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Summary of the risk management plan (RMP) for Harvoni (ledipasvir/sofosbuvir)

This is a summary of the risk management plan (RMP) for Harvoni, which details the measures to be taken in order to ensure that Harvoni is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Harvoni, which can be found on Harvoni's EPAR page.

Overview of disease epidemiology

Harvoni is used to treat chronic (long-term) hepatitis C, an infectious disease of the liver caused by the hepatitis C virus (HCV). It is estimated that between 1.1% and 1.3% of the population in the EU is infected with the virus, which can cause long-term complications such as cirrhosis (scarring of the liver), liver failure or liver cancer, and may lead to death.

Across the globe, most hepatitis C infections occur in the Western Pacific, South East Asia, and the Eastern Mediterranean region. There are several varieties (or genotypes) of the HCV, with genotype 1 being the most common in Europe.

Young adults and men are more frequently infected. HCV is usually transmitted through contact with blood of an infected person. The main risk factors for infection are illegal drug use, unsafe injections and blood transfusions.

Summary of treatment benefits

Harvoni was investigated in three main studies involving a total of around 2,000 patients infected with hepatitis C of genotype 1 who did not have liver failure. In all three studies, the main measure of effectiveness was the number of patients whose blood tests did not show any sign of hepatitis C virus 12 weeks after the end of treatment.

In these studies, patients were given Harvoni, with or without ribavirin, for 8, 12 or 24 weeks, depending on the characteristics of the patients. Around 94% to up to 99% of patients given Harvoni alone tested negative for the virus 12 weeks after the end of treatment. The addition of ribavirin was not needed for most patients.

Results of the studies also showed that patients who have compensated cirrhosis (scarring of the liver but who maintained liver function) had a higher likelihood of clearing the virus when treatment was extended to 24 weeks. Patients whose infection was resistant to other antiviral medicines could also benefit from extending treatment to 24 weeks.

Supportive data showed that Harvoni in combination with ribavirin would be of benefit for some patients with genotype 3 virus, as well as for patients with genotype 1 or 4 and decompensated cirrhosis (scarring of the liver with reduced liver function) and/or for those who had received a liver transplant.

Unknowns relating to treatment benefits

In the main studies of Harvoni, most patients were white males under the age of 65. There is no evidence to suggest that results would be different in non-white, female, or older patients.

Summary of safety concerns

Important identified risks

There are currently no important identified risks for Harvoni.

Important potential risks

Risk	What is known
Risk of reduced effectiveness in patients taking Harvoni with rifampicin, carbamazepine, phenytoin and St. John's wort	The antibiotic rifampicin lowers the levels of Harvoni in the blood, which could lead to Harvoni not being effective in the treatment of HCV infection. Carbamazepine and phenytoin (medicines used to treat epilepsy and prevent seizures) are expected to do the same. St. John's wort (a herbal medicine used to treat depression) is expected to do the same. Therefore, Harvoni should not be administered with rifampicin, carbamazepine, phenytoin or St. John's wort.
Risk of reduced effectiveness in patients taking Harvoni and omeprazole	Omeprazole (or similar acid reducing medicines to reduce stomach acid, known as proton pump inhibitors) might lower the levels of ledipasvir –one of the active substances in Harvoni- in the blood, which could lead to Harvoni not being effective in the treatment of HCV infection. Therefore the recommended dose of omeprazole is limited to 20 mg or the equivalent of 20 mg omeprazole if another proton pump inhibitor is used. Proton pump inhibitors and Harvoni should be taken at the same time. Proton pump inhibitors should not be taken before Harvoni.
Risk of kidney problems in patients infected with both HCV and HIV, and who are taking Harvoni with tenofovir and with a "boosted" protease inhibitor	People with the HCV virus who are also infected with HIV might take medicines for both diseases. Medicines for HIV sometimes include tenofovir and may also include medicines from a class known as protease inhibitors, which are often combined with a "booster", a medicine that prolongs their action in the body. The triple combination of Harvoni plus tenofovir plus the booster can make tenofovir's blood levels rise, which might lead to kidney problems that can sometimes be serious or even fatal. The frequency of kidney problems is very low: in clinical studies involving tenofovir, the frequency of increased creatinine (a substance in the blood used as a measure of how the kidneys are working) was 0.2% (1 out of 500 patients) and of kidney failure was 0.06% (3 out of 5000 patients). Kidney problems are preventable by measuring creatinine blood levels at the start of treatment and during treatment, by avoiding use of other medicines that may damage the kidneys, and by the doctor considering stopping tenofovir if kidney problems develop.
Risk of interaction	The use of Harvoni with the cholesterol-lowering medicine rosuvastatin might

Risk	What is known
with medicines containing rosuvastatin	increase the blood levels of the latter, which could lead to problems in muscles, blood, and kidneys. Therefore, the use of rosuvastatin with Harvoni is contraindicated.
Digoxin build-up when taken with Harvoni	Digoxin (a medicine to treat heart rythm problems) can be taken with Harvoni, but digoxin levels might increase and build-up, which could lead to heart problems. Therefore, the doctor should monitor the blood levels of digoxin.

