic observation and demonstrate that Harvoni ± RBV is efficacious in this patient population. In studies GS-US-337-1118, GS-US-337-0115 (ION-4), and GS-US-337-0122 (ELECTRON-2), treatment with Harvoni ± RBV for 12 weeks resulted in high SVR12 rates. No effect of NS5A RAPs or RAVs on SVR12 was observed, and importantly, no effect of NS5B RAPs on SVR12 was observed. These findings suggest that previous exposure to SOF does not impact the efficacy of Harvoni.

Clinical virology analyses performed in patients with all HCV genotypes using data from six Harvoni Phase II and III studies (GS-US-337-0115 (ION-4); GS-US-337-0121 (SIRIUS); GS-US-337-1118; GSUS- 337-0122 (ELECTRON-2); GS-US-337-1468 (LEPTON); GS-US-337-1119) support the retreatment study findings. These analyses did not indicate an effect of NS5A or NS5B RAPs or RAVs on SVR12. Overall, high SVR12 rates were achieved in the presence of baseline NS5A or NS5B RAPs irrespective of patient population and genotype. These findings suggest that the virologic outcomes in non-genotype 1 patients that have previously failed a SOF containing regimen would be consistent with those seen in genotype 1 patients and that Harvoni would be efficacious in these patients.

In summary, when the totality of data is considered, Harvoni would be expected to have a similar virologic effect in non-genotype 1 patients that have failed a SOF containing regimen as in genotype 1 patients. Given the unmet medical need in the increasing number of patients who have previously failed a SOF containing regimen and the known efficacy and safety profile of Harvoni, Gilead believes that Harvoni provides an important treatment option for these patients.

3. *Does ACPM consider the submitted data in HIV-HCV co-infected GT 1 and GT 4 patients would support the dose recommendation for co-infected subjects of all 6 genotypes?*

Gilead acknowledges the data in patients with HCV/HIV co-infection is limited to patients with GT 1 and 4 HCV infection. Available evidence suggests that direct acting antivirals (DAAs) specific for the treatment of HCV infection; achieve comparable virologic responses in HCV/HIV co-infected patients and HCV mono-infected patients. This evidence is supported by study GS-US-337-0115 (ION-4) where treatment with Harvoni for 12 weeks resulted in high and similar SVR12 rates in treatment naive and treatment experienced HCV/HIV co-infected patients irrespective of cirrhosis and antiretroviral regimen, and across sub-populations, with the exception of black patients who achieved lower SVR12 rates (89.6%) than the overall population. This difference in efficacy, by race, has not been observed in other studies of Harvoni including those in similar populations, and is not supported by pharmacokinetic findings. Importantly, the SVR12 rates observed in HCV/HIV co-infected patients were comparable to those observed in HCV mono-infected patients. Additionally, the pharmacokinetic data in this study did not indicate any clinically relevant differences in SOF, GS-331007 (predominant circulating

SOF metabolite), or ledipasvir (LDV) exposure parameters in HCV/HIV co-infected patients on 3 different antiretroviral regimens when compared to HCV mono-infected patients. The safety profile in HCV/HIV co-infected patients was also consistent with the known safety profile of Harvoni.

The majority of treatment regimens approved for use in HCV/HIV co-infected patients require the use of RBV ± Peg-IFN, with the exception of SOF + daclatasvir (DCV) for patients with genotype 1 or 3 HCV infection and SOF + asunaprevir for patients with genotype 1 HCV infection. The use of RBV and Peg-IFN is associated with significant toxicities that lead to tolerability and adherence issues. Up to 70% of patients with HCV/HIV co-infection are ineligible for treatment with IFN containing regimens due to absolute or relative contraindications. There is therefore an unmet medical need for simple Peg-IFN and RBV free treatment options that are safe, efficacious and have fewer drug-drug interactions.

Harvoni has displayed consistently high SVR12 rates across all genotypes and patient populations, and a favourable safety profile. The data available for Harvoni in HCV/HIV co-infected patients with genotype 1 and 4 HCV infection demonstrate similar efficacy and safety in both genotypes and consistent SVR12 rates to HCV mono-infected patients. As such, there is no reason to suggest that the efficacy of Harvoni would be different in HCV/HIV co-infected patients with genotype 2, 3, 5 and 6 HCV infection.

Harvoni provides an important treatment option for HCV/HIV co-infected patients, especially for patients that currently have no treatment option or for those where RBV and IFN treatments are not a viable option. Gilead believes that the available data supports a treatment regimen and duration for HCV/HIV co-infected patients that mirrors that of HCV mono-infected patients. This is consistent with dosage recommendations for Daklinza, another DAA used for treatment of HCV infection.

