**MINISTRY OF HEALTH OF UKRAINE**
**BOGOMOLETS NATIONAL MEDICAL UNIVERSITY**
**FACULTY OF PHARMACY**
**DEPARTMENT OF CLINICAL PHARMACOLOGY**
**AND CLINICAL PHARMACY**

Theme of master's work

# CLINICAL AND PHARMACOLOGICAL LIMITATIONS OF PRESCRIBING DIRECT-ACTING ANTIVIRAL DRUGS IN THE TREATMENT OF CHRONIC VIRAL HEPATITIS C

Department of Clinical Pharmacology and Clinical Pharmacy
(Head - Doctor of Medical Sciences, Professor Khaitovich M.V.)
Scientific supervisor, Doctor of Medical Sciences, Professor Pinsky L.L.
Creator: SAHIHI Basma

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TABLE OF CONTENT

# LIST OF ABBREVIATIONS

- ACE - Angiotensin-Converting Enzyme
- AUC – Area Under The Curve
- BCRP – Breast Cancer Resistance Protein
- CHC - Chronic Hepatitis C
- DAA – Direct-Acting Antivirals
- ECG – Electrocardiogram
- G-CSF – Granulocyte Colony Stimulating Factor
- HCV – Hepatitis C Virus
- NS5-A – Nonstructural Protein 5A
- Peg-interferon – Pegylated interferon
- P-gp – P-glycoprotein
- RBV – Ribavirin
- SVR – Sustained Virologic Response
- TPO – Thrombopoetin
- WHO – World Health Organization

# INTRODUCTION

**Relevance of the topic.** Over the past decades, the strategy of virus elimination in patients with chronic hepatitis C (CHC) has changed dramatically. More than 10 years ago, a combination of pegylated interferons with ribavirin was used, which, within 6-12 months of treatment, induced significant side effects: severe depression, hyperthermia, autoimmune reactions, alopecia, neutropenia, anemia, and others. With the advent of new standards for HCV virus elimination with direct antiviral drugs (DPP), which demonstrate not only 95-98 percent effectiveness during a 3-month course of treatment, but a minimum number of adverse reactions. However, the widespread introduction of these pharmacotherapeutic technologies, when not only infectious disease specialists and gastroenterologists, but also general practitioners and general practitioners, are involved in the treatment of CHC, significantly increases the likelihood of developing undesirable, and in some cases dangerous, side interactions of these drugs (drugs).

**The aim of the study** is to analyze the clinical and pharmacological interaction of direct antiviral drugs (DAPs) sofosbuvir and velpatasvir for the treatment of chronic viral hepatitis C (CHC) with cardiotropic and lipid-lowering drugs.

**Research objectives:**

1. Determine the clinical and pharmacological limitations of the combined use of PPLS with antiarrhythmic drugs.
2. Establish potential adverse interactions when using PPLS with antihypertensive drug groups.
3. Evaluate the possibility of using PPLS with lipid-lowering drugs in patients with CHC.

**Object of study:** direct-acting drugs for the treatment of chronic viral hepatitis C and their combination with cardiotropic and lipid-lowering drugs.

**Subject of study:** the use of a combination of direct antiviral drugs with cardiotropic and lipid-lowering drugs in patients with chronic viral hepatitis C.

**Research methods.** Bibliosemantic, statistical and graphical methods were used in the work.

**Practical significance of the obtained results.** Practical recommendations have been developed for physicians and pharmacists to prevent the prescription of dangerous combinations of direct antiviral drugs for the treatment of CHC with cardiotropic and lipid-lowering drugs.

**Approbation of the results of master's work.** The main results of the master's work are presented at: The Sixth Universiade in Clinical Pharmacology "Clinical and pharmacological restrictions in the appointment of direct-acting antiviral drugs in the treatment of chronic viral hepatitis C" (April 12, 2022, Kyiv); April student scientific session of the National Medical University named after O.O. Bogomolets "Clinical and pharmacological restrictions in the appointment of direct-acting antiviral drugs in the treatment of chronic viral hepatitis C" (April 19, 2022, Kyiv); 26th International medical congress of students and young scientists (13-15th of April, 2022, Ternopil, Ukraine) "Clinical and pharmacological limitations in prescribing direct-acting antiviral drugs in the treatment of chronic viral hepatitis C".

**Scientific novelty of the obtained results.**

1. For the first time, data on adverse interactions between cardiotropic and lipid-lowering drugs and direct antiviral drugs in the treatment of chronic hepatitis C were systematized.