Missing information

Risk	What is known
No information on use in children	The safety and efficacy of Harvoni have not yet been established in children below 18 years of age, thus treatment with Harvoni is not recommended in this population.
Limited information on the use in pregnant or breastfeeding women	The effects of Harvoni on pregnant women or on the unborn child are not known. As a precautionary measure, it is preferable not to use Harvoni during pregnancy. It is not known whether the active substances in Harvoni (ledipasvir or sofosbuvir) pass into human breast milk. Mothers should be instructed not to breastfeed if they are taking Harvoni.
Limited information on patients infected both with HCV and HIV	Harvoni can be used with several HIV medicines and this information can be found in the medicine's product information. Patients should tell their doctor if they are taking a medicine that contains tenofovir.
Limited information on patients infected both with HCV and HBV (Hepatitis B virus)	Harvoni can be used in patients with HCV and HBV co-infection. However, more information on the use of Harvoni in patients with HCV/HBV co-infection is needed. A clinical study will provide more information on these patients.
Limited information on use in patients with severely decreased kidney function or patients on dialysis	Harvoni can be given to patients with mild or moderate kidney disease. The safety of Harvoni in patients with severely decreased kidney function is not established. A clinical study will provide information about these patients. Results from separate studies of ledipasvir and sofosbuvir in patients with severely reduced kidney function show that ledipasvir can be given to patients with severely reduced renal function. Blood levels of sofosbuvir and its main breakdown product in the body were 2.71 times and 5.51-fold higher respectively in patients with severely decreased kidney function. In patients on dialysis, the drug level of sofosbuvir's main breakdown product was 13.8-fold higher when sofosbuvir was given 1 hour before dialysis and 21.7-fold higher when sofosbuvir was dosed 1 hour after dialysis.
Development of viral resistance	Data is missing on how well Harvoni will work to re-treat patients who were not successful with previous Harvoni treatment due to the virus becoming

Risk	What is known
	resistant to ledipasvir.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Harvoni can be found on Harvoni's EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
GS-US-337-1115 (formerly BP-US-337-0103) (Interventional clinical study)	To evaluate the pharmakokinetics (extent to which Harvoni achieves adequate levels in the body) and the safety of an age-appropriate paediatric ~~H~~arvoni formulation, in healthy adult volunteers	Missing information: Safety in children	Planned	Final study report April 2016
GS-US-337-1116 (formerly BP-US-337-0104) (Interventional clinical study)	To evaluate how the body breaks down Harvoni and the efficacy and safety of Harvoni for 12 weeks in adolescents and children	Missing information: Safety in children	Planned	Final study report June 2019
GS-US-334-0154 (Interventional clinical study)	To evaluate the safety, efficacy and pharmacokynetics of sofosbuvir+ribavirin for 24 weeks in subjects with chronic genotype 1 or 3 HCV infection and severe renal impairment	Missing information: Safety in patients with severe renal impairment or end-stage renal disease	Started	Final study report July 2017

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
GS-US-337-0115 (Interventional clinical study)	To evaluate the safety and efficacy of treatment with Harvoni ± ribavirin in subjects with HCV/HIV co-infection	Missing information: Safety in patients with HCV/HIV co-infection	Started	March 2017
GS-US-337-0122 Electron 2: A Phase 2, Multicenter, Open-Label Study to Assess the Efficacy and Safety of Sofosbuvir Containing Regimens for the Treatment of Chronic HCV Infection.	To evaluate the safety and efficacy of combination therapy with sofosbuvir-containing regimens for the treatment of chronic HCV infection	One part of the study will provide safety information in patients with HCV/HBV co-infection	Started	June 2016
GS-US-337-1118 An Open-Label, Multicenter Study To Evaluate The Efficacy And Safety Of Sofosbuvir/Ledipasvir Fixed-Dose Combination ± Ribavirin For 12 or 24 Weeks In Chronic Genotype 1 HCV Infected Subjects Who Participated In A Prior Gilead-Sponsored HCV Treatment Study	To determine the efficacy of Harvoni±ribavirin and to evaluate the emergence of viral resistance to ledipasvir and sofosbuvir during and after treatment discontinuation	Safety, efficacy, and development of resistance	Started	January 2017
BP-US-337-1117 (Noninterventional clinical study)	To evaluate growth and possible reappearance of HCV in adolescents and children who received Harvoni in study GS-US-337-1116	Missing information: Safety in children	Planned	March 2024

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
GS-US-248-0123 A Long Term Follow-up Registry Study of Subjects Who Did Not Achieve Sustained Virologic Response in Gilead-Sponsored Trials in Subjects with Chronic Hepatitis C Infection	To evaluate HCV viral sequences and the persistence or evolution of treatment-emergent viral mutations in subjects who fail to clear the infection after treatment with certain oral antiviral containing regimen in a previous hepatitis C study sponsored by the company	Development of resistance	Started	July 2020
GS-(name not available yet) A prospective observational drug utilization study of Harvoni in adults with HCV/HIV co-infection is planned	To characterise the postmarketing use of Harvoni+tenofovir+ booster in adult HCV/HIV coinfected patients and the rates of adverse events and adverse drug reactions	HCV/HIV co-infection	Planned	To be determined
GS-(name not available yet) A clinical study to assess the effect of LDV on CYP3A probe midazolam	To assess the effect of ledipasvir on a CYP3A probe drug	Drug interaction	Planned	To be determined

Studies which are a condition of the marketing authorisation

None of the above studies are a condition of the marketing authorisation.

Summary of changes to the risk management plan over time

Major changes to the Risk Management Plan over time

Not applicable.

This summary was last updated in 10-2014.