4. *Does ACPM consider the submitted data are adequate to support the proposed 12 weeks of LDV/SOF+RBV for GT 3 patients who are treatment naïve, with and without cirrhosis?*

Gilead acknowledges the number of patients with GT 3 HCV infection in the study GS-US-337-0122 (ELECTRON-2) was limited, however Gilead believes the available data support the proposed regimen of Harvoni + RBV for 12 weeks in treatment naïve patients with genotype 3 HCV infection with or without cirrhosis.

Study GS-US-337-0122 (ELECTRON-2) shows that high SVR12 rates were achieved in patients with and without cirrhosis following treatment with Harvoni + RBV for 12 weeks. The SVR12 rates were comparable to those observed in other HCV genotypes and the safety profile did not differ from the known safety profile of Harvoni and RBV. These findings are supported by a study conducted in Canada in treatment naïve, genotype 3 that was presented at European Association for the Study of the Liver (EASL) in April this year. In this study, an overall SVR12 of 89% (99/111 patients) was reported and SVR12 rates of 94% (66/77 patients) and 79% (31/39 patients) were reported in patients with or without cirrhosis, respectively.

The currently approved regimens for treatment naive patients with genotype 3 HCV infection are SOF + RBV for 16 to 24 weeks and SOF + DCV for 12 weeks. The SVR12 rates reported in study GS-US-337-0122 (ELECTRON-2) are comparable to those observed following treatment with SOF + RBV for 24 weeks (94%; 99/105 patients) and SOF + DCV for 12 weeks (99%; 100/101 patients). The established efficacy profile of SOF and RBV provides further reassurance of the efficacy of Harvoni in genotype 3 patients.

The available data in genotype 3 patients, when considered with the body of efficacy data for Harvoni, which has consistently demonstrated high SVR12 rates and a favourable safety profile across all genotypes and patient populations, supports the use of Harvoni in

these patients. Harvoni + RBV provides a shorter treatment option than the SOF + RBV option and an alternative option to SOF + DCV.

5. *Does ACPM support the proposed indication: Harvoni is indicated for the treatment of chronic hepatitis C infection in adults?*

Gilead believes that the available efficacy and safety data along with the known efficacy and safety profile of Harvoni support the revised indication proposed in this application.

The Dosage and Administration section of the proposed PI has been updated as per the Delegate's recommendation (see response to Question 6) and clearly provides the prescriber dosage recommendations for each population. Additionally, the Clinical Trials section provides the prescriber information on the efficacy of Harvoni in different populations. To direct the prescriber to these sections of the PI, Gilead proposes to add cross references to the indication (see below). Gilead wishes to note that the proposed indication for Harvoni mirrors that of Daklinza, which is approved for treatment of multiple genotypes, but not all, of HCV infection.

> *Harvoni is indicated for the treatment of chronic hepatitis C infection in adults (see DOSAGE AND ADMINISTRATION and CLINICAL TRIALS).*

6. *Does ACPM consider Table 17 in the proposed PI requires amendments?*

Gilead has noted the Delegate's comments on the proposed PI in the Delegate's Overview and has revised the PI accordingly.

Dosage and Administration section:

- The Dosage and Administration table has been revised so that it is presented similarly to the US prescribing information as suggested by the Delegate. The treatment regimens and durations presented are consistent with those proposed by Gilead throughout this response.
- A sentence regarding the use of Harvoni in patients with HCV/HIV co-infection has been added as suggested by the Delegate. Gilead proposes to add this sentence above the Dosage and Administration table, consistent with the US prescribing information.
- A sentence regarding the insufficient data in genotype 4 patients with decompensated liver disease has been added as suggested by the Delegate.

Clinical Trials section:

- The data for genotype 2, 3, 4, 5 and 6 HCV infection have been presented in tables consistent with the European Summary of Product Characteristics as suggested by the Delegate.
- A sentence regarding the absence of data in non-genotype 1 patients who have previously failed a sofosbuvir-containing regimen has been added as suggested by the Delegate.

A clean and annotated copy of the proposed PI is provided.

Summary of other issues raised by the TGA Delegate

The Delegates' comments are presented in bold print, and are followed by Gilead's response. Issues discussed in the responses above have not been repeated in this section.

The submitted data are limited in the following settings:

- ***non-GT 1 cirrhotic patients/non-GT 1 pre and post liver transplant subjects***
- ***Non-GT 1 cirrhotic patients***

As discussed throughout this response, Gilead believes that the totality of data support the use of Harvoni in non-genotype 1 patients including those with cirrhosis. Harvoni has

demonstrated consistently high efficacy and a favourable safety profile across genotypes and patient populations. Data in patients with cirrhosis have been presented for each genotype, and although the number of patients is small, the SVR12 rates achieved are similar to those observed in patients without cirrhosis and consistent across genotypes. These findings suggest that treatment with Harvoni is consistent in achieving high SVR12 rates and that a lack of efficacy would be extremely unlikely.

In the more difficult to treat treatment experienced patients with cirrhosis, study GS-US-337-0121 (SIRIUS) demonstrated that treatment with Harvoni + RBV for 12 weeks is as effective as treatment with Harvoni for 24 weeks providing these patients with a shorter treatment option. While RBV contributes to additional AEs, these AEs are largely mild to moderate in severity, and should not preclude the availability of this regimen to patients.

Harvoni provides an important treatment option and an opportunity for cure in these patients who currently have limited options and that are at high risk of end stage liver disease and hepatocellular carcinoma.

- ***Non-GT 1 pre and post liver transplant subjects***

The small number of patients able to obtain a liver transplant, and the limited prognosis of even those who receive a transplant, highlight the need for safe and efficacious HCV therapy for patients with recurrent HCV infection post-liver transplantation.

In the studies GS-US-337-0123 (SOLAR-1) and GS-US-337-0124 (SOLAR-2), post transplantation patients with genotype 1 and 4 HCV infection and compensated liver disease achieved high SVR12 rates after 12 weeks of treatment. These SVR12 rates were consistent across the two genotypes and similar to the SVR12 rates observed in other patient populations. These studies also showed that treatment with Harvoni + RBV was generally safe and well tolerated in this population.

The efficacy of Harvoni in patients with genotype 5 and 6 HCV infection and compensated liver disease has been established in studies GS-US-337-1119 and GS-US-337-0122 where these patients achieved high SVR12 rates comparable to those observed in patients with genotype 1 HCV infection. Given that post-transplantation patients with compensated liver disease have an extremely urgent need for treatment, and given the similarity in efficacy between patients with genotypes 1, 4, 5, or 6 HCV infection, it is reasonable to anticipate that post-transplantation patients with compensated liver disease and genotype 5 or 6 HCV infection will benefit from treatment with Harvoni + RBV. Gilead believes Harvoni is an important treatment option and addresses an unmet medical need in these patients that have been fortunate enough to receive a liver transplant and who currently have limited treatment options.

- ***non-GT 1 patients with decompensated cirrhosis***

Gilead wishes to clarify that it does not currently intend to make a recommendation for non-genotype 1 patients with decompensated cirrhosis. As acknowledged by the Delegate, data from genotype 4 patients with decompensated cirrhosis is available however there it is insufficient to determine the optimal treatment duration for these patients.

- ***Relative paucity of women enrolled in these studies, all studies are majority male and paucity of data from populations other than those of White ethnicity***

The lower number of women and patients with ethnicities other than White ethnicity enrolled in the studies presented in this application are reflective of patient demographics. The recent Harvoni Periodic Benefit-Risk Evaluation Report submitted to the TGA in July 2016 provides prescription data from the US and Europe which shows that the majority of patients are male (approximately 60 to 70%), and of White ethnicity (56% in the US and 85% in Europe).

In general, the overall high SVR12 rates and the small number of patients in subgroups have limited the ability to assess the relationship between SVR12 and demographic characteristics. Pre-specified analyses of subgroups in studies GS-US-337-1119, GS-US-337-0115, and GS-US-337-0122 indicated that SVR12 rates were generally consistent with those observed in the overall population, with high SVR12 rates observed in most subgroups. The findings are consistent with the subgroup analyses performed in the Harvoni registration studies GS-US-337-0102 (ION-1), GS-US-337-0108 (ION- 3) and GS-US-337-0109 (ION-2). In study GS-US-337-0115, Black patients had lower SVR12 rates (89.6%) than the overall population however this observation was not seen in other studies.

Based on the totality of data, there is no reason to suggest that demographic characteristics impact the overall efficacy and safety conclusions for Harvoni.

Conclusion

The efficacy of Harvoni ± RBV has been shown to be consistently high across all genotypes and subpopulations of HCV infected patients. The only subpopulation where there are insufficient data to determine the optimal treatment duration is in non-genotype 1 patients with decompensated liver disease. In the other subpopulations questioned by the Delegate, there is no reason to expect that a lack of efficacy can be anticipated. Available data in these populations, although limited, consistently demonstrated high SVR12 rates. Gilead considers the overall benefit-risk ratio for these patients to be beyond question. Harvoni ± RBV addresses an important unmet medical need and provides an opportunity for cure in a number of patient populations that currently have limited or no other treatment options.

Advisory Committee Considerations

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

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Harvoni fixed dose combination tablet containing 90 mg ledipasvir (LDV)/400 mg sofosbuvir (SOF) to have an overall positive benefit–risk profile for the Delegate's amended indication;

> *Harvoni (ledipasvir/sofosbuvir fixed-dose combination) is indicated for the treatment of chronic hepatitis C (CHC) genotype (GT) 1, 4, 5, 6 infection in adults.*

In making this recommendation the ACPM

- Noted that in Australia, HCV GT 1 and GT 3 are the most common genotypes; the prevalence of GT 3 is higher than in Europe and is similar to that in the US.
- Noted that the submitted in vitro data suggested lower activity of ledipasvir in GT 2 and 3.
- Expressed concern that Harvoni is not registered for the treatment of HCV GT 2 patients in any jurisdiction at the time of this approval.
- Expressed concerns that there are limited efficacy data in some HCV patient subpopulations including patients with HCV GT 2 and GT 3.
- Was of the view that Harvoni addresses an important unmet medical need in uncommon genotypes (4, 5, and 6).

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI.

Specific Advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *Does ACPM consider the submitted data in GT 2 CHC patients adequate to support the approval and proposed dose recommendation for GT 2 CHC patients?*

The ACPM noted that the only available data on GT 2 are from 26 patients who had LDV/SOF treatment for 12 weeks. Although SVR12 was 96% in this small patient sample, the low number of patients provides insufficient evidence to support registration.

2. *Does ACPM consider the submitted data adequate to support the proposed 12 weeks of Harvoni +ribavirin (RBV) for re-treatment of non-GT 1 patients who have previously failed SOF-containing regimens?*

The ACPM agreed, that the submitted data is adequate to support the proposed 12 weeks of Harvoni + ribavirin (RBV) for re-treatment of patients with genotypes 4, 5 and 6 who have previously failed SOF-containing regimens, provided that these patients were failing SOF without another non-DDA.

3. *Does ACPM consider the submitted data in HIV-HCV co-infected GT 1 and GT 4 patients would support the dose recommendation for co-infected subjects of all genotypes?*

There is sufficient data on GT 1 and GT 4 from the ION-4 study but none on GT 2, 3, 5, 6. The higher SVR12 does provide some reassurance that results from non-co-infected patients may be generalizable to GT 5 and GT 6 patients.

4. *Does ACPM consider the submitted data are adequate to support the proposed 12 weeks of LDV/SOF+RBV for GT 3 patients who are treatment naïve, with and without cirrhosis?*

The submitted evidence (26 treatment naïve individuals receiving proposed 12 weeks RBV+ Harvoni) is insufficient to prove adequate evidence of efficacy especially considering the suboptimal (64% to 82% SVR12) in the samples treated with Harvoni in the absence of RBV or in the presence of prior treatment. This is of major concern given the high prevalence of GT 3 in the Australian population.

5. *Does ACPM support the proposed indication: Harvoni is indicated for the treatment of chronic hepatitis C infection in adults?*

The ACPM noted that the submitted evidence is not sufficient to support registration for HCV GT 2 and GT 3.

6. *Does ACPM consider Table 17 in the proposed Product Information requires amendments?*

The ACPM support the dosing table proposed by the Delegate, but advises to delete the row relating to genotype 3.

The opinion of 8 weeks treatment for naïve non cirrhotics with favourable virological markers should be referred in as in current PI.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Harvoni ledipasvir / sofosbuvir 90 mg / 400 mg tablet, indicated for:

> *Harvoni (ledipasvir/sofosbuvir fixed-dose combination) is indicated for the treatment of chronic hepatitis C (CHC) infection in adults.*
>
> *(see Precautions and clinical trials sections for information on the available data for HCV patients of each genotype, see dosage and administration section for recommended regimens and treatment durations for different patient subgroups).*

Specific conditions of registration applying to these goods

The Harvoni containing ledipasvir/sofosbuvir 90 mg/400 mg Risk Management Plan (RMP): Version 1.1, 23 June 2015, (DLP 31 May 2015) with Australian Specific Annex (version 1.2, June 2016), included with submission PM-2016-03086-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI for Harvoni 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>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au