2. A significant prevalence (26.9%) of the combined use of PPLS with statins was established, which is accompanied by myalgia, the symptoms of which decrease when statins are replaced with drugs from the fibrate group.

3. Physicians were well aware of the dangerous combination of PPLS with amiodarone and digoxin and the absence of such combinations in the examined medical records.

4. The frequency of prescribing Carvedilol (9.3%; 11 out of 118 cases) was established in the treatment of CHC with PPLS, which is potentially dangerous in

this therapy. The drugs of choice in this group of patients may be other beta-blockers: Atenolol, Bisoprolol, Propranolol, which do not induce side effects along with PPLS.

5. The appointment of Amplodipine as part of antihypertensive therapy together with PPLS for the treatment of CHC was detected in 11.9% of cases (14 out of 118 patients with CHC), which is a potentially dangerous combination. A reasonable alternative in this clinical situation is Nifedipine, which has no side effects when combined with PPLS.

5. The use of ACE inhibitors and angiotensin II receptor inhibitors (sartans) in HCV virus-eliminating therapy is quite safe and does not require additional adjustment of pharmacotherapy regimens. The safety of the simultaneous appointment of PPLS with Enalapril, Losartan has been proven.

# Section 1. CURRENT PROBLEMS OF PREVALENCE AND METHODS OF TREATMENT OF CHRONIC VIRAL HEPATITIS C

## 1.1. Prevalence, laboratory and instrumental methods of verification of chronic viral hepatitis C.

The hepatitis C virus is one of many hepatotropic agents capable of inducing liver fibrosis and the development of hepatocellular carcinoma. The global prevalence of this chronic viral pathology of the liver is 3-4% of the world's population [1, 2]. Only a small proportion of patients infected with HCV clear the virus on their own, and the majority (more than 80 percent of patients) develop chronic viral hepatitis C. The greatest problem for doctors and patients is anicterus and a small number of symptoms in HCV.

Simulated results were analyzed to determine the year in which each country would meet the WHO HCV requirements of reduced incidence (up to 80%) and mortality (up to 65%), and diagnostic (90%) and treatment (80%) coverage by level. 2015. Of the 45 high-income countries studied, 11 (Australia, Canada, France, Germany, Iceland, Italy, Japan, Spain, Sweden, Switzerland, United Kingdom) will eliminate HCV by 2030, five countries (Austria, Malta, the Netherlands, New Zealand and South Korea) until 2040 and one state (Saudi Arabia) until 2050 [2].

In the other 28 countries, HCV is not expected to be eliminated until 2050. The situation improved significantly in three countries (Canada, Germany and Sweden). In most (29) countries the situation will not change from the preliminary analysis. If high-income countries maintain current levels of diagnosis and treatment, only 24% of countries are on track to achieve elimination of HCV by 2030, and 62% are at least 20 years behind [3].

When conducting a nationwide retrospective cohort study, it was found that emigrants play a significant role in the progression of the spread of CHC, who make up 31.25% of the total structure of HCV carriers in North Africa - 31.25%, South America - 28.23%, in Southeast Asia - 19, sixteen%. Cirrhosis was established in emigrants in 22% of patients. SVR-12 data were available for 111 (91%) patients, of

which 100 (90%) achieved a viral elimination level of 12. Notably, only 65% of patients with genotype 3 infection achieved a viral elimination level of 12 [4].

To assess the likelihood of reinfection, 597 patients (mean age 44.5 years) were examined, in whom the level of viral elimination was noted after treatment. During follow-up, re-infection occurred in 42 patients (9 women, 33 men). High reinfection rates were associated with homelessness (24.3/100 PY), co-injection drug use (reinfection rate 26.2/100 years per year), and young age (20-24 years). The majority of re-infected patients were successfully treated [5].

The progression of CHC over many years occurs with minimal clinical symptoms, and without adequate hepatotropic and virus-eliminating therapy can lead to significant liver damage. These symptoms are usually nonspecific: fatigue, dyspepsia, occasional dark urine, discoloration of the stool. Over the years, inflammation of the liver can induce the progression of fibrosis and, in very advanced cases, cirrhosis. In patients with cirrhosis, decompensation is accompanied by increased fatigue, accumulation of fluid in the abdominal cavity (ascites), bleeding from the veins of the esophagus or stomach (varicose veins), and confusion (hepatic encephalopathy). Patients with advanced stages of fibrosis have an increased likelihood of developing hepatocellular carcinoma.

The priority of modern hepatology is the detection and cure of the disease before the development of liver cirrhosis and its complications.

Currently, there are highly effective and well-tolerated oral drugs for the treatment of hepatitis C. However, although research is ongoing, there is currently no effective hepatitis C vaccine [6].

**Geographical distribution of CHC**

CHC is most prevalent in the Eastern Mediterranean and Europe, where more than 12 million people have been identified in each of these areas. When conducting epidemiological studies, it was found that about 10 million people are chronically infected in Southeast Asia and the Western Pacific Ocean, 9 million in Africa, and 5 million in the USA with CHC [2].

**Laboratory diagnosis of hepatitis C virus**

To identify patients with CHC, there are two stages in the diagnosis of this pathology.

1. A serological test for HCV antibodies detects a patient infected with the virus.

2. If the test for antibodies to HCV is positive, it is advisable to prescribe a polymerase chain reaction to verify the virus in the blood itself, as well as a quantitative assessment of the virus and its genotype.

In clinical practice, it is important for physicians to understand that the expensive laboratory method of polymerase chain reaction is unsuitable for screening primary verification of CHC, since in 30 percent of cases this test will be negative in the presence of CHC.

Another significant factor in the laboratory diagnosis of CHC is that even after successful pharmacotherapeutic elimination of HCV, a high titer of anti-HCV IgG antibodies remains in the blood of patients for many years, and often for life, which unreasonably worries patients.

Important in assessing the state of the liver in patients with CHC before prescribing pharmacotherapy is the assessment of the severity of fibrosis, and during treatment, the assessment of the dynamics of this indicator. For this, ultrasonic research methods are used - elastometry, elastography, as well as modern laboratory tests - Fibromax, Fibrotest, Fib-4, Fib-8 and others.

**Hepatitis C virus genotypes**

Hepatitis C genotypes are different types of the virus from the first to the sixth. For each genotype, there may be other subtypes, denoted by lowercase letters (for example, genotype 1a). The genotype is of great importance because it can influence the options and duration of pharmacotherapy. The geographic distribution of genotypes varies. In North America, genotype 1 is the most common, followed by genotypes 3 and 2. The laboratory polymerase chain reaction test can be used to establish the viral genotype of the hepatitis C virus [1]. It is important that when prescribing interferon therapy, the most difficult to treat is genotype 1, which required a 12-month course of therapy. When prescribing direct antiviral drugs, the 3rd genotype

of the hepatitis C virus, which was previously most easily eliminated with the help of interferon therapy, presents the greatest difficulty.

## 1.2. The use of interferon therapy and ribavirin for HCV virus elimination in patients with CHC and their side effects.

The combination of pegylated interferon and ribavirin has been the standard of care for CHC for many years. Previously, only short interferons were used for treatment, but the addition of polyethylene glycol side chains to interferon (pegylation) improved bioavailability and allowed injections to be made once a week instead of three. When using pegylated interferons, the frequency of a persistent viral response to treatment increased by 2 times [7]. Ribavirin plus pegylated interferon improved response rates in most cases, increasing to 42-46% in genotype 1 patients and 76-82% in genotype 2 and 3 patients. Ribavirin was contraindicated in patients with hemolytic anemia or renal insufficiency. Drugs used to treat CHC have a complex side effect profile and are less effective in patients who have not completed the entire course of treatment or who have received less than 80% of the total intended dose [8, 9]. An important point before prescribing this method of treatment is the laboratory exclusion of autoimmune diseases in patients.

We present the most common side effects when prescribing interferon therapy in combination with ribavirin [10, 11]. Patients should be made aware of the possible pathological symptoms that may occur during treatment, as they can sometimes be hazardous to health: severe depression, and norexia, autoimmune complications, anemia, neutropenia.

### 1.2.1. Hematological side effects when using interferon therapy and ribavirin.

The goal of antiviral therapy in CHC is to carry out virulemination, which will reduce the stage of liver fibrosis and improve the quality of life of patients. Sustained virological response (viral clearance rate) is defined as undetectable HCV RNA in plasma 6 months after completion of therapy, which usually lasts 6-12 months. In 98.3% of patients, this leads to long-term elimination of HCV [12]. The combination

of pegylated interferon (PEG-Interferon)-2a or -2b with ribavirin has previously been the most effective therapy for chronic HCV infection. Both drugs had a significant effect on virological and histological responses, and this combined treatment resulted in a successful virus clearance rate of 40 to 50 percent in patients with CHC genotype 1 and 80 percent in patients with CHC genotype 2 or 3 [13, 14].

Both peg-interferon and ribavirin have serious side effects that impair adherence to therapy and lead to a high rate of dose reduction and treatment discontinuation in clinical trials and in practice. Hematological problems such as anemia, neutropenia, and thrombocytopenia have been documented to cause dose reduction in more than 40% of subjects, resulting in a 10-20% decrease in virological response [15, 16].

Management of antivirals for hematological side effects of HCV infection may be an important method to improve treatment outcomes.

### 1.2.2. Pharmacotherapeutic methods for the correction of anemia in the appointment of virus-eliminating therapy in patients with CHC

Anemia is the most common side effect of antiviral drugs. Mean hemoglobin levels decrease by 2–3 g/dl during the first 4 weeks of combination therapy with marked compensatory reticulocytosis [17].

There was a decrease in hemoglobin concentration below 12 g/dl in 52% of patients treated with Interferon-2a with RBV therapy (mean decrease of 3.7 g/dl). Severe anemia (hemoglobin 10 g/dl) developed in 9-13% of patients receiving combined treatment with interferons and ribavirin. 30 percent of patients had moderate anemia (hemoglobin 11 g/dl) [17]. Female sex, age > 60 years, higher dose of ribavirin by body weight (12 mg/kg or more), rate of hemoglobin fall in the second week, Asian race, and lower creatinine clearance are all predictors of anemia in CHC therapy [18, 19].

Anemia caused by CHC treatment is due to simultaneous hemolysis and suppression of the hematopoietic function of the bone marrow [20]. Ribavirin causes a dose-dependent hemolytic anemia that is reversible 4–8 weeks after discontinuation of the drug [21].

Patients with CHC receiving combination therapy may also develop hematological complications independent of ribavirin. Interferon suppresses bone marrow function [22], limits the proliferation of erythroid progenitor cells, enhances erythroid cell apoptosis, promotes autoimmune hemolytic reactions, reduces kidney function, and impairs compensatory reticulocytosis in ribavirin-associated hemolytic anemia [23].

With CHC, chronic anemia can be observed, which is accompanied by a violation of iron metabolism, hemolysis, and a low concentration of erythropoietin. These complications are the result of a high concentration of pro-inflammatory cytokines [24, 25], which enhance the synthesis of hepcidin produced in the liver [26, 27], which in some cases leads to the development of hemochromatosis.

Anemia is also accompanied by a decrease in the concentration of erythropoietin [28]. This hormone is synthesized by the kidneys when there is insufficient oxygen supply [29]. In CHC patients treated with interferons and ribavirin, endogenous erythropoietin levels were abnormally low for their degree of anemia [30, 31]. The most common side effect that results in dose reduction or discontinuation of treatment is ribavirin-induced anemia [32]. However, in patients with CHC who have not previously received treatment or have not responded to a previous course of treatment, maintaining a daily dose of ribavirin is essential [33, 34].

Clinical data on the effect of treatment adherence on viral clearance in patients with genotype 1 showed that patients who received less than 80% of the dose of Interferon or ribavirin for less than 80% of the time had a poor viral response [33]. Patients with genotype 1 who received less than 60% of the total dose of ribavirin had a significantly lower viral elimination rate [35, 36].

Increased exposure to Ribavirin has been associated with an increased risk of low viral clearance [37]. Anemia can exacerbate other treatment-related side effects, including shortness of breath and exhaustion, and can have a serious impact on both brain function and quality of life [38]. As a result, this has a significant negative impact on adherence to anti-HCV treatment.

Erythropoietic growth factors. In order not to reduce the patient's chances of virus elimination efficacy, many clinicians have begun using growth factors such as recombinant human erythropoietin to treat anemia in patients with hepatitis C in order to maintain a constant dose of Ribavirin [39, 40]. The clinical efficacy of these drugs, that is, a significant increase in hemoglobin concentration, usually occurs after 2 to 6 weeks.

Precautions when prescribing erythropoietins: arterial hypertension, headache, reaction at the injection site, an increase in the number of platelets in the blood and an increased risk of thrombosis are possible side effects [41]. It is extremely important to rule out any potential side effects before starting treatment with erythropoietins. Among them are uncontrolled hypertension, iron deficiency anemia and allergy to human albumin products [42, 43, 44].

### 1.2.3. Neutropenia as a side effect in the use of interferons and ribavirin in patients with CHC

Treatment with interferons induces a decrease in neutrophils and lymphocytes in the peripheral blood. The number of neutrophils, as well as the level of hemoglobin, drops sharply during the first two weeks of treatment, remains stable during the course of treatment, and quickly returns to baseline after treatment is stopped. PEGylated interferons cause more pronounced neutropenia than non-pegylated interferons. When standard doses of interferons are used to treat CHC, the absolute neutrophil count is reduced by 30-50% compared to baseline [45, 46]. The toxicity of interferons for the bone marrow is the main one in the pathogenesis of neutropenia [47, 48].

The package insert for Interferon-2alpha and Interferon-2beta recommends a dose reduction for patients with neutrophil counts below 750 cells/mm3 and discontinuation of the drug for patients with neutrophil counts below 500 cells/mm3.

Granulocyte colony stimulating factor (G-CSF) – Filgrastim, lenograstim and nartograstim are commercially available recombinant versions of G-CSF. A significant

increase in the number of neutrophils can be observed within 24 hours after the administration of G-CSF. Important is the need to control the level of neutrophils in the blood no earlier than 3-4 days after the administration of the drug. Earlier laboratory control does not reflect the real pharmacotherapeutic efficacy of this drug.

Of the side effects of this drug, it should be noted: moderate bone pain, muscle pain, fever, nausea, vomiting and local skin reactions, which can be reduced if the injection time is not earlier than 2 days before or after the administration of interferons [49, 50].

### 1.2.4. Thrombocytopenia as a side effect in the use of interferons and ribavirin in patients with CHC

With the combined appointment of interferons and ribavirin, thrombocytopenia is due to reversible suppression of the bone marrow due to the action of interferon. The decrease in platelet production is due to decreased hepatic production of thrombopoietin [51] and virus-induced bone marrow suppression [52]. To correct thrombocytopenia, the dose of interferons is reduced, and interferon therapy is stopped if it falls below 20 x 109 / l [53, 54].

Eltrombopag appears to bind to the TPO receptor at a distance from the TPO binding site and appears to initiate signal transduction by a mechanism different from that of first-generation thrombocytopenic growth factors [55].

Eltrombopag has an additive rather than competitive effect on platelet synthesis. In chronic immunological thrombocytopenic purpura, it causes a dose-dependent increase in platelet proliferation and differentiation [56] without recurrence of thrombocytopenia after discontinuation of therapy [62].

## 1.3. Current regimens for prescribing direct antiviral drugs (DAPs) for the treatment of CHC

DAAs (direct acting agents, protease inhibitors, nucleotide polymerase inhibitors and NS5A inhibitors) unlike interferons and ribavirin, these drugs stop the growth

of the hepatitis C virus. Protease inhibitors and nucleotide polymerase inhibitors are used in the following combination therapy for CHC:

- boceprevir (Victrelis)
- simeprevir (olisio)
- Technivie (ombitasvir/paritaprevir/ritonavir)
- Viekira Pak (ombitasvir/paritaprevir/ritonavir and dasabuvir)
- Zepatier (grazoprevir and elbasvir)
- Sovaldi (sofosbuvir)
- Harvoni (sofosbuvir and ledipasvir)
- Daklinza (daclatasvir)
- Epclusa (sofosbuvir and velpatasavir)
- Maviret (Glecaprevir and Pirbrentasavir)

**Dosing regimen for direct antiviral drugs**

**Victrelis (Oceprevir)**

- 800 mg is taken three times a day, and simeprevir 150 mg is taken once a day with meals in combination with ribavirin.

**Technivie (ombitasvir/paritaprevir/ritonavir)**

• For chronic hepatitis C (CHC) genotype 4 without cirrhosis, Technivie is administered with ribavirin for 12 weeks.

• Each tablet contains ombitasvir 12.5 mg, paritaprevir 75 mg and ritonavir 50 mg.

• Two tablets are taken twice daily with meals, with ribavirin dosed according to weight: 1000 mg per day for patients weighing less than 75 kg and 1200 mg per day for patients weighing 75 kg or more.

**Viekira Pak (ombitasvir/paritaprevir/ritonavir and dasabuvir)**

- Vikeyra is prescribed for people with chronic hepatitis C genotype 1a or 1b, including those with or without cirrhosis and no signs of liver failure. Viekira Pak contains ombitasvir 12.5mg, paritaprevir 75mg and ritonavir 50mg per tablet, along with dasabuvir 250mg tablets. It can be administered with or without ribavirin. Since

genotype 1a is the most resistant to therapy, Viekira is administered with ribavirin for 12 weeks in the absence of cirrhosis and 24 weeks in the presence of cirrhosis. If there is no cirrhosis of the liver, Vikira is usually given alone for 12 weeks; in the presence of cirrhosis of the liver (or in some cases of previous therapy), it must be administered with ribavirin for 12 weeks. Vikira can also be given to people who have had a liver transplant.

**Zepatier (grazoprevir and elbasvir)**

- Zepatier is a combination of elbasvir 50 mg and grazoprevir 100 mg that is used to treat chronic hepatitis C genotypes 1 and 4 with or without cirrhosis and specific resistance mutations. While Zepatier can be given to individuals who have never been treated, it is more useful for those who have not responded to PegInterferon/Ribavirin and protease inhibitors. One tablet is taken once daily with or without food and may be administered with or without Ribavirin as described above, depending on the patient. Patients who have previously been treated or who have certain resistance ("NS5A") mutations are given a different dose and for a longer period of time than others. Genotype 1a patients with NS5A mutations and genotype 4 patients with PegInterferon/Ribavirin failure are treated with Zepatier and Ribavirin for 16 weeks; genotypes 1a and 4, in which PegInterferon/Ribavirin was ineffective, were treated for 12 weeks with Ribavirin and protease inhibitors.

**Sovaldi (sofosbuvir)**

• Sovaldi is used to treat chronic hepatitis C genotypes 1 and 4 with PegInterferon/Ribavirin or genotypes 2 and 3 with ribavirin alone. The drug is taken one 400 mg tablet orally with or without food. All genotypes are treated within 12 weeks, except for three, which are treated within 24 weeks. One advantage of Sovaldi is that it can be used to treat genotype 1 patients who are not eligible for interferon therapy; these patients can take Sovaldi alone for 24 weeks. Patients awaiting a liver transplant may take Sovaldi with Ribavirin for up to 48 weeks to try to prevent HCV infection in the new liver.

**Harvoni (sofosbuvir and ledipasvir)**

• Harvoni is a nucleotide inhibitor analogue that combines ledipasvir 90 mg and sofosbuvir 400 mg in one tablet that can be taken with or without food. Harvoni is used to treat chronic hepatitis C genotypes 1, 4, 5 and 6. Harvoni can be used alone to treat all genotypes, regardless of previous therapy and whether they have cirrhosis. The inclusion of Harvoni Ribavirin, on the other hand, expands the treatment options for people with genotype 1 liver cirrhosis and liver failure (decompensated cirrhosis). With the exception of genotype 1 with cirrhosis, all treatments last 12 weeks.

**Daklinza (daclatasvir)**

• Daklinza is an NS5A inhibitor used to treat chronic hepatitis C genotype 3. It is given in combination with Sovaldi (sofosbuvir). For people without cirrhosis, 30 or 60 mg tablets are given orally once a day along with sofosbuvir for 12 weeks, with the exact dose varying depending on drug interactions with other drugs the patient is taking. Patients with cirrhosis of the liver are not given a certain time, but there is no prohibition on the use of this drug even with significantly reduced liver function.

**Maviret (Glecaprevir and Pirbrentasavir)**

• Indicated for hepatitis C genotype 1-6 without cirrhosis and compensated cirrhosis. Indicated for genotype 1 patients previously treated with either an NS5A inhibitor or an NS3/4A protease inhibitor, but not both. Take 3 tablets per day orally with food for 8-12 weeks.

**Epclusa (sofosbuvir and velpatasavir)**

- a fixed-dose combination of sofosbuvir, a hepatitis C virus (CHC) nucleotide analogue, an NS5B polymerase inhibitor, and velpatasvir, an NS5A inhibitor of CHC. Indicated for the treatment of adult patients with chronic HCV genotype 1, 2, 3, 4, 5 or 6 infections without cirrhosis or with compensated cirrhosis AND with decompensated cirrhosis for use in combination with ribavirin. One tablet (400 mg sofosbuvir and 100 mg velpatasvir) is taken orally once a day with or without food.

**Ribavirin**

Ribavirin (also known as ibavir, rebetol, or virazole) is a guanosine nucleoside that is used to treat hepatitis C.

Ribavirin can be used with Daclatasvir and Sofosbuvir, Eplusa (Sofosbuvir, Velpatasvir), Harvoni (Sofosbuvir, Ledipasvir), Simeprevir and Sofosbuvir, Vikeyra Pak (Ombitasvir, Paritaprevir, Ritonavir, Dasabuvir), Technivi (Ritonavir, Ombita (Elbasvir, Grazoprevir). In individuals with CHC genotype 1a, weight-based addition of ribavirin to Technivie treatment increased sustained virologic response (viral clearance rate12) from 90% to 97% after 12 weeks of daily dosing and from 90.9% to 100% in patients with CHC genotype 4. In HCV patients with genotype 5, treatment with ribavirin increased the rate of viral elimination (sustained virological response).

In individuals with genotype 1 infection, combination treatment with ribavirin and peginterferon alfa-2a results in a viral clearance rate of 44 percent and a viral clearance rate of 70 percent in patients with genotype 2–6 infection. The inclusion of ribavirin in combination therapy depends on the patient profile, for example, whether a patient with HCV genotype 3 has the Y93H genetic variant, as well as compensated cirrhosis [57].

## 1.4. Potentially dangerous combinations of PPLS with groups of cardiotropic and lipid-lowering drugs 22

### 1.4.1. Drug interactions between PPLS against CHC and amiodarone (antiarrhythmic drug)

**Analyzing the possibility of the combined use of Ledipasvir / Sofosbuvir + Amiodarone** can lead to serious symptomatic bradycardia. The mechanism of this effect is unknown.

**The combination Ombitasvir/paritaprevir/+dasabuvir+amiodarone may not be safe as amiodarone** is a CYP3A4 substrate and exposure may be increased due to ritonavir inhibition of CYP3A4, which may cause cardiac arrhythmias. Co-administration is contraindicated on the product label in Europe, but the US product label recommends caution and patient monitoring.

**When co-administered with elbasvir/grazoprevir and amiodarone, amiodarone** concentrations may increase as it is metabolized by CYP3A4 and grazoprevir

is a weak inhibitor of CYP3A4 in vitro. Because amiodarone has a narrow therapeutic index and unpredictable therapeutic levels, patients should be closely monitored for signs and symptoms of toxicity. Therapeutic drug monitoring and/or ECG during treatment is required. Elbasvir/grazoprevir concentrations may be elevated due to weak inhibition of CYP3A4 and P-gp by amiodarone.

**Co-administration of glecaprevir/pibrentasvir + amiodarone** may be associated with increased amiodarone concentrations due to weak inhibition of CYP3A4 by glecaprevir/pibrentasvir. Because amiodarone has a narrow therapeutic index and unpredictable therapeutic levels, patients should be closely monitored for signs and symptoms of toxicity. Glecaprevir/pibrentasvir concentrations may be elevated due to P-gp inhibition by amiodarone.

### 1.4.2. Drug interactions between PPLS against CHC with other antiarrhythmic drugs

**The combination of Ombitasvir / paritaprevir / + dasabuvir + quinidine** can lead to dangerous complications, since quinidine is a substrate of CYP3A4, and its exposure can be markedly increased due to inhibition of CYP3A4 by ritonavir. Co-administration is contraindicated on the product label in Europe, but the product label in the US suggests caution and monitoring of the therapeutic concentration.

**Co-administration of ledipasvir/sofosbuvir + digoxin is associated** with an increase in digoxin concentrations due to ledipasvir inhibition of P-gp. It is recommended to control the therapeutic concentration of digoxin.

**Co-administration of ledipasvir /sofosbuvir + quinidine** may increase ledipasvir or quinidine concentrations due to P-gp inhibition. Caution should be exercised because quinidine has a narrow therapeutic index, and close clinical observation is recommended.

**Co-administration of Ombitasvir / paritaprevir / + dasabuvir** with digoxin (0.5 mg once) increases Cmax, AUC and Cmin of digoxin by 15%, 16% and 1% due to inhibition of P-gp by paritaprevir. There are no clinically significant changes in

exposure to ombitasvir, paritaprevir, ritonavir or dasabuvir. Preliminary dose adjustment of digoxin is not required, but appropriate monitoring of serum digoxin levels is recommended.

### 1.4.3. Drug interactions between PPLS against CHC and beta-blockers

When analyzing the interaction of the combination Ombitasvir / paritaprevir / r + dasabuvir + bisoprolol, it was found that bisoprolol is a substrate of CYP3A4, and its exposure may increase due to inhibition of CYP3A4 by ritonavir. Close monitoring is recommended and dose reduction of bisoprolol may be required.

Based on metabolism and clearance, a clinically significant interaction of **Ombitasvir/paritaprevir/r+dasabuvir+labetalol is possible.** It is believed that the metabolism of labetalol occurs through conjugation involving UGT1A1 and UGT2B7. Since ombitasvir / paritaprevir / ritonavir + dasabuvir inhibit UGT1A1, an increase in labetalol concentrations may be observed. Careful monitoring of blood pressure is recommended and, if necessary, dose reduction is possible.

**Co-administration of ledipasvir/sofosbuvir + carvedilol** is unsafe as both carvedilol and ledipasvir are P-gp inhibitors. Concentrations of both drugs may be increased. Elevated concentrations of carvedilol may cause toxicity, including dizziness, bradycardia, and gastrointestinal disturbances.

**Ombitasvir / paritaprevir / r + dasabuvir + carvedilol.** Carvedilol undergoes glucuronidation via UGT 1A1, 2B4 and 2B7 and is further metabolized via CYP2D6 and, to a lesser extent, CYP 2C9 and 1A2. Ombitasvir / paritaprevir / ritonavir + dasabuvir can potentially increase carvedilol concentrations. Careful monitoring is recommended.

When glecaprevir / pibrentasvir + carvedilol are used together, it should be borne in mind that Carvedilol is a substrate and inhibitor of P-gp. Concentrations of both carvedilol and glecaprevir/pibrentasvir may be elevated. Due to the potential increase in carvedilol concentrations, careful monitoring of side effects, including heart rate and blood pressure, is recommended.

### 1.4.4. Drug interactions between PPLS and calcium channel blockers

**Co-administration of ledipasvir/sofosbuvir + amlodipine** may increase amlodipine or ledipasvir concentrations due to P-gp inhibition. Careful monitoring of heart rate, blood pressure and increased side effects of amlodipine are recommended.

**Ledipasvir / Sofosbuvir + Diltiazem.** Diltiazem levels may be elevated due to ledipasvir inhibition of P-gp, and close monitoring of heart rate and blood pressure is recommended.

**With the combined use of Ledipasvir / sofosbuvir + felodipine,** the concentration of felodipine may increase due to inhibition of P-gp by ledipasvir. Caution is necessary and careful monitoring of blood pressure and heart rate is recommended.

**Ombitasvir / paritaprevir / r + dasabuvir + nicardipine.** Nicardipine is a CYP3A4 and P-gp substrate. Exposure to nicardipine may be increased due to CYP3A4 inhibition by ritonavir, which may lead to hypotension and cardiac arrhythmias.

**Ombitasvir / paritaprevir / r + dasabuvir + verapamil.** Verapamil is a CYP3A4 substrate and exposure may be increased due to ritonavir inhibition of CYP3A4. With the simultaneous use of calcium channel blockers, clinical monitoring is recommended.

**Co-administration of elbasvir/grazoprevir and felodipine.** Felodipine is a CYP3A4 and P-gp substrate; concentrations may increase due to the additive effect of grazoprevir's weak CYP3A4 inhibition and elbasvir's weak P-gp inhibition. It is not recommended to change the dose beforehand, but careful monitoring of blood pressure and heart rate is recommended.

**Ombitasvir / paritaprevir / r + dasabuvir + nifedipine.** Nifedipine is a CYP3A4 and P-gp substrate. Nifedipine exposure may be increased due to CYP3A4 inhibition by ritonavir, which may lead to hypotension and cardiac arrhythmias. Careful monitoring is recommended.

**Ombitasvir / paritaprevir / r + dasabuvir + amlodipine.** Amlodipine is a substrate of CYP3A4, and its co-administration increases the AUC of amlodipine by 2.6 times.

**Ombitasvir / Paritaprevir / r + Dasabuvir + Diltiazem.** Diltiazem is a CYP3A4 substrate and exposure may be increased due to ritonavir inhibition of CYP3A4. Use with caution due to expected increase in exposure to paritaprevir. With the simultaneous use of calcium channel blockers, clinical monitoring is recommended.

**Co-administration of glecaprevir/pibrentasvir and diltiazem.** Diltiazem is a CYP3A4 and P-gp substrate. Concentrations may increase due to P-gp inhibition and weak CYP3A4 inhibition by glecaprevir /pