# EU Risk Management Plan for Sovaldi® (Sofosbuvir)

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## RMP version to be assessed as part of this application:

| Version number: | Data lock point for this RMP: | Date of final sign off: |
|---|---|---|
| 14.0 | 15 July 2025 | 08 Dec 2025 |

**Rationale for submitting an updated RMP:**

Updated the list of safety concerns to remove the important identified risks: "Cardiac arrhythmia (bradycardia) when SOF-containing regimens are used concomitantly with amiodarone" and "HBV reactivation in HBV/HCV coinfected patients", and to remove targeted follow-up questionnaire related to the important identified risk of cardiac arrhythmia (bradycardia) when SOF-containing regimens are used concomitantly with amiodarone.

## Summary of significant changes in this RMP:

| Part | Module/Annex | Significant changes to RMP |
|---|---|---|
| Part I | Table Part I.1: Product Overview | None |
| Part II<br>Safety Specification | Section Part II: Module SI: Epidemiology of the indication and target populations(s) | None |
| | Section Part II: Module SII: Non-clinical part of the safety specification | None |
| | Section Part II: Module SIII: Clinical study exposure | None |
| | Section Part II: Module SIV: Populations not studied in clinical studies | None |
| | Section Part II: Module SV: Postauthorization experience | Information updated with Postmarketing exposure data |
| | Section Part II: Module SVI: Additional EU requirements for the safety specification | None |
| | Section Part II: Module SVII: Identified and potential risks | Updated to reflect the removal of the important identified risks "Cardiac arrhythmia (bradycardia) when SOF-containing regimens are used concomitantly with amiodarone" and "HBV reactivation in HBV/HCV coinfected patients". |

| Part | Module/Annex | Significant changes to RMP |
|---|---|---|
| | Section Part II: Module SVIII: Summary of the safety concerns | Updated to reflect the removal of the important identified risks “Cardiac arrhythmia (bradycardia) when SOF-containing regimens are used concomitantly with amiodarone” and “HBV reactivation in HBV/HCV coinfected patients”. |
| Part III<br>Pharmacovigilance Plan | | Removal of targeted questionnaire collecting information on bradyarrhythmia. |
| Part IV<br>Plan for post-authorization efficacy studies | | None |
| Part V<br>Risk Minimization Measures | | Updated to reflect the removal of the important identified risks “Cardiac arrhythmia (bradycardia) when SOF-containing regimens are used concomitantly with amiodarone” and “HBV reactivation in HBV/HCV coinfected patients”. |
| Part VI<br>Summary of RMP | | Updated to reflect the removal of the important identified risks “Cardiac arrhythmia (bradycardia) when SOF-containing regimens are used concomitantly with amiodarone” and “HBV reactivation in HBV/HCV coinfected patients”. |
| Part VII<br>Annexes | | Updated Annex 4 to reflect the removal of the targeted questionnaire for bradyarrhythmia.<br>Updated Annex 8 to reflect the changes in this RMP. |

## Other RMP versions under evaluation:

| RMP Version number | Submitted on | Procedure number |
|---|---|---|
| None | Not applicable | Not applicable |

## Details of the currently approved RMP:

| Version number: | Approved with procedure | Date of approval (opinion date) |
|---|---|---|
| 12.0 | EMEA/H/C/002798/WS2356/0081 | 12 January 2023 (CHMP Opinion) |

| | |
|---|---|
| **QPPV name:** | Rainer Heissing |
| **QPPV signature:** | The RMP has been reviewed and approved by the QPPV and the electronic signature is on file. |

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# GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

| | |
|---|---|
| ADR | Adverse drug reaction |
| AFP | Alpha-fetoprotein |
| AE | Adverse event |
| A-H | Atrial-to-His bundle |
| ALT | Alanine aminotransferase |
| ANRS | Agence Nationale de Recherche sur le Sida e les hépatitis (French National Agency for AIDS and Hepatitis Research) |
| AST | Aspartate aminotransferase |
| ATC | Anatomical Therapeutic Chemical classification system |
| AUC | Area under the curve |
| $AUC_{tau}$ | Area under the curve from time 0 to the end of the dosing interval |
| $AUC_{inf}$ or $AUC_{0\text{-}inf}$ | Area under the curve from time 0 to infinity |
| BCRP | Breast cancer resistance protein |
| BSEP | Bile salt export pump |
| CDC | Centers for Disease Control |
| CHC | Chronic hepatitis C |
| CHMP | Committee for Medicinal Products for Human Use |
| $C_{max}$ | Maximum concentration |
| $C_{min}$ | Minimum concentration |
| CPT | Child-Pugh-Turcotte (score) |
| CYP | Cytochrome P450 |
| DA | *N*-desethylamiodarone |
| DAA | Direct acting antiviral |
| DCV | Daclatasvir |
| DDI | Drug-drug interaction |
| DNA | Deoxyribonucleic acid |
| ECG | Electrocardiogram |
| eCTD | Electronic common technical document |
| EASL | European Association for the Study of the Liver |
| EC | European Commission |
| EEA | European Economic Area |
| EMA | European Medicines Agency |
| EPAR | European Public Assessment Report |
| EPC | Epclusa (sofosbuvir/velpatasvir) |
| ESRD | End-stage renal disease |
| EU | European Union |
| FDA | Food and Drug Administration |
| FDC | Fixed dose combination |
| GI | Gastrointestinal |

| | |
|---|---|
| GLE | Glecaprevir |
| GT | Genotype |
| GZR/EBR | Grazoprevir/elbasvir |
| HBcAg | Hepatitis B core antigen |
| HBsAg | Hepatitis B surface antigen |
| HBV | Hepatitis B virus |
| hCav | Human L-type calcium channel |
| HCC | Hepatocellular carcinoma |
| hHCN4 | Human hyperpolarization-activated, cyclic nucleotide-gated channel 4 |
| HCP | Healthcare professional |
| HCV | Hepatitis C virus |
| HIV | Human Immunodeficiency Virus |
| HVN | Harvoni (ledipasvir/sofosbuvir) |
| IDU | Injection drug use/Injection drug user |
| IFN | Interferon |
| IL28B | Interleukin 28B |
| INN | International nonproprietary name |
| IRB | Institutional Review Board |
| LDV | Ledipasvir (GS-5885) |
| MAA | Marketing Authorization Application |
| MAH | Marketing Authorization Holder |
| MATE | Multidrug and toxin extrusion protein |
| MoH | Ministry of Health |
| mtDNA | Mitochondrial deoxyribonucleic acid |
| NA | Not applicable |
| NASH | Nonalcoholic steatohepatitis |
| NDA | New drug application |
| NIAID | National Institute of Allergy and Infectious Diseases |
| NOAEL | No observed adverse effect level |
| NS3/4A | Nonstructural protein 3/4A |
| NS5A | Nonstructural protein 5A |
| NS5B | Nonstructural protein 5B |
| OAT | Organic anion transporter |
| OATP | Organic anion transporting polypeptide |
| OCT | Organic cation transporter |
| OMB/PTV/r | Ombitasvir/paritaprevir/ritonavir |
| OMB/PTV/r + DSV | Ombitasvir/paritaprevir/ritonavir + dasabuvir |
| PASS | Post-authorization safety study |
| PBRER | Periodic benefit risk evaluation report |
| PD | Pharmacodynamics |

| | |
|---|---|
| PEG | Pegylated interferon-alfa-2a/b |
| Pgp | P-glycoprotein |
| PI | Protease inhibitor |
| PIB | Pibrentasvir |
| PIL | Patient Information Leaflet |
| PK | Pharmacokinetics |
| PRAC | Pharmacovigilance Risk Assessment Committee |
| PSUR | Periodic Safety Update Report |
| PT | Preferred Term |
| Q1/Q2/Q3/Q4 | Quarter 1/2/3/4 |
| QPPV | Qualified Person for Pharmacovigilance |
| QT | Electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur |
| QTc | QT interval corrected for heart rate |
| RBV | Ribavirin |
| RMP | Risk Management Plan |
| RNA | Ribonucleic acid |
| SmPC | Summary of Product Characteristics |
| SMV | Simeprevir |
| SOF | Sofosbuvir |
| SVR | Sustained virologic response |
| UGT | Uridine diphosphate glucuronosyltransferase |
| UGT1A | UDP-glucuronosyltransferase 1 family, polypeptide A |
| UK | United Kingdom |
| US | United States |
| USA | United States of America |
| VEGF | Vascular endothelial growth factor |
| VEL | Velpatasvir, GS-5816 |
| VSV | Vosevi (sofosbuvir/velpatasvir/voxilaprevir) |
| WHO | World Health Organization |

# PART I: PRODUCT OVERVIEW

## Table Part I.1. Product Overview

| | |
|---|---|
| **Active substance(s) (INN or common name):** | Sofosbuvir |
| **Pharmaco-therapeutic group(s) (ATC Code):** | Direct Acting Antivirals<br>(J05AP08) |
| **Marketing Authorization Holder** | Gilead Sciences Ireland UC |
| **Medicinal products to which this RMP refers:** | 1 |
| **Invented name(s) in the European Economic Area (EEA)** | Sovaldi |
| **Marketing authorization procedure** | Centralized |
| **Brief description of the product** | *Chemical class*<br>Sofosbuvir: Nonstructural protein 5B (NS5B) inhibitor |
| | *Summary of mode of action*<br>Sofosbuvir is a nucleotide analogue that potently inhibits genotype 1 to 6 hepatitis C virus (HCV) ribonucleic acid (RNA) replicons in vitro and has demonstrated high sustained virological response (SVR) rates when administered with ribavirin (RBV) and with pegylated interferon (PEG) + RBV. |
| | *Important information about its composition*<br>None |
| **Hyperlink to the Product Information** | Sovaldi Summary of Product Characteristics (SmPC) |
| **Indication(s) in the EEA** | Current: Sovaldi is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults and pediatric patients aged 3 years and above. |
| | Proposed: Not applicable |

<table>
<tr><td>Dosage in the EEA</td><td>Current: The recommended dose of Sovaldi in adults is one 400 mg tablet, taken orally, once daily with food. Sovaldi should be used in combination with other medicinal products.<br>The recommended dose of Sovaldi in pediatric patients aged 3 years and above is based on weight (as detailed in Table 1). Sovaldi should be taken with food.<br>Sovaldi oral granules are available for patients for the treatment of chronic HCV-infection in pediatric patients aged 3 years and above having difficulty in swallowing film-coated tablets.<br>Table 1. <u>Dosing for pediatric patients aged 3 years and above using Sovaldi tablets or oral granules</u>
<table>
<tr><th>Body Weight (kg)</th><th>Dosing of Sovaldi Tablets or Oral Granules</th><th>Sofosbuvir Daily Dose</th></tr>
<tr><td>≥ 35</td><td>one 400 mg tablet once daily<br>or<br>two 200 mg tablets once daily<br>or<br>two 200 mg sachets of granules once daily</td><td>400 mg /day</td></tr>
<tr><td>17 to < 35</td><td>one 200 mg tablet once daily<br>or<br>one 200 mg sachets of granules once daily</td><td>200 mg/day</td></tr>
<tr><td>< 17</td><td>one 150 mg sachets of granules once daily</td><td>150 mg/day</td></tr>
</table>
Proposed: Not applicable</td></tr>
<tr><td>Pharmaceutical form(s) and strengths</td><td>Current: Film-coated tablet/400mg<br>Film-coated tablet/200 mg<br>Granules sachet/200 mg<br>Granules sachet/150 mg<br>Proposed: Not applicable</td></tr>
<tr><td>Is/Will the product be subject to additional monitoring in the EU?</td><td>No</td></tr>
</table>

# PART II: SAFETY SPECIFICATION

# PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

## SI.1. Hepatitis C

### SI.1.1. Incidence

The rate of new hepatitis C virus (HCV) infections is difficult to determine due to the asymptomatic nature of acute infections. Worldwide, it is estimated that there were 1.75 million new HCV infections in 2015 {The Polaris Observatory HCV Collaborators 2017, World Health Organization (WHO) 2017}. Unsafe healthcare procedures and injection drug use are the leading causes of new HCV infections globally{World Health Organization (WHO) 2017}.

The World Health Organization (WHO) reports that the Eastern Mediterranean Region and the European region have higher rates of infection compared to other world regions {World Health Organization (WHO) 2017} (Table SI.1). Variation in HCV incidence is largely determined by differences in practices, transmission risk factors, and access to care by region (Table SI.1).

**Table SI.1. Incidence Estimates of HCV Infection by WHO Region {World Health Organization (WHO) 2017}**

| | Incidence rate per 100,000 | | Total number (000) | |
|---|---|---|---|---|
| **WHO region** | **Best estimate** | **Uncertainty interval** | **Best estimate** | **Uncertainty interval** |
| African region | 31.0 | 22.5-54.4 | 309 | 222-544 |
| Region of the Americas | 6.4 | 5.9-7.0 | 63 | 59-69 |
| Eastern Mediterranean Region | 62.5 | 55.6-65.2 | 409 | 363-426 |
| European Region | 61.8 | 50.3-66.0 | 565 | 460-603 |
| South-East Asia Region | 14.8 | 12.5-26.9 | 287 | 243-524 |
| Western Pacific Region | 6.0 | 5.6-6.6 | 111 | 104-124 |
| **Global** | 23.7 | 21.3-28.7 | 1,751 | 1,572-2,120 |

### SI.1.2. Prevalence

The prevalence of HCV infection worldwide is estimated to be 1% (approximately 71 million people) and varies considerably among different regions {World Health Organization (WHO) 2017}. Estimates of HCV viraemic prevalence through modelling found that, in 2015, the range of prevalence estimates by country spanned from 0.1% in the Netherlands to as high as 7.0% in Gabon {The Polaris Observatory HCV Collaborators 2017}.

The WHO estimates that HCV prevalence in Europe is approximately 1.5%, corresponding to 14 million people living with HCV {World Health Organization (WHO) 2017} (Table SI.1). The highest viraemic prevalence in 2015 was observed in Eastern Europe (3.3%, 95% Uncertainty Interval 2.1-3.4) and the lowest was observed in Western Europe (0.5%, 95% Uncertainty Interval 0.4-0.8) {The Polaris Observatory HCV Collaborators 2017}. In Central Europe, the viraemic prevalence was estimated to be 1.1% in 2015 (95% Uncertainty Interval 0.8-1.0).

The available data from Europe indicate a wide variation in viraemic prevalence between countries, ranging from 0.1% to 3.3% {The Polaris Observatory HCV Collaborators 2017}. The lowest HCV prevalence estimates (0.2% or lower) were observed in the Netherlands and Austria and the highest (2.0% or higher) were from Romania, Latvia and Russia.

The true prevalence is likely to be higher as general population studies may exclude high-risk subgroups like active injection drug users (IDUs), the homeless, the incarcerated, and veterans. The HCV infection rate is substantially higher in these subgroups as illustrated by a study that showed that HCV prevalence among prisoners in Spain was 22.7% {Saiz de la Hoya 2011}. Studies have shown that the overall prevalence is higher than national estimates when these subgroups are considered {Chak 2011, Gish 2005}.

Injection drug use has become the main risk for HCV transmission in developed countries with well-established HCV screening programs of blood products and lower HCV prevalence. Among 71 million HCV-infected persons, 5.6 million (8%) currently inject drugs {World Health Organization (WHO) 2017}. For example, in Northern European countries such as Norway and Sweden, or in the United Kingdom (UK) or Canada, IDU is the main risk factor for HCV transmission, accounting for more than half of HCV-infected patients (ie, Norway 67%, Sweden 65%, Canada 58% and UK 90%). In some countries with increasing HCV prevalence, the increase may be explained by a dramatic increase in IDU {Cornberg 2011}.

Globally, HCV genotype 1 is the most prevalent, accounting for 44% of all infections, followed by genotype 3 (25% of all infections) and genotype 4 (15% of all infections) {The Polaris Observatory HCV Collaborators 2017}. Infection with HCV genotype 1 accounts for the majority (60%) of infections in high-income and upper-middle income countries; in contrast, genotype 3 is common in lower middle-income countries (36%) and genotype 4 is common in low-income countries (45%).

**Table SI.2. Prevalence estimates of HCV infection by WHO region {World Health Organization (WHO) 2017}**

| | Estimates of the prevalence of HCV infection (%) | | | Estimated number of persons living with HCV (millions) | | |
|---|---|---|---|---|---|---|
| | | Uncertainty interval | | | Uncertainty interval | |
| **WHO region** | **Best** | **Lower** | **Higher** | **Best** | **Lower** | **Higher** |
| African region | 1.0 | 0.7 | 1.6 | 11 | 7 | 16 |
| Region of the Americas | 0.7 | 0.6 | 0.8 | 7 | 6 | 8 |
| Eastern Mediterranean Region | 2.3 | 1.9 | 2.4 | 15 | 13 | 15 |
| European Region | 1.5 | 1.2 | 1.5 | 14 | 11 | 14 |
| South-East Asia Region | 0.5 | 0.4 | 0.9 | 10 | 8 | 18 |
| Western Pacific Region | 0.7 | 0.6 | 0.8 | 14 | 10 | 15 |
| **Global** | 1.0 | 0.8 | 1.1 | 71 | 62 | 79 |

### SI.1.3. Demographics of the Population in the Authorized Indication

#### SI.1.3.1. HCV Infection by Gender

The rate of chronicity in HCV infection appears to be lower in women, particularly younger women. Being of the male sex has been associated with accelerated progression of hepatic fibrosis among those infected with HCV {Shepard 2005}.

#### SI.1.3.2. Hepatitis C Infection by Age

Worldwide, prevalence rates tend to increase with age and peak in ages 55-64 years {Alter 2007, Mohd Hanafiah 2013}. In Turkey, Spain, Italy, Japan, and China, people over 50 years of age account for the highest prevalence of infections, indicating a cohort effect in which the risk for HCV infection was higher in the distant past (ie, 40-60 years previously). Young adults (ages 20 to 35 years) are at highest risk for acute infection, with an incidence 6 times higher than those over 40 years of age {Armstrong 2000, Kantar Health 2014, Mohd Hanafiah 2013}.

There are limited data on the prevalence of HCV infection among adolescents 12<18 years of age. It is estimated that approximately 2.1 to 3.5 million individuals 15 years of age or younger are chronically infected with HCV {European Association for the Study of the Liver (EASL) 2018, Nwaohiri 2018}. The prevalence varies by geographic location. The estimated prevalence of HCV infection in children is up to 0.4% in Europe and the United States (US), and up to 6% in resource-limited countries {El-Shabrawi 2013, Khaderi 2014}. The natural history of chronic HCV infection in children differs from that in adults since HCV infection in children is relatively benign. In general, the burden of disease is much lower in this age group than among older persons. A recent meta-analysis of primary national data sources and peer-reviewed papers used mathematical modeling to determine that the HCV antibody seroprevalence rate among subjects

10-19 years of age in 2005 was 1.2-1.3% in Western and Central Europe, 1.4-1.6% in Eastern Europe, and 0.6% in North America {Mohd Hanafiah 2013}. It must be noted that anti-HCV is a sign of previous and current infection that does not differentiate acute from chronic infections. Data from Europe and the United States show that the seroprevalence of anti-HCV among patients aged 10-19 has dropped in several countries since 2005 (Table SI.3) {Kantar Health 2014}. Whether these estimates have been influenced by changes in HCV surveillance and/or availability of highly effective DAA treatment is unclear.

**Table SI.3. Estimated Number of Seroprevalent HCV Cases Among Patients Aged 10-19 in Different European Countries and United States**

| Country | Number of cases in 2005 | Number of cases in 2015 |
|---|---|---|
| United Kingdom | 9,731 | 945 |
| France | 3,658 | 4,367 |
| Germany | 3,544 | 1,016 |
| Italy | 28,491 | 855 |
| Spain | 8,221 | 8,675 |
| United States | 134,554 | 6,573 |

### SI.1.3.3. HCV Infection by Ethnicity

There are differences in the rate of chronic HCV infection, response to treatment, and development of complications among different racial and ethnic groups with HCV infection. In particular, African Americans appear to have a higher rate of chronic HCV infection than Caucasians and Hispanic whites, along with higher viral loads, lower clearance rates, and lower responses to anti-HCV therapy {Pyrsopoulos 2005}.

### SI.1.3.4. Risk Factors for Hepatitis C

People at increased risk for hepatitis C infection include the following {Centers for Disease Control and Prevention (CDC) 2015}:

- Current injection drug users
- Past injection drug users, including those who injected only one time or many years ago
- Recipients of donated blood, blood products, and organs
- People who received a blood product for clotting problems made before 1987
- Hemodialysis patients or persons who spent many years on dialysis for kidney failure
- People who received body piercing, acupuncture, or tattoos done with non-sterile instruments

- People with known exposures to HCV virus, such as
  - Health care workers injured by needle sticks
  - Recipients of blood or organs from a donor who tested positive for HCV
- Human immunodeficiency virus (HIV)-infected persons
- Children born to mothers infected with HCV

Less common risks include:

- Having sexual contact with a person who is infected with HCV
- Sharing personal care items, such as razors or toothbrushes, that may have come in contact with the blood of an infected person

### SI.1.4. Main Existing Treatment Options

Approved DAA-based treatment regimens are generally well tolerated and result in high sustained virologic response (SVR) at 12 weeks following completion of all treatment (SVR12) rates across most, but not all, patient populations.

The following approved HCV DAAs are recommended in the 2020 European Association for the Study of the Liver (EASL) guidelines {European Association for the Study of the Liver 2020}:

- SOF-containing products
  - Sovaldi (sofosbuvir, SOF)
  - Epclusa (sofosbuvir/velpatasvir, EPC)
  - Vosevi (sofosbuvir/velpatasvir/voxilaprevir, VSV)
- Glecaprevir/pibrentasvir (GLE/PIB)
- Grazoprevir/elbasvir (GZR/EBR)

According to the 2020 EASL guidelines {European Association for the Study of the Liver 2020}:

- SOF-containing regimens, EPC and VSV with or without RBV, are among the recommended treatment options for patients with genotypes 1-6 including treatment of adolescents (EPC), children aged 3-11 years who are treatment-naïve or -experienced, without cirrhosis or with compensated cirrhosis (Child-Pugh A) (EPC, pending approval of granule formulations), those with HIV/HCV coinfection (EPC and VSV), decompensated liver disease (EPC), post-transplant recurrence (EPC), and those who are DAA failures (VSV, or SOF + GLE/PIB).

For patients with decompensated cirrhosis, the SOF-containing regimen of EPC is the only currently approved HCV regimen that is recommended by the EASL guidelines. The currently available SOF-free regimens described in the EASL guidelines (GLE/PIB and GZR/EBR) are contraindicated in patients with decompensated cirrhosis (Child-Pugh C for GLE/PIB and Child-Pugh B and C for GZR/EBR).

### SI.1.5. Natural History of the Indicated Condition including Mortality and Morbidity

The natural course of HCV infection and disease varies widely. Several factors have been associated with accelerated progression of hepatic fibrosis among those infected with HCV, or with increased incidence of HCV-related complications of chronic liver disease and hepatocellular carcinoma (HCC). These factors are HIV and hepatitis B virus (HBV) coinfections, inflammation, male sex, older age at acquisition of HCV infection, obesity, smoking, and excessive alcohol consumption {Shepard 2005}.

Although HCV-related liver disease is a leading cause of mortality in adults and is the primary reason for liver transplantation in many developed countries ({Kim 2005, Kim 2001, World Health Organization (WHO) 2005}), the vast majority of carriers die with, rather than from, this infection. In fact, many patients remain asymptomatic and unaware that they have been infected with the virus. Acute HCV infection usually occurs within the first six months of exposure to HCV and is typically asymptomatic; however, 20-30% of patients may experience malaise, fatigue, weakness, anorexia, or right upper quadrant pain, followed by jaundice.

Following the acute phase, 5-25% of HCV patients spontaneously resolve the infection within 2-12 weeks, while the rest develop chronic HCV disease. Patients with chronic HCV disease tend to be minimally symptomatic over the course of 20-40 years. A subset of patients (approximately 20%) develops nonspecific symptoms, including mild fatigue and malaise, nausea, and right upper quadrant pain. Patients with persistent viremia and years of chronic infection are at risk of fibrosis and cirrhosis, but the extent of liver damage and the time course of disease progression vary among individuals.

Approximately 15-35% of HCV patients will develop cirrhosis after 25-30 years of infection {Thrift 2017}. Although cirrhosis distorts the structure and degrades the function of the liver, it can remain asymptomatic for several years as healthy tissue compensates for diseased tissue. However, once cirrhosis is established, complications such as jaundice, ascites, variceal hemorrhage, and encephalopathy may ensue. The development of these complications defines decompensated cirrhosis, or end-stage liver disease. Decompensated liver disease was estimated to be present in 11.7% of HCV patients with cirrhosis in 2010, and this proportion is expected to rise at least through 2030 {Davis 2010}. In patients with decompensated cirrhosis, the five-year survival rate is 50% {Fattovich 1997}. In addition, approximately 10-25% of patients with cirrhosis may develop HCC ({Hezode 2003, Poynard 1997, Seeff 1999}).

Worldwide, more than 500,000 deaths occur from hepatitis C-related diseases, which include cirrhosis and liver cancer, every year. The mortality rate among HCV-infected persons was estimated to be 12 times higher than the mortality rate in the general population in a large US cohort study, suggesting that over 50,000 deaths in the US were related to HCV infection in 2010

{Mahajan 2014}. A Danish cohort study found that the higher risk of death among younger HCV-infected patients compared to an age- and sex-matched comparison cohort was due primarily to unnatural deaths (i.e. deaths related to mental and behavioral disorders, psychoactive substance use, and external causes), whereas excess mortality in older HCV-infected patients was due to liver-related deaths {Omland 2011}.

### SI.1.6. Important Co-morbidities

Infection with HCV is associated with numerous extrahepatic clinical manifestations, including autoimmune and lymphoproliferative disorders in addition to diseases of the cardiovascular, renal, metabolic, and central nervous system {Cacoub 2016}. A number of comorbidities in HCV patients have also been associated with antiviral treatment with interferon and/or ribavirin. Below is a list of important conditions that have evidence of higher risk among HCV-infected patients {Cacoub 2016}:

#### SI.1.6.1. Cardiovascular Disease

Cardiovascular disease risk appears to be elevated among HCV-infected patients compared to the general population. As measured by the Framingham risk score, cardiovascular disease was found to be 2.4% higher in HCV patients from New York based clinics compared to the US general population (NHANES sample) ($p < 0.001$) {Kakinami 2013}. Studies have also shown higher risk of coronary artery disease among HCV-positive patients {Roed 2012}. Recent studies indicate that carotid atherosclerosis is quite common in patients with chronic HCV infection. The prevalence has been reported to range from 42 to 53% {Roed 2012}, and rises to 78% among those with hepatic steatosis {Roed 2012}.

Previous reports have identified significant positive associations between chronic HCV status and any of the following conditions: carotid-artery plaque, intima-media thickness, coronary flow reserve by transthoracic Doppler echocardiography, carotid plaque score, brachial artery endothelium-dependent dilatation, and pulse wave velocity {Roed 2012}.

Further, positive associations have been observed between chronic HCV infection and coronary artery disease (CAD) defined in other ways, including angiographic documentation (> 50% stenosis) and modified Reardon severity score system {Roed 2012}. A recent retrospective cohort study found a positive association with chronic HCV and coronary heart events, defined by CAD onset, chronic stable angina, unstable angina, or acute myocardial infarction {Paydak 2014}. Other studies show positive associations between HCV infection and cardiomyopathy (either dilated or hypertrophic) {Roed 2012}, as well as a study that found HCV positive subjects to have almost twice the risk of stroke compared to HCV negative subjects {Roed 2012}.

#### SI.1.6.2. Depression

Depressive symptoms are frequently recognized in both untreated and treated HCV patients. The previous standard of care for HCV, PEG plus RBV is associated with a high rate of depression (10 to 40% depending on the screening method used) and other mental and neuropsychiatric syndromes {Hauser 2002, Papafragkakis 2012, Raison 2005}. An estimated 24 to 70 percent of

people with chronic hepatitis C were found to be clinically depressed, as compared to 6 to 10% in the general population {Coughlan 2002, Schafer 2007}. In another study, a three-fold risk was observed in HCV seropositive patients when compared to the general US population {Basseri 2010}.

### SI.1.6.3. Diabetes Mellitus Type 2

An increased prevalence of insulin resistance {Serfaty 2009} and, subsequently, diabetes mellitus has been observed within HCV patient populations {Allison 1994, Caronia 1999, Knobler 1998, Mason 1999, Simo 1996}. HCV infection has been identified as a risk factor for the development of insulin resistance in patients with visceral obesity {Eguchi 2009}, while diabetes also has been identified as a risk factor for rapid progression of fibrosis in HCV infection {Ortiz 2002}. A proposed mechanism for this relationship is hepatocyte dysfunction in severe HCV infection, which may lead to insufficient carbohydrate metabolism and glucose homeostasis {Petrides 1989}. Host cell adaptive mechanisms or viral proteins themselves (ie, in genotype 1 infection) may disrupt the insulin signaling pathway in hepatocytes and liver inflammation may induce cytokines, thus promoting insulin resistance.

Reports from North America, Europe, and the Middle East consistently found an increased prevalence of diabetes among patients with chronic HCV infection (24% to 62%) compared with people with alternate forms of liver disease and other control groups (3% to 13%) {Mehta 2000}. Moreover, HCV was associated with over 40% increased risk of type 2 diabetes compared with the general US population {Basseri 2010}.

### SI.1.6.4. Hepatitis B

Due to overlapping routes of transmission, HBV and HCV coinfection is not uncommon among individuals in HBV endemic areas who also have a high risk of parenteral infections, such as injection drug users {Pallas 1999}, patients on hemodialysis {Reddy 2005}, patients undergoing organ transplantation {Aroldi 2005} and HIV-positive individuals {Zhou 2007}. The prevalence of HBV and HCV coinfection varies from 9% to 30% depending on the geographic region {Liaw 1995, Zarski 1998}. HCV coinfection with HBV also has exhibited higher rates of progression to cirrhosis from liver fibrosis {Chen 2006}.

Although liver disease activity and progression are generally more severe in the presence of HCV/HBV coinfection, an inverse relationship in the replicative levels of the 2 viruses exists, suggesting viral interference. Usually, HCV is the dominant virus, and HBV replication is suppressed in the presence of HCV coinfection, with resultant lower HBV deoxyribonucleic acid (DNA) levels and decreased hepatitis B surface antigen (HBsAg) and hepatitis B core antigen (HBcAg) levels in coinfected patients compared to HBV monoinfected patients {Amin 2006, Biliotti 2008, Bini 2010, Chu 1998, Crockett 2005, Konstantinou 2015, Liaw 2004, Raimondo 2005, Saravanan 2009, Tyson 2013, Wiegand 2015}. The converse has also been observed, with some patients experiencing high HBV DNA levels while others present alternating phases of dominance of one virus over the other {Konstantinou 2015}.

HBV reactivation in HCV/HBV coinfected patients has been observed following effective treatment of HCV, both with older regimens involving PEG+RBV and also with newly approved DAAs (interferon-free regimens):

- *HBV reactivation with PEG+RBV*: HBV reactivation following successful treatment of HCV with PEG+RBV has been reported in HCV/HBV coinfected patients {Hamzaoui 2013, Liu 2012, Potthoff 2009, Yalcin 2003, Yu 2013}. HBV reactivation has been reported to occur in 14% to 38% of HCV/HBV coinfected patients following PEG+RBV or interferon (IFN) + RBV treatment {Liu 2012, Vigano 2009, Yu 2013}, and the risk of viremia was increased in cases where the virologic response to HCV therapy was sustained (HBV reactivation occurred in 31% of patients who experienced HCV sustained virologic response [SVR] and 11% of patients without HCV SVR) {Liu 2012}.

- *HBV reactivation with approved DAAs*: Unlike PEG and RBV, the approved DAAs for HCV treatment do not have any inhibitory effect on HBV; these DAAs can be used without interferon. Literature articles have reported HBV reactivation in HCV/HBV coinfected patients following treatment of HCV with DAAs {Balagopal 2015, Belperio 2017, Chen 2017, Collins 2015, Ende 2015, Hayashi 2016, Kasahara 2017, Londono 2017, Ogawa 2017, Ou 2017, Takayama 2016, Wang 2017}. Many of the reported cases did not involve clinical flares and resolved either spontaneously or following addition of anti-HBV therapy. Severe cases of HBV reactivation are rare, but there have been reports where HBV reactivation has resulted in acute hepatic failure with the need for a liver transplant {Ende 2015} or a fatal outcome {Benallai 2017, Macera 2017}. Class labeling has been issued for DAAs approved in the EU and other territories regarding the risk of HBV reactivation in HBV/HCV coinfected patients. The labeling recommends HBV screening prior to initiation of HCV therapy, monitoring for HBV reactivation while on HCV treatment and appropriate management per current clinical guidelines should HBV reactivation occur.

### SI.1.6.5. HIV

HIV coinfection may alter the natural history of HCV infection, and also contribute to the increasing burden of HCV infection, by accelerating liver fibrosis {Eyster 1993, Mohsen 2003, Rockstroh 1996}. Since the advent of highly-active antiretroviral therapy in the mid-90s, there has been a three-to nine-fold increase in HCV-associated mortality, and HCV infection is associated with up to half of all deaths in patients with HIV {Basseri 2010, Bica 2001, Cacoub 2001, Martin-Carbonero 2001, Soriano 1999}.

Globally, an estimated four to five million people are coinfected with HCV and HIV {Operskalski 2011}. In the US and Western Europe, estimates of coinfection rates range from 15% to over 50% of the HIV-positive population {Quaranta 1994, Rockstroh 2003, Rockstroh 2006, Soriano 2002}. The high prevalence of coinfection is attributed to the shared parenteral route of transmission. Consequently, coinfection with HCV and HIV is particularly common among hemophiliacs and injection drug users. Furthermore, individuals with chronic HIV and HCV coinfection have a greatly elevated risk of accelerated liver, kidney, and cardiovascular disease progression {Operskalski 2011}.

### SI.1.6.6. Obesity/Hepatic Steatosis

Obesity is associated with non-alcoholic fatty liver disease and non-alcoholic steatohepatitis, diseases that could potentially lead to fibrosis and cirrhosis {Angulo 1999}, and has been identified as a risk factor for rapid fibrosis progression in HCV infection {Ortiz 2002}.

Furthermore, fibrosis stage has been associated with hepatic steatosis {Negro 2009} and the degree of necroinflammatory activity in obese patients with HCV {Adinolfi 2001, Clouston 2001}. In addition, genotype 3 infection may induce steatosis and the degree of severity may correlate with viral load {Serfaty 2009}. Slightly increased prevalence rates of obesity within HCV patients in the US and Canada (24 and 29%, respectively) were found as compared with the general population {Basseri 2010, Chen 2008}.

### SI.1.6.7. Renal Insufficiency

Hepatitis C virus infection is a persistent public health concern among end stage renal disease patients who receive dialysis. Before testing of blood products for HCV and the availability of erythropoiesis-stimulating agents, patients on dialysis commonly acquired HCV through blood transfusions. Transmission still may occur because of contaminated medical equipment, patient-to-patient exposure, or other nosocomial routes {Martin 2008}. Differences in patient behavior and community exposures may contribute to persistence of HCV in hemodialysis units and also to variation in HCV prevalence and seroconversion among units {Fissell 2004}.

Prevalence rates of HCV infection are higher in dialysis patients compared to the general population worldwide {Fabrizi 2002}. HCV infection has been reported in 6 to 38% of dialysis patients in the US {Basseri 2010, Fissell 2004}. The prevalence of anti-HCV seropositivity among patients undergoing regular dialysis in Western Europe ranges between 3% and 23% {Fissell 2004}. HCV infection was reported in nearly 15% of dialysis patients in Japan, {Fissell 2004}, and as high as 80% in countries with single center samples, such as Egypt and Morocco {Martin 2008}.

Glomerular disease and other kidney diseases are extrahepatic manifestations of HCV infection {Fabrizi 2013, Kamar 2013}. Chronic HCV infection is associated with a higher risk of mixed cryoglobulinemia, membranoproliferative glomerulonephritis (MPGN), and other glomerulonephritis diseases {Fabrizi 2013, Kamar 2013}. Renal failure is reported to occur in 11% to 49% of patients with decompensated cirrhosis, particularly in older patients and patients with more advanced liver disease {Carvalho 2012}.

# PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

## Table SII.1. Table of Key Safety Findings from Non-Clinical Studies

| Key Safety Findings (from non-clinical studies) | Relevance to human use |
|---|---|
| **Toxicity** | |
| Single-dose toxicity<br>SOF (administered as GS-9851) has minimal toxicity after oral dosing to rats (no observed adverse effect level [NOAEL] at 1800 mg/kg; SA-PSI-7851-09-0001). | SOF is given in adult humans at 400 mg.<br>The GS-331007 exposure at the NOAEL is approximately 26-fold higher when compared with the clinical exposure at 400 mg. |
| Repeat-dose toxicity<br>Exploratory and definitive repeat dose toxicity studies have been conducted in mice, rats, and dogs (0515-09260; SA-PSI-7851-08-001; SA-PSI-7851-08-002; SA-PSI-7851-09-0002; SA-PSI-7851-09-0003; SA-PSI-7977-09-0006; SA-PSI-7977-09-0007; SA-PSI-7977-09-0008; SA-PSI-7977-10-0003; SA-PSI-7977-10-0004; TX-334-2012). The target organs identified were gastrointestinal (GI) tract (dog), heart (rat and dog), and liver (dog). Slight (< 10%) hematological changes in red cell indices/erythropoiesis were also noted in the dogs.<br>These target organs were identified at adverse (dog) or lethal (rat) doses/exposures of GS-9851 in the nonclinical species. | To date, manifestations of these target organ toxicities have not been observed in clinical studies with SOF. |
| Reproductive & Developmental Toxicity<br>SOF did not have any adverse effects in reproductive and developmental toxicity studies (SA-PSI-7977-10-0005; SA-PSI-7977-10-0008; SA-PSI-7977-11-0008; TX-334-2003). Animal data indicate that SOF has no effect on fertility, does not cause reproductive or fetal toxicity, and has no effects on behavior, reproduction, or development of offspring.<br>The predominant circulating metabolite GS-331007 was a predominant component observed in the milk of lactating rats at a milk to plasma ration of 0.1 at 1 hour post-dose (SA-PSI-7977-11-0008). | Animal data indicate that SOF does not cause reproductive or fetal toxicity.<br>Because there are no clinical data with SOF in pregnant women, as a precaution, it is preferable to avoid use of SOF during pregnancy. The predominant circulating metabolite GS-331007 is excreted in rat milk. It is not known whether SOF and its metabolites are excreted in human breast milk. Mothers should be instructed not to breast-feed if they are taking SOF. |
| Nephrotoxicity<br>SOF and GS-331007 showed little potential for drug-drug interactions mediated by renal transporters. GS-331007, cleared renally, was not a substrate, and showed little or no inhibition of the renally expressed transporters such as organic anion transporter (OAT)1, OAT3, OCT2, and multidrug and toxin extrusion 1 (MATE1) transporter (AD-334-2005). | The nonclinical data indicate a low likelihood for nephrotoxicity in humans. |

| Key Safety Findings (from non-clinical studies) | Relevance to human use |
|---|---|
| Hepatotoxicity<br>SOF and GS-331007 showed little potential for drug-drug interactions mediated by hepatic transporters. Sofosbuvir is not a meaningful substrate, inhibitor, or inducer of CYP enzymes and does not inhibit uridine diphosphate glucuronosyltransferase (UGT)1A1 (AD-334-2013). Sofosbuvir and GS-331007 were not substrates or inhibitors of studied hepatic transporters (eg, OCT1, organic anion transporting polypeptide [OATP]1B1, OATP1B3, and bile salt export pump [BSEP]; AD-334-2004; AD-334-2005; PC-PSI-7977-11-0007).<br>In dogs, dosing with GS-9851 at 1500 mg/kg/day for 7 days (SA-PSI-7851-08-002) resulted in alterations in serum chemistry that were suggestive of liver injury (increased mean serum alanine transaminase, aspartate transaminase [AST], and bilirubin levels in both sexes) with associated histopathologic findings (hepatocellular hypertrophy, glycogen depletion, microvesiculation, and apoptosis). The serum chemistry changes and histopathologic findings were not observed at the end of the 14-day recovery period. In all other studies with SOF or GS-9851, liver related serum chemistry and histopathologic findings were not observed after daily oral doses up to 500 mg/kg/day for 9 months. | It should be noted that the alterations in serum chemistry with the associated histopathologic findings were only observed at 1500 mg/kg/day; Day 7 GS-331007 exposure (AUC) at 1500 mg/kg/day (sexes combined) is 123-fold higher when compared with the mean clinical exposure at 400 mg. No alterations were found at lower doses up to 500 mg/kg/day for 9 months. Additionally, Phase 2 and 3 clinical safety data with SOF do not indicate a clinically relevant adverse effect on the liver. |
| Genotoxicity<br>SOF was negative for mutagenic potential in a bacterial reverse mutation test, negative in a chromosome aberration test using human peripheral blood lymphocytes, and negative in a mouse micronucleus assay (SA-PSI-7851-08-003; SA-PSI-7851-08-004; SA-PSI-7851-08-005). | SOF is considered nongenotoxic. |
| Carcinogenicity<br>Two-year oral gavage carcinogenicity studies with SOF were conducted in rats (TX-334-2001) and mice (TX-334-2002).<br>In rats (TX-334-2001), SOF administered at 75, 250, and 750 mg/kg/day did not have any carcinogenic effect and did not affect the survivability of the animals.<br>In mice (TX-334-2002), SOF administered at 20, 60, and 200 mg/kg/day for males and 60, 200, and 600 mg/kg/day for females did not affect the survivability or induce neoplastic/non-neoplastic changes at any dose level. No evidence of carcinogenic potential was observed in this study. | Carcinogenicity studies in rats and mice do not indicate any carcinogenicity potential for SOF administered at doses up to 600 mg/kg/day in mouse and 750 mg/kg/day in rat. Exposure to GS-331007 in these studies was at least 7 times (mouse) and 15 times (rat). |

| Key Safety Findings (from non-clinical studies) | Relevance to human use |
|---|---|
| **Safety Pharmacology** | |
| General Safety Pharmacology<br>In a battery of safety pharmacology studies, the effects of GS-9851 on the central nervous, cardiovascular, and respiratory systems were examined. There were no findings in the nonclinical safety pharmacology studies to suggest clinically relevant adverse neurological, cardiovascular, or respiratory effects (SA-PSI-7851-08-006; SA-PSI-7851-08-007; SA-PSI-7851-08-008; SA-PSI-7851-08-009; PC-PSI-7851-08-0023; PC-PSI-7851-08-0028; PC-PSI-7851-09-0001). | The nonclinical data indicate a low likelihood for neurological, cardiovascular, or respiratory effects in humans. |
| Cardiovascular<br>In a 7-day repeat dose dog study, an increase (19%) in QT/QTc interval was observed in male but not female dogs at the high dose of 1500 mg/kg/day (SA-PSI-7851-08-002). There were no other waveform changes or electrocardiogram (ECG) findings.<br>The changes in the QT/QTc intervals may be related to the poor condition of the 1500 mg/kg/day high dose animals. There were no cardiovascular findings in the single dose study in telemetry monitored animals up to 1000 mg/kg, nor in dogs given daily oral doses of SOF up to 500 mg/kg/day for 9 months.<br>In rats, high doses of GS-9851 at 2000 mg/kg/day caused multifocal cardiac myofiber degeneration that may have led to the death of several rats by Day 5 in the 7-day range-finding study (SA-PSI-7851-08-001). The myocardial findings were not associated with hematologic evidence of inflammation or higher serum AST concentration. Other biomarkers of myocardial damage (eg, troponins) were not evaluated in this initial toxicity study. Myocardial degeneration was also observed in a few rats at the same high dose 3 and 17 days after cessation of dosing, suggesting no or a slow resolution/recovery.<br>In a 7-day rat toxicity study (Study TX-334-2012) using SOF alone, no early mortalities and no evidence of cardiac toxicity was observed at the high dose of 2000 mg/kg/day. GS-331007 exposure (AUC) at 2000 mg/kg/day SOF was also 29-fold (sexes combined) higher than the mean clinical exposure at 400 mg. | At the adverse dose of 1500 mg/kg/day in dogs in the 7 day study, systemic exposure ($C_{max}$) to the predominant metabolite GS-331007 was approximately 90-fold greater than the plasma concentration measured in HCV infected subjects at the SOF therapeutic dose of 400 mg once daily (human GS-331007 $C_{max}$ of 0.582 μg/mL).<br>While the 7-day repeat dose rat study with GS-9851 indicated a potential toxicity, subsequent 7-day rat study with SOF at the same doses and exposures was well tolerated. In the 4-week repeat dose rat study with GS-9851 (SA-PSI-7851-09-0003), these myocardial findings were not observed at the highest tested dose (500 mg/kg/day) and there were no changes in the levels of creatine kinase and troponin I when compared to controls. Longer duration studies (up to 26 weeks; SA-PSI-7977-09-0007; SA-PSI-7977-10-0004) with SOF in rats did not show evidence of cardiac toxicity suggesting the effect observed in the 7-day study in rats was related to the very high systemic exposure achieved at lethal dose level. At the lethal dose of 2000 mg/kg/day GS-9851 in the 7 day study, systemic exposures to the predominant metabolite GS-331007 was approximately 29-fold (sexes combined) greater than the exposure in HCV-infected subjects at the therapeutic dose of 400 mg. In the 26-week chronic study (SA-PSI-7977-10-0004), there were no cardiac changes at exposure margins up to 9-fold (sexes combined). Taken together, the data suggest that the observed mortalities and cardiac toxicity in Study SA-PSI-7851-08-001 were the result of GS-491241 and that SOF, at similar exposures, does not produce the same effect.<br>Furthermore, the thorough QT study conducted in healthy subjects at the supratherapeutic dose of 1200 mg did not reveal any effect of SOF on the QTc interval, and there were no clinically significant changes in ECG or wave morphology (P7977-0613). Taken together, the potential for SOF and its metabolites to induce clinically meaningful QT prolongation is considered low. |

| Key Safety Findings (from non-clinical studies) | Relevance to human use |
|---|---|
| Cardiovascular Effects with Amiodarone<br>Nonclinical studies (7 in vitro studies and 1 ex vivo study) have been conducted to evaluate a potential pharmacodynamic and/or pharmacokinetic mechanistic interaction between amiodarone and SOF in combination with another DAA. In the ex vivo guinea pig heart study, prolongation of the A-H interval was observed when amiodarone was combined with DCV, SMV or SOF compared to amiodarone alone. The triple combination of amiodarone, SOF and DCV resulted in the largest prolongation of the A-H interval, reflecting the observed clinical phenomenon (PC-334-2029 Addendum 1). Results from electrophysiology studies suggest that the human L-type calcium channel 3.2 (hCav3.2) and human hyperpolarization-activated, cyclic nucleotide-gated channel 4 (hHCN4) channels were not involved. Contradictory to the ex vivo guinea pig heart data, hCav1.2 channel may be indirectly inhibited by amiodarone with SOF or LDV (PC-334-2030, PC-334-2031, PC-334-2032).<br>Data from in vitro studies show that amiodarone and its metabolite *N*-desethylamiodarone (DA) were neither inhibitors nor substrates of efflux transporters P-glycoprotein (Pgp) and BCRP, and hepatic uptake transporters OATP1B1 and OATP1B3 (AD-334-2028, AD-334-2029). Both amiodarone and DA appeared to be tightly bound (> 99%) to plasma and atrial tissue and all the tested anti-HCV agents including SOF and its nucleoside metabolite GS-331007 did not affect free fractions of both compounds (AD-334-2030, AD-334-2033). | The nonclinical data indicate that multiple pharmacodynamic and pharmacokinetic processes may contribute to the observed clinical phenomenon of symptomatic bradycardia in patients treated with amiodarone, SOF and another HCV DAA.<br>The potential of amiodarone and DA to be victims or perpetrators of drug interactions mediated by these transporters is low. Amiodarone and the HCV DAAs are unlikely to cause drug-drug interactions through efflux and hepatic uptake transporters, and plasma or atrial tissue binding displacement. |
| **Other Toxicity-Related Information** | |
| Secondary Pharmacodynamics<br>Sofosbuvir has shown a low potential for toxicity in in vitro studies, since no significant cytotoxicity was observed when a panel of cell lines was treated with SOF. Specifically, SOF shows a low potential for mitochondrial toxicity, since no significant effects were observed on mitochondrial deoxyribonucleic acid levels or mitochondrial biogenesis in SOF-treated cells (PC-334-2012; PC-334-2013; PC-334-2015; PC-PSI-7851-08-0009; PC-PSI-7977-09-0007). Furthermore, no measurable inhibition of human deoxyribonucleic acid (DNA), RNA, or mitochondrial polymerases was observed with the triphosphate form of SOF in vitro, indicating a low likelihood for off-target effects (PC-334-2013; PC-PSI-7851-08-0029; PC-PSI-7851-09-0015). | The nonclinical data indicate a low likelihood for cytotoxicity in humans. |

| Key Safety Findings (from non-clinical studies) | Relevance to human use |
|---|---|
| **Mechanisms for Drug Interactions** | |
| Transporter Drug Interactions<br>Nonclinical data show that SOF is a substrate for the intestinal efflux transporter Pgp and breast cancer resistance protein (BCRP) (8215026; PC PSI-7977-11-0006). Coadministration with inhibitors or inducers of these intestinal efflux transporters may affect the absorption of SOF from the GI tract (AD-334-2002). | Clinical data also show that SOF is a substrate for Pgp and that its intestinal absorption is limited by efflux transport by these transporters (P7977-1819).<br>For example, the known Pgp and BCRP inhibitor, cyclosporine, was noted to increase A-B permeability through Caco-2 cells, corresponding to complete inhibition of efflux transport, and caused an increase in SOF levels in a clinical drug-drug interaction study. Therefore, administration with potent inducers of intestinal Pgp may decrease the absorption of SOF and lead to reduced delivery of the pharmacologically active triphosphate into the liver. However, coadministration with less potent inducers or those that do not markedly affect intestinal Pgp induction are unlikely to affect SOF levels. |

# PART II: MODULE SIII - CLINICAL STUDY EXPOSURE

## SIII.1. Clinical Study Exposure

The tables in this section present exposure data to SOF in subjects with HCV infection from the following studies:

- GS-US-281-0101, GS-US-334-0101, GS-US-334-0107, GS-US-334-0108, GS-US-334-0109, GS-US-334-0110, GS-US-334-0111, GS-US-334-0114, GS-US-334-0115, GS-US-334-0116, GS-US-334-0118, GS-US-334-0119, GS-US-334-0123, GS-US-334-0124, GS-US-334-0125, GS-US-334-0126, GS-US-334-0131, GS-US-334-0133, GS-US-334-0138, GS-US-334-0139, GS-US-334-0146, GS-US-334-0148, GS-US-334-0151, GS-US-334-0153, GS-US-334-0154, GS-US-334-1111, GS-US-334-1112, GS-US-334-1113, GS-US-334-1114, GS-US-334-1274, GS-US-334-1344, GS-US-334-1379, GS-US-337-0101, GS-US-337-0122, GS-US-337-1903, GS-US-342-0102, GS-US-342-0104, GS-US-342-0109, GS-US-342-1139, GS-US-342-1140, P2938-0212, P2938-0515, P2938-0721, P7851-1101, P7851-1102, P7977-0111, P7977-0221, P7977-0312, P7977-0422, P7977-0523 (part 1-5), P7977-0613, P7977-0724, P7977-0814, P7977-0915, P7977-1231, P7977-1318, P7977-1819, P7977-1910 and P7977-2025.

- An additional 1371 subjects were exposed to SOF in the following expanded access, compassionate use, and collaborative studies: GS-US-334-0139 (n=114), EA-US-334-0132 (n = 1), GS-FR-334-0157 (n = 306), GS-US-334-0152 (n = 25), CU-US-334-0134 (n = 1), IN-US-334-0141 (n = 359), IN-US-334-0143 (n = 108), CO-US-334-0112 (n = 61), CO-US-334-0136 (n = 211), CO-US-334-0137 (n = 168) and CO-US-334-0150 (SWIFT-C, n = 17). These subjects are not included in the tables below.

**Table SIII.1. Duration of Sofosbuvir Exposure in Subjects with HCV Infection**

| Duration Of Exposure | Patients | Patient-days |
|---|---|---|
| 1 day | 7524 | - |
| 1 week | 6884 | - |
| 4 weeks | 6715 | - |
| 8 weeks | 6585 | 794,296 |
| 12 weeks | 5875 | 745,298 |
| 16 weeks | 2880 | 490,326 |
| 24 weeks | 2181 | 396,275 |
| **Total patient-days** | | **802,129** |

NOTE: Patient-days is the sum of days that patients were exposed to SOF.

**Table SIII.2 Sofosbuvir Exposure by Age Group and Gender in Subjects with HCV Infection**

| | Patients | | Patient-days | |
|---|---|---|---|---|
| **Age Group** | **Male** | **Female** | **Male** | **Female** |
| 3-<6 | 3 | 10 | 414 | 1273 |
| 6-<12 | 11 | 30 | 1595 | 4217 |
| 12-<18 | 31 | 21 | 4530 | 3130 |
| 18-24 | 161 | 116 | 8288 | 7473 |
| 25-34 | 470 | 301 | 37,340 | 25,009 |
| 35-44 | 773 | 450 | 77,505 | 42,186 |
| 45-54 | 1535 | 841 | 186,913 | 94,094 |
| 55-64 | 1448 | 803 | 167,240 | 85,876 |
| 65-74 | 276 | 216 | 29,921 | 22,735 |
| 75-84 | 7 | 20 | 637 | 1668 |
| ≥85 | 1 | 0 | 85 | 0 |

Note: Patient-days is the sum of days that patients were exposed to SOF.

**Table SIII.3 Sofosbuvir Exposure by Dose in Subjects with HCV Infection**

| **Dose** | **Patients** | **Patient-days** |
|---|---|---|
| 12.5 mg | 6 | 6 |
| 25 mg | 16 | 39 |
| 50 mg | 36 | 2638 |
| 100 mg | 99 | 6745 |
| 200 mg | 131 | 6231 |
| 400 mg | 7259 | 786,227 |
| 800 mg | 16 | 16 |
| 1200 mg | 59 | 59 |

Note: Patient-days is the sum of days that patients were exposed to SOF.

**Table SIII.4 Sofosbuvir Exposure by Racial Origin in Subjects with HCV Infection**

| Race | Number of Patients | Patient-days |
|---|---|---|
| Black or African American | 560 | 43,184 |
| White | 5412 | 592,339 |
| Asian | 1345 | 144,927 |
| American Indian or Alaska Native | 47 | 4268 |
| Native Hawaiian or Other Pacific Islander | 40 | 3856 |
| Other | 102 | 11,267 |
| Multiple | 2 | 6 |
| Not Permitted* | 16 | 2282 |
| Missing | 0 | 0 |
| **Total** | **7524** | **802,129** |

* Not permitted' means either the site was not allowed to collect or the subject refused to provide race information.
Note: Patient-days is the sum of days that patients were exposed to SOF.

**Table SIII.5 Sofosbuvir Exposure in Special Populations**

| Special Population | | Number of Patients | Patient-days |
|---|---|---|---|
| Renal impairment | Normal | 6 | 6 |
| | Mild | 6 | 6 |
| | Moderate | 6 | 6 |
| | Severe | 26 | 3129 |
| | End-stage renal disease | 6 | 12 |
| Hepatic impairment | Moderate (Child-Pugh-Turcotte [CPT] Classification B) | 54 | 11,177 |
| | Severe (CPT Classification C) | 8 | 56 |
| Cirrhosis | | 1454 | 192,972 |
| HIV/HCV coinfection | | 692 | 96,295 |
| Pediatrics[a] | | 106 | 15,159 |
| Bleeding disorder | | 16 | 1854 |

Note: Patient-days is the sum of days that patients were exposed to SOF.
a Pediatric includes subjects aged 3 < 18 years

# PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL STUDIES

## SIV.1. Exclusion Criteria in Pivotal Clinical Studies within the Development Program

### Table SIV.1. Important Exclusion Criteria in Pivotal Studies in the Development Program

| Criterion | Reason for Exclusion | Considered to be Missing Information |
|---|---|---|
| Pregnancy and lactation | Limited information on the use in this patient population | No<br>Rationale: SOF has not been shown to be teratogenic in nonclinical studies. Safety in pregnancy is monitored on an ongoing basis through routine pharmacovigilance and data are presented periodically in periodic safety update reports/periodic benefit-risk evaluation reports (PSURs/PBRERs). No safety concerns regarding use of SOF in pregnancy have been identified. |
| History of clinically significant hemoglobinopathy | When SOF is used in combination with PEG+RBV or RBV, the contraindications applicable to PEG and/or RBV are also applicable to combination therapies of SOF with these agents. | No<br>Rationale: Hemoglobinopathy is a contraindication for RBV. |
| History of significant cardiac disease | When SOF is used in combination with PEG+RBV or RBV, the contraindications applicable to PEG and/or RBV are also applicable to combination therapies of SOF with these agents. | No<br>Rationale: A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous 6 months, is a contraindication for both PEG and RBV. |
| Porphyria | When SOF is used in combination with PEG+RBV or RBV, the contraindications applicable to PEG and/or RBV are also applicable to combination therapies of SOF with these agents. | No<br>Rationale: Porphyria is a contraindication for RBV. |

## SIV.2. Limitations to Detect Adverse Reactions in Clinical Study Development Programs

**Table SIV.2. Ability of the Clinical Study Development Program to Detect Adverse Drug Reactions**

| Ability to Detect Adverse Reactions | Limitation of Study Program | Discussion of Implications for Target Population |
|---|---|---|
| Which are rare | Approximately 7524 subjects[a] have been exposed to SOF in the SOF clinical study program. | The clinical study population is large enough to detect at least uncommon adverse drug reactions (ADRs). |
| Due to prolonged exposure | There is no experience with prolonged exposure (ie, over 1 year) to SOF in the SOF clinical study program. | The proposed duration of SOF treatment is no more than 24 weeks or up to the time of liver transplantation; therefore, the target population should not be exposed to SOF for longer periods. |
| Due to cumulative effects | Safety data from clinical studies is available for the proposed duration of treatment. | No cumulative effects of SOF have been identified in the SOF clinical study program. |
| Which have a long latency | Safety data was collected for up to 30 days after the last dose was administered. | No ADRs to SOF with a long latency have been identified in the SOF clinical study program. |

a Includes subjects as of 05 December 2018

## SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Study Development Programs

While some of these populations were not included in the original SOF clinical studies, since then many of these populations have been studied in the LDV/SOF, SOF/VEL and SOF/VEL/VOX clinical program.

## Table SIV.3. Exposure of Special Populations Included or not in Clinical Study Development Programs

| Type of special population | Exposure | Considered to be Missing Information |
|---|---|---|
| Children (<3 years of age) | No subjects aged < 3 years of age have been exposed to SOF in clinical studies | No<br>Rationale: SOF is not indicated in patients < 3 years old. No specific risks in pediatric patients are anticipated and ongoing review of pediatric data presented in PSURs/PBRERs has not identified any safety concerns regarding off-label pediatric use. |
| Pregnant women | Not included in the clinical development program | No<br>Rationale: SOF has not been shown to be teratogenic in nonclinical studies. Safety in pregnancy is monitored on an ongoing basis through routine pharmacovigilance and data are presented periodically in PSURs/PBRERs. No safety concerns regarding use of SOF in pregnancy have been identified. |
| Breastfeeding women | Not included in the clinical development program | No<br>Rationale: Safety in breastfeeding women is monitored on an ongoing basis through routine pharmacovigilance and data are presented periodically in PSURs/PBRERs. No safety concerns regarding use of SOF in breastfeeding have been identified. |
| Patients with end stage renal failure or severe renal insufficiency | Thirty-two (32) subjects with HCV and end stage renal failure or severe renal impairment were exposed to SOF in clinical studies. Twenty (20) subjects with HCV and severe renal impairment were exposed to SOF+RBV for 24 weeks (Cohorts 1 and 2) and 18 subjects with HCV and severe renal impairment were exposed to LDV/SOF for 12 weeks in Study GS-US-334-0154 (Cohort 3); 95 subjects with HCV on dialysis for ESRD were exposed to LDV/SOF for 8-24 weeks in Study GS-US-337-4063; 59 subjects with HCV on dialysis for ESRD were exposed to SOF/VEL for 12 weeks in Study GS-US-342-4062. | No<br>Rationale: No safety signals or toxicities were identified in subjects with severe renal impairment or ESRD in studies GS-US-334-0154, GS-US-337-4063, and GS-US-342-4062. No dosage adjustment of SOF is required for patients with renal impairment, including ESRD requiring dialysis. Given that there are now clinical study data regarding the use of SOF+RBV, LDV/SOF, and SOF/VEL in subjects with HCV infection and severe renal impairment or ESRD which indicates that treatment with SOF or SOF-combination products is safe and well tolerated and there are no additional pharmacovigilance activities ongoing to provide further information on this safety concern, safety in patients with ESRD or severe renal insufficiency is not considered as a category of 'missing information' in this EU-RMP. |

| Type of special population | Exposure | Considered to be Missing Information |
|---|---|---|
| Patients with HBV coinfection relevant comorbidities | Patients with HBV coinfection were excluded from the Phase 3 clinical studies for SOF submitted at the time of the original marketing authorization application.<br>The safety of the SOF-containing regimen, LDV/SOF, has been assessed in 8 subjects with untreated chronic HBV infection in Study GS-US-337-0122 and in 103 subjects with isolated hepatitis B core antibody positivity in Study GS-US-337-0131. HBV reactivation was not observed in these patients. Safety in patients with HBV coinfection is also being investigated in Study GS-US-337-1655 (a Phase 3b study in Taiwan evaluating the safety and efficacy of LDV/SOF for 12 weeks in 100 subjects with HCV infection and untreated HBV coinfection). | No<br>Rationale: Given that there are now clinical study data regarding the use of SOF-containing regimens in HBV coinfected patients, and there is currently labeling for SOF-containing products regarding the risk of HBV reactivation in HBV/HCV coinfected patients based on postmarketing data, the safety in patients with HBV coinfection is not considered as a category of 'missing information' in this EU-RMP. |
| Population of different racial and/or ethnic origin | In the Phase 3 study population, the percentages of subjects who were black/African American, Asian, or American/Indian/Alaska Native/Pacific Islander/other were 8.2%, 4.0%, and 2.8%, respectively; the remaining 85% were Caucasian. | No<br>Rationale: SOF PK was not substantially altered in black patients when compared to nonblack patients, suggesting that no dose adjustment is required in these patients. Based on the data from the GS-US-334-0110 study with SOF+PEG+RBV and the National Institute of Allergy and Infectious Diseases (NIAID) sponsored 11-I-0258 study with SOF+RBV, there are adequate safety data in black subjects to conclude that the safety profile is similar between blacks and non-blacks. |
| Patients with previous HCC | Not included in the clinical development program | No<br>A study has been conducted jointly between Gilead and other marketing authorization holders (MAHs) of DAAs, to assess the impact of DAA treatment on the incidence of HCC recurrence in patients with previous HCC. Following the completion of the study, the conclusion was that DAA treatment had no impact on the safety of patients with a previous HCC, and this topic was no longer considered an area of missing information. |

# PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

## SV.1. Post-Authorization Exposure

### SV.1.1. Method Used to Calculate Exposure

Patient exposure to marketed Sovaldi is estimated from sales (or prescription) data. It should be noted that the use of sales data for patient exposure calculations will generally overestimate patient exposure due to the accumulation of drug stocks at pharmacies/distributors and wastage.

***Sales Data***

The number of bottles sold cumulatively was multiplied by 28 to provide the number of tablets sold. As SOF is taken once daily, this figure was divided by 365.25 to provide patient-years of treatment. Given the various treatment durations for which Sovaldi can be administered (ie, 12 weeks, 24 weeks, or up to 48 weeks for patients awaiting liver transplantation), patient exposure has been standardized to patient-years.

***Prescription Data***

Estimates of the total treated patients and demographics of HCV infected patients exposed to SOF in the EU (in 5 EU countries: UK, France, Germany, Italy, and Spain) were obtained from prescription data from the following source:

- IMS/GERS by country converted to DoT (Days of Treatment)
- DoT consolidated to provide EU5 aggregate
- Using a patient calculation estimate regarding treatment duration DoT are converted to patient numbers by brand

Therapy Watch HCV EU5 is a quarterly tracking study of the hepatitis C market for Gilead. Data has been collected on a continuous basis, with sample launched in batches to ensure coverage across each month in the quarter. Per wave, 250 HCV treaters are surveyed across EU5 and HCV patient record forms (PRFs) from recently seen patients are completed online, including the following:

- 7 dynamic PRFs (treatment naïve/experienced who were initiated on treatment in last 12 weeks) each wave
- 7 total PRFs collected each wave (last 7 HCV patients seen, irrespective of treatment status)

## SV.1.2. Exposure

### SV.1.2.1. Exposure Based on Sales Data

Cumulative patient exposure to SOF since first marketing approval in the US on 06 December 2013 to 30 June 2025 is estimated to be 233,022 patient-years, including 35,542 patient-years in the EU and is presented in PSURs. In line with the trend for declining use of single agent SOF, sales in some territories are negative due to return of stock from wholesalers.

### SV.1.2.2. Exposure Based on Prescription Data

Based on prescription data from UK, France, Germany, Italy and Spain, most patients exposed to SOF were Caucasian/White males and between the ages of 26-35 years.

# PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

## SVI.1. Potential for Misuse for Illegal Purposes

There are no data to suggest that there is potential for SOF to be misused for illegal purposes.

# PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

## SVII.1. Identification of Safety Concerns in the Initial RMP submission

Not applicable.

## SVII.2. New Safety Concerns and Reclassification with a Submission of an updated RMP

No new important identified, important potential risks or missing information have been identified for SOF since the submission of the last RMP.

Risks previously classified as important removed from the list of safety concerns, along with the reasons for their removal, are presented Table SVII.1.

**Table SVII.1. Reason for Removing Important Risks and Missing Information from the List of Safety Concerns in the RMP**

| Safety Concern Removed | Reason for Removal From the List of Safety Concerns |
|---|---|
| **Identified risk** | |
| Cardiac arrhythmia (bradycardia) when SOF-containing regimens are used concomitantly with amiodarone | Recommended by PRAC to remove the important identified risk of Cardiac arrhythmia (bradycardia) when SOF-containing regimens are used concomitantly with amiodarone from the list of safety concerns.<br>There are no outstanding additional risk minimization measures or additional PV activities for this risk.<br>Given that the management of this risk is fully integrated into standard clinical practice, the risk is considered fully characterized and appropriately managed.<br>The risk will continue to be monitored through routine pharmacovigilance |
| HBV reactivation in HBV/HCV coinfected patients | Recommended by PRAC to remove the important identified risk of HBV reactivation in HBV/HCV coinfected patients from the list of safety concerns.<br>There are no outstanding additional risk minimization measures or additional PV activities for this risk.<br>Given that the management of this risk is fully integrated into standard clinical practice, the risk is considered fully characterized and appropriately managed.<br>The risk will continue to be monitored through routine pharmacovigilance |

Following removal of these safety concerns by the MAH, there will be no safety concerns for Sovaldi in the EU-RMP.

## SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

### SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

#### SVII.3.1.1. Important Identified Risks

There are no important identified risks for Sovaldi.

#### SVII.3.1.2. Important Potential Risks

There are no important potential risks for Sovaldi.

### SVII.3.2. Presentation of the Missing Information

There is no missing information for Sovaldi.

# PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

## Table SVIII.1. Summary of Safety Concerns

| | |
|---|---|
| **Important Identified Risks** | None |
| **Important Potential Risks** | None |
| **Missing Information** | None |

# PART III: PHARMACOVIGILANCE PLAN

## III.1. Routine Pharmacovigilance Activities

### Routine Pharmacovigilance Activities Beyond ADRs Reporting and Signal Detection:

### Specific Adverse Reaction Follow-up Questionnaires

There are no specific adverse reaction follow-up questionnaires in Annex 4.

### Other Forms of Routine Pharmacovigilance Activities

There are no other forms of routine pharmacovigilance activities for any of the safety concerns.

## III.2. Additional Pharmacovigilance activities

There are no ongoing or planned additional pharmacovigilance activities for any of the safety concerns.

**Table Part III.1. Ongoing and Planned Additional Pharmacovigilance Activities**

| Study title | Rationale and Study Objectives | Study Design and Study Populations | Milestones | Due dates |
|---|---|---|---|---|
| **Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization** | | | | |
| None | | | | |
| **Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances** | | | | |
| None | | | | |
| **Category 3 - Required additional pharmacovigilance activities** | | | | |
| None | | | | |

## III.3. Summary Table of additional Pharmacovigilance activities

### Table Part III.2. Ongoing and Planned Additional Pharmacovigilance Activities

| Study (Status) | Summary of Objectives | Safety Concerns Addressed | Milestones | Due dates |
|---|---|---|---|---|
| **Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization** | | | | |
| None | | | | |
| **Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances** | | | | |
| None | | | | |
| **Category 3 - Required additional pharmacovigilance activities** | | | | |
| None | | | | |

# PART IV:
# PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are no planned or ongoing post-authorization efficacy studies.

# PART V:
# RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

## V.1. Routine risk minimization measures

The routine risk minimization measures for Sovaldi in the EU comprise the SmPC, the package leaflet (PL), and the legal status of the product. Sovaldi is subject to restricted medical prescription, whereby therapy should be initiated by a physician experienced in the management of HCV infection (SmPC Section 4.2). There are no individual safety concerns for Sovaldi.

**Table Part V.1. Description of Routine Risk Minimization Measures by Safety Concern**

| Safety concern | Routine risk minimization activities |
|---|---|
| **Important Identified Risks** | |
| None | |
| **Important Potential Risks** | |
| None | |
| **Missing information** | |
| None | |

## V.2. Additional Risk minimization measures

Routine risk minimization activities are described in Part V Section V.1 No additional risk minimization measures are warranted as there are no safety concerns for the medicinal product.

## V.3. Summary risk minimization measures

**Table Part V.2. Summary Table of Pharmacovigilance and Risk Minimization Activities by Safety Concern**

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| **Important identified risk(s)** | | |
| None | | |
| **Important potential risk(s)** | | |
| None | | |
| **Missing information** | | |
| None | | |

# PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

## I. Summary of risk management plan for SOVALDI (Sofosbuvir)

This is a summary of the risk management plan (RMP) for Sovaldi. The RMP details important risks of Sovaldi, how these risks can be minimized, and how more information will be obtained about Sovaldi's risks and uncertainties (missing information).

Sovaldi's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Sovaldi should be used.

This summary of the RMP for Sovaldi should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Sovaldi's RMP.

## II. The Medicine and What is it Used for

Sovaldi is authorized for treatment of chronic hepatitis C (CHC) in adults and pediatric patients aged 3 years and above (see SmPCs for the full indication). It contains sofosbuvir (SOF) as the active substance and it is given orally.

Further information about the evaluation of Sovaldi's benefits can be found in Sovaldi's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/sovaldi.

## III. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of Sovaldi, together with measures to minimize such risks and the proposed studies for learning more about Sovaldi's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the public (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Sovaldi is not yet available, it is listed under 'missing information' below.

## III.A. List of Important Risks and Missing Information

Important risks of Sovaldi are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Sovaldi. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

**Table Part VI.1. List of Important Risks and Missing Information**

| | |
|---|---|
| **Important Identified Risks** | None |
| **Important Potential Risks** | None |
| **Missing Information** | None |

## III.B. Summary of Important Risks

Sovaldi has been assigned the legal status of a medicine subject to medical prescription in the European Union (EU), whereby Sovaldi therapy should be initiated by a doctor experienced in the management of HCV infection (as described in section 4.2 of the SmPC).

There are no important risks or missing information for Sovaldi.

## III.C. Post-authorization Development Plan

### III.C.1. Studies which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or a specific obligation of Sovaldi.

### III.C.2. Other Studies in Post-Authorization Development Plan

There are no studies required for Sovaldi.

# PART VII: ANNEXES

**Table of Contents**

**Annex 1. EudraVigilance Interface**

This XML file is submitted electronically and can be provided on request.

**Annex 2. Tabulation Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program**

**Annex 3. Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan**

**Annex 4. Specific Adverse Drug Reaction Follow-up Forms**

None

**Annex 5. Protocols for Proposed and Ongoing Studies in RMP Part IV**

None

**Annex 6. Details of Proposed Additional Risk Minimization Measures (if applicable)**

Not applicable

**Annex 7. Other Supporting Data (Including Referenced Material)**

The following information is included in this annex:

- Referenced material (Refer to REFERENCES)

**Annex 8. Summary of Changes to the Risk Management Plan over Time**

# 1. REFERENCES

Adinolfi LE, Gambardella M, Andreana A, Tripodi MF, Utili R, Ruggiero G. Steatosis accelerates the progression of liver damage of chronic hepatitis C patients and correlates with specific HCV genotype and visceral obesity. Hepatology 2001;33 (6):1358-64.

Allison ME, Wreghitt T, Palmer CR, Alexander GJ. Evidence for a link between hepatitis C virus infection and diabetes mellitus in a cirrhotic population. J Hepatol 1994;21 (6):1135-9.

Alter MJ. Epidemiology of hepatitis C virus infection. World J Gastroenterol 2007;13 (17):2436-41.

Amin J, Law MG, Bartlett M, Kaldor JM, Dore GJ. Causes of death after diagnosis of hepatitis B or hepatitis C infection: a large community-based linkage study. Lancet 2006;368 (9539):938-45.

Angulo P, Keach JC, Batts KP, Lindor KD. Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis. Hepatology 1999;30 (6):1356-62.

Armstrong GL, Alter MJ, McQuillan GM, Margolis HS. The past incidence of hepatitis C virus infection: implications for the future burden of chronic liver disease in the United States. Hepatology 2000;31 (3):777-82.

Aroldi A, Lampertico P, Montagnino G, Passerini P, Villa M, Campise MR, et al. Natural history of hepatitis B and C in renal allograft recipients. Transplantation 2005;79 (9):1132-6.

Balagopal A, Thio CL. Another Call to Cure Hepatitis B. CID 2015;61:1307-9.

Basseri B, Yamini D, Chee G, Enayati PD, Tran T, Poordad F. Comorbidities associated with the increasing burden of hepatitis C infection. Liver Int 2010;30 (7):1012-8.

Belperio P. Hepatitis C: Evaluation of Hepatitis B Reactivation Among 62,920 Veterans Treated With Oral Veterans Treated With Oral Hepatitis C Antivirals [Abstract]. Hepatology 2017:7.

Benallai DC, Perez BM, G. VM, Soria IC, Alvarez AC. Prior HBV Infection. A Case of Reactivation Following Treatment with Sofosbuvir/Ledipasvir in a Patient Coinfected with HCV and HIV [Abstract]. SED Gastrointestinal Diseases Week; 2017 09-11 June; Madrid, Spain.

Bica I, McGovern B, Dhar R, Stone D, McGowan K, Scheib R, et al. Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. Clin Infect Dis 2001;32 (3):492-7.

Biliotti E, Kondili LA, Furlan C, Ferretti G, Zacharia S, De Angelis M, et al. Acute hepatitis B in patients with or without underlying chronic HCV infection. J Infect 2008;57 (2):152-7.

Bini EJ, Perumalswami PV. Hepatitis B virus infection among American patients with chronic hepatitis C virus infection: prevalence, racial/ethnic differences, and viral interactions. Hepatology 2010;51 (3):759-66.

Cacoub P, Comarmond C, Domont F, Savey L, Desbois AC, Saadoun D. Extrahepatic manifestations of chronic hepatitis C virus infection. Therapeutic advances in infectious disease 2016;3 (1):3-14.

Cacoub P, Geffray L, Rosenthal E, Perronne C, Veyssier P, Raguin G. Mortality among human immunodeficiency virus-infected patients with cirrhosis or hepatocellular carcinoma due to hepatitis C virus in French Departments of Internal Medicine/Infectious Diseases, in 1995 and 1997. Clin Infect Dis 2001;32 (8):1207-14.

Caronia S, Taylor K, Pagliaro L, Carr C, Palazzo U, Petrik J, et al. Further evidence for an association between non-insulin-dependent diabetes mellitus and chronic hepatitis C virus infection. Hepatology 1999;30 (4):1059-63.

Carvalho GC, Regis Cde A, Kalil JR, Cerqueira LA, Barbosa DS, Motta MP, et al. Causes of renal failure in patients with decompensated cirrhosis and its impact in hospital mortality. Ann Hepatol 2012;11 (1):90-5.

Centers for Disease Control and Prevention (CDC). Hepatitis C FAQs for Health Professionals. Updated: 31 May 2015.

Chak E, Talal AH, Sherman KE, Schiff ER, Saab S. Hepatitis C virus infection in USA: an estimate of true prevalence. Liver Int 2011;31 (8):1090-101.

Chen G, Wang C, Chen J, Ji D, Wang Y, Wu V, et al. Hepatitis B reactivation in hepatitis B and C coinfected patients treated with antiviral agents: A systematic review and meta-analysis. Hepatology 2017.

Chen SL, Morgan TR. The natural history of hepatitis C virus (HCV) infection. Int J Med Sci 2006;3 (2):47-52.

Chen W, Wong T, Tomlinson G, Krahn M, Heathcote EJ. Prevalence and predictors of obesity among individuals with positive hepatitis C antibody in a tertiary referral clinic. J Hepatol 2008;49 (5):711-7.

Chu CM, Yeh CT, Liaw YF. Low-level viremia and intracellular expression of hepatitis B surface antigen (HBsAg) in HBsAg carriers with concurrent hepatitis C virus infection. J Clin Microbiol 1998;36 (7):2084-6.

Clouston AD, Jonsson JR, Purdie DM, Macdonald GA, Pandeya N, Shorthouse C, et al. Steatosis and chronic hepatitis C: analysis of fibrosis and stellate cell activation. J Hepatol 2001;34 (2):314-20.

Collins JM, Raphael KL, Terry C, Cartwright EJ, Pillai A, Anania FA, et al. Hepatitis B Virus Reactivation During Successful Treatment of Hepatitis C Virus With Sofosbuvir and Simeprevir. Clin Infect Dis 2015;61 (8):1304-6.

Cornberg M, Razavi HA, Alberti A, Bernasconi E, Buti M, Cooper C, et al. A systematic review of hepatitis C virus epidemiology in Europe, Canada and Israel. Liver Int 2011;31 Suppl 2:30-60.

Coughlan B, Sheehan J, Hickey A, Crowe J. Psychological well-being and quality of life in women with an iatrogenic hepatitis C virus infection. Br J Health Psychol 2002;7 (Pt 1):105-16.

Crockett SD, Keeffe EB. Natural history and treatment of hepatitis B virus and hepatitis C virus coinfection. Ann Clin Microbiol Antimicrob 2005;4:13.

Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings LW. 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 (2):513-21, 21 e1-6.

Eguchi Y, Mizuta T, Ishibashi E, Kitajima Y, Oza N, Nakashita S, et al. Hepatitis C virus infection enhances insulin resistance induced by visceral fat accumulation. Liver Int 2009;29 (2):213-20.

El-Shabrawi MH, Kamal NM. Burden of pediatric hepatitis C. World J Gastroenterol 2013;19 (44):7880-8.

Ende AR, Kim NH, Yeh MM, Harper J, Landis CS. Fulminant hepatitis B reactivation leading to liver transplantation in a patient with chronic hepatitis C treated with simeprevir and sofosbuvir: a case report. J Med Case Rep 2015;9:164.

European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C: Final update of the series. J Hepatol 2020:1-49.

European Association for the Study of the Liver (EASL). EASL Recommendations on Treatment of Hepatitis C 2018. Journal of Hepatology (Abstracts) 2018;2018.

Eyster ME, Diamondstone LS, Lien JM, Ehmann WC, Quan S, Goedert JJ. Natural history of hepatitis C virus infection in multitransfused hemophiliacs: effect of coinfection with human immunodeficiency virus. The Multicenter Hemophilia Cohort Study. J Acquir Immune Defic Syndr 1993;6 (6):602-10.

Fabrizi F, Plaisier E, Saadoun D, Martin P, Messa P, Cacoub P. Hepatitis C virus infection, mixed cryoglobulinemia, and kidney disease. Am J Kidney Dis 2013;61 (4):623-37.

Fabrizi F, Poordad FF, Martin P. Hepatitis C infection and the patient with end-stage renal disease. Hepatology 2002;36 (1):3-10.

Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology 1997;112 (2):463-72.

Fissell RB, Bragg-Gresham JL, Woods JD, Jadoul M, Gillespie B, Hedderwick SA, et al. Patterns of hepatitis C prevalence and seroconversion in hemodialysis units from three continents: the DOPPS. Kidney Int 2004;65 (6):2335-42.

Gish RG, Afdhal NH, Dieterich DT, Reddy KR. Management of hepatitis C virus in special populations: patient and treatment considerations. Clin Gastroenterol Hepatol 2005;3 (4):311-8.

Hamzaoui L, El Bouchtili S, Siai K, Mahmoudi M, Azzouz MM. Hepatitis B virus and hepatitis C virus co-infection: a therapeutic challenge. Clin Res Hepatol Gastroenterol 2013;37 (1):e16-20.

Hauser P, Khosla J, Aurora H, Laurin J, Kling MA, Hill J, et al. A prospective study of the incidence and open-label treatment of interferon-induced major depressive disorder in patients with hepatitis C. Mol Psychiatry 2002;7 (9):942-7.

Hayashi K, Ishigami M, Ishizu Y, Kuzuya T, Honda T, Nishimura D, et al. A case of acute hepatitis B in a chronic hepatitis C patient after daclatasvir and asunaprevir combination therapy: hepatitis B virus reactivation or acute self-limited hepatitis? Clin J Gastroenterol 2016;9 (4):252-6.

Hezode C, Lonjon I, Roudot-Thoraval F, Mavier JP, Pawlotsky JM, Zafrani ES, et al. Impact of smoking on histological liver lesions in chronic hepatitis C. Gut 2003;52 (1):126-9.

Kakinami L, Block RC, Adams MJ, Cohn SE, Maliakkal B, Fisher SG. Risk of cardiovascular disease in HIV, hepatitis C, or HIV/hepatitis C patients compared to the general population. Int J Clin Pract 2013;67 (1):6-13.

Kamar N, Alric L, Izopet J, Rostaing L. Hepatitis C virus and kidney disease. Clin Res Hepatol Gastroenterol 2013;37 (4):328-33.

Kantar Health. Epi Database - Hepatitis C Prevalence EU & US. Available at: www.epidb.com. Accessed: October 2016. 2014.

Kasahara M, Matsumoto Y, Kawahara Y, Eto M, Seki M, Sano M. A Case of Hepatitis B Virus Reactivation After the Initiation of Oral Ledipasvir-Sofosbuvir Therapy [Abstract G1702889]. The 38th Kinki Regional Meeting of the Japanese Society of Hospital Pharmacists; 2017 25-26 February; Osaka City, Osaka Prefecture.

Khaderi S, Shepherd R, Goss JA, Leung DH. Hepatitis C in the pediatric population: transmission, natural history, treatment and liver transplantation. World J Gastroenterol 2014;20 (32):11281-6.

Kim AI, Saab S. Treatment of hepatitis C. Am J Med 2005;118 (8):808-15.

Kim WR, Gross JB, Jr., Poterucha JJ, Locke GR, 3rd, Dickson ER. Outcome of hospital care of liver disease associated with hepatitis C in the United States. Hepatology 2001;33 (1):201-6.

Knobler H, Stagnaro-Green A, Wallenstein S, Schwartz M, Roman SH. Higher incidence of diabetes in liver transplant recipients with hepatitis C. J Clin Gastroenterol 1998;26 (1):30-3.

Konstantinou D, Deutsch M. The spectrum of HBV/HCV coinfection: epidemiology, clinical characteristics, viralinteractions and management. Ann Gastroenterol 2015;28 (2):221-8.

Liaw YF. Role of hepatitis C virus in dual and triple hepatitis virus infection. Hepatology 1995;22 (4 Pt 1):1101-8.

Liaw YF, Chen YC, Sheen IS, Chien RN, Yeh CT, Chu CM. Impact of acute hepatitis C virus superinfection in patients with chronic hepatitis B virus infection. Gastroenterology 2004;126 (4):1024-9.

Liu JY, Sheng YJ, Hu HD, Zhong Q, Wang J, Tong SW, et al. The influence of hepatitis B virus on antiviral treatment with interferon and ribavirin in Asian patients with hepatitis C virus/hepatitis B virus coinfection: a meta-analysis. Virol J 2012;9:186.

Londono MC, Lens S, Marino Z, Bonacci M, Ariza X, Broquetas T, et al. Hepatitis B reactivation in patients with chronic hepatitis C undergoing anti-viral therapy with an interferon-free regimen. Aliment Pharmacol Ther 2017:1-6.

Macera M, Stanzione M, Messina V, D'Adamo G, Sangiovanni V, Mioglioresi L, et al. Interferon-Free Regimens in Hepatitis B Surface Antigen/Anti-Hepatitis C Virus Positive Patients: The Need to Control Hepatitis B Virus Replication to Avoid Hepatitis B Virus Reactivation. Clin Gastroenterol Hepatol 2017;15 (11):1800-2.

Mahajan R, Xing J, Liu SJ, Ly KN, Moorman AC, Rupp L, et al. Mortality among persons in care with hepatitis C virus infection: the Chronic Hepatitis Cohort Study (CHeCS), 2006-2010. Clin Infect Dis 2014;58 (8):1055-61.

Martin-Carbonero L, Soriano V, Valencia E, Garcia-Samaniego J, Lopez M, Gonzalez-Lahoz J. Increasing impact of chronic viral hepatitis on hospital admissions and mortality among HIV-infected patients. AIDS Res Hum Retroviruses 2001;17 (16):1467-71.

Martin P, Fabrizi F. Hepatitis C virus and kidney disease. J Hepatol 2008;49 (4):613-24.

Mason AL, Lau JY, Hoang N, Qian K, Alexander GJ, Xu L, et al. Association of diabetes mellitus and chronic hepatitis C virus infection. Hepatology 1999;29 (2):328-33.

Mehta SH, Brancati FL, Sulkowski MS, Strathdee SA, Szklo M, Thomas DL. Prevalence of type 2 diabetes mellitus among persons with hepatitis C virus infection in the United States. Ann Intern Med 2000;133 (8):592-9.

Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global Epidemiology of Hepatitis C Virus Infection: New Estimates of Age-Specific Antibody to HCV Seroprevalence. Hepatology 2013;57 (4):1333-42.

Mohsen AH, Easterbrook PJ, Taylor C, Portmann B, Kulasegaram R, Murad S, et al. Impact of human immunodeficiency virus (HIV) infection on the progression of liver fibrosis in hepatitis C virus infected patients. Gut 2003;52 (7):1035-40.

Negro F, Sanyal AJ. Hepatitis C virus, steatosis and lipid abnormalities: clinical and pathogenic data. Liver Int 2009;29 Suppl 2:26-37.

Nwaohiri A, Schillie S, Bulterys M, Kourtis AP. Hepatitis C Virus Infection in Children: How Do We Prevent It and How Do We Treat It? Expert Rev Anti Infect Ther 2018;16 (9):689-94.

Ogawa E, Furusho N, Murata M, Kaseida F, Toyoda K, Hayashi J. Hepatitis B Virus (HBV) Reactivation after Direct-Acting Antiviral (DAA) Therapy for Hepatitis C in Patients with Past HBV Infection [Abstract G1674552]. The 91st Annual Meeting of the Japanese Association for Infectious Diseases; 2017 06-08 April; Shinjuku-ku, Tokyo.

Omland LH, Jepsen P, Krarup H, Schonning K, Lind B, Kromann-Andersen H, et al. Increased Mortality Among Persons Infected With Hepatitis C Virus. Clin Gastroenterol Hepatol 2011;9 (1):71-8.

Operskalski EA, Kovacs A. HIV/HCV co-infection: pathogenesis, clinical complications, treatment, and new therapeutic technologies. Curr HIV/AIDS Rep 2011;8 (1):12-22.

Ortiz V, Berenguer M, Rayon JM, Carrasco D, Berenguer J. Contribution of obesity to hepatitis C-related fibrosis progression. Am J Gastroenterol 2002;97 (9):2408-14.

Ou P, Fang Z, Chen J. Hepatitis B reactivation in a chronic hepatitis C patient treated with ledipasvir and sofosbuvir: A case report. Clin Res Hepatol Gastroenterol 2017;41 (2):e17-e8.

Pallas JR, Farinas-Alvarez C, Prieto D, Delgado-Rodriguez M. Coinfections by HIV, hepatitis B and hepatitis C in imprisoned injecting drug users. Eur J Epidemiol 1999;15 (8):699-704.

Papafragkakis H, Rao MS, Dhillon S, Moehlen M, Martin P. Depression and pegylated interferon-based hepatitis C treatment. International Journal of Interferon, Cytokine and Mediator Research 2012;4:25–35.

Paydak H, Pothineni NV, Vallurupalli S, Mehta JL. Hepatitis C Patients Have a Higher Risk of Atrial Fibrillation [Abstract]. International Academy of Cardiology Annual Scientific Sessions 2014: 19th World Congression on Heart Disease; 2014 July 25-28; Boston MA United States.

Petrides AS, DeFronzo RA. Glucose and insulin metabolism in cirrhosis. J Hepatol 1989;8 (1):107-14.

Potthoff A, Berg T, Wedemeyer H, Group H-NBCCS. Late hepatitis B virus relapse in patients co-infected with hepatitis B virus and hepatitis C virus after antiviral treatment with pegylated interferon-a2b and ribavirin. Scand J Gastroenterol 2009;44 (12):1487-90.

Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet 1997;349 (9055):825-32.

Pyrsopoulos NT, Jeffers L. Chronic Hepatitis C in African Americans. Clinics in Liver Disease 2005;9 (2005):427-38.

Quaranta JF, Delaney SR, Alleman S, Cassuto JP, Dellamonica P, Allain JP. Prevalence of antibody to hepatitis C virus (HCV) in HIV-1-infected patients (nice SEROCO cohort). J Med Virol 1994;42 (1):29-32.

Raimondo G, Cacciamo G, Saitta C. Hepatitis B virus and hepatitis C virus co-infection: additive players in chronic liver disease? Ann Hepatol 2005;4 (2):100-6.

Raison CL, Borisov AS, Broadwell SD, Capuron L, Woolwine BJ, Jacobson IM, et al. Depression during pegylated interferon-alpha plus ribavirin therapy: prevalence and prediction. J Clin Psychiatry 2005;66 (1):41-8.

Reddy GA, Dakshinamurthy KV, Neelaprasad P, Gangadhar T, Lakshmi V. Prevalence of HBV and HCV dual infection in patients on haemodialysis. Indian J Med Microbiol 2005;23 (1):41-3.

Rockstroh JK. Management of hepatitis B and C in HIV-co-infected patients. Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology 2003;34 (Suppl 1):S59-S65.

Rockstroh JK. Influence of viral hepatitis on HIV infection. J Hepatol 2006;44 (1 Suppl):S25-7.

Rockstroh JK, Spengler U, Sudhop T, Ewig S, Theisen A, Hammerstein U, et al. Immunosuppression may lead to progression of hepatitis C virus-associated liver disease in hemophiliacs coinfected with HIV. Am J Gastroenterol 1996;91 (12):2563-8.

Roed T, Lebech AM, Kjaer A, Weis N. Hepatitis C virus infection and risk of coronary artery disease: a systematic review of the literature. Clin Physiol Funct Imaging 2012;32 (6):421-30.

Saiz de la Hoya P, Marco A, Garcia-Guerrero J, Rivera A. Hepatitis C and B prevalence in Spanish prisons. Eur J Clin Microbiol Infect Dis 2011;30 (7):857-62.

Saravanan S, Velu V, Nandakumar S, Madhavan V, Shanmugasundaram U, Murugavel KG, et al. Hepatitis B virus and hepatitis C virus dual infection among patients with chronic liver disease. J Microbiol Immunol Infect 2009;42 (2):122-8.

Schafer A, Wittchen HU, Seufert J, Kraus MR. Methodological approaches in the assessment of interferon-alfa-induced depression in patients with chronic hepatitis C - a critical review. Int J Methods Psychiatr Res 2007;16 (4):186-201.

Seeff LB. Natural history of hepatitis C. Am J Med 1999;107 (6B):10S-5S.

Serfaty L, Capeau J. Hepatitis C, insulin resistance and diabetes: clinical and pathogenic data. Liver Int 2009;29 Suppl 2:13-25.

Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis 2005;5 (9):558-67.

Simo R, Hernandez C, Genesca J, Jardi R, Mesa J. High prevalence of hepatitis C virus infection in diabetic patients. Diabetes Care 1996;19 (9):998-1000.

Soriano V, Garcia-Samaniego J, Valencia E, Rodriguez-Rosado R, Munoz F, Gonzalez-Lahoz J. Impact of chronic liver disease due to hepatitis viruses as cause of hospital admission and death in HIV-infected drug users. Eur J Epidemiol 1999;15 (1):1-4.

Soriano V, Sulkowski M, Bergin C, Hatzakis A, Cacoub P, Katlama C, et al. Care of patients with chronic hepatitis C and HIV co-infection: recommendations from the HIV-HCV International Panel. AIDS 2002;16 (6):813-28.

Takayama H, Sato T, Ikeda F, Fujiki S. Reactivation of hepatitis B virus during interferon-free therapy with daclatasvir and asunaprevir in patient with hepatitis B virus/hepatitis C virus co-infection. Hepatol Res 2016;46 (5):489-91.

The Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol 2017;2:161–76.

Thrift AP, El-Serag HB, Kanwal F. Global epidemiology and burden of HCV infection and HCV-related disease. Nat Rev Gastroenterol Hepatol 2017;14 (2):122-32.

Tyson GL, Kramer JR, Duan Z, Davila JA, Richardson PA, El-Serag HB. Prevalence and predictors of hepatitis B virus coinfection in a United States cohort of hepatitis C virus-infected patients. Hepatology 2013;58 (2):538-45.

Vigano M, Aghemo A, Iavarone M, Rumi MG, Agnelli F, Lampertico P, et al. The course of inactive hepatitis B in hepatitis-C-coinfected patients treated with interferon and ribavirin. Antivir Ther 2009.

Wang C, Ji D, Chen J, Shao Q, Li B, Liu J, et al. Hepatitis due to Reactivation of Hepatitis B Virus in Endemic Areas Among Patients With Hepatitis C Treated With Direct-acting Antiviral Agents. Clinical Gastroenterology and Hepatology 2017;15 (1):132–6.

Wiegand SB, Jaroszewicz J, Potthoff A, Honer Zu Siederdissen C, Maasoumy B, Deterding K, et al. Dominance of hepatitis C virus (HCV) is associated with lower quantitative hepatitis B surface antigen and higher serum interferon-gamma-induced protein 10 levels in HBV/HCV-coinfected patients. Clin Microbiol Infect 2015;21 (7):710 e1-9.

World Health Organization (WHO). Global Hepatitis Report. 2017.

World Health Organization (WHO), The Department of Immunization Vaccines and Biologicals. State of the art of vaccine research and development. Initiative for Vaccines Research Team of the Department of Immunization, Vaccines and Biologicals June, 2005.

Yalcin K, Degertekin H, Yildiz F, Kilinc N. A severe hepatitis flare in an HBV-HCV coinfected patient during combination therapy with alpha-interferon and ribavirin. J Gastroenterol 2003;38 (8):796-800.

Yu ML, Lee CM, Chen CL, Chuang WL, Lu SN, Liu CH, et al. Sustained hepatitis C virus clearance and increased hepatitis B surface antigen seroclearance in patients with dual chronic hepatitis C and B during posttreatment follow-up. Hepatology 2013;57 (6):2135-42.

Zarski JP, Bohn B, Bastie A, Pawlotsky JM, Baud M, Bost-Bezeaux F, et al. Characteristics of patients with dual infection by hepatitis B and C viruses. J Hepatol 1998;28 (1):27-33.

Zhou J, Dore GJ, Zhang F, Lim PL, Chen YM. Hepatitis B and C virus coinfection in The TREAT Asia HIV Observational Database. J Gastroenterol Hepatol 2007;22 (9):1510-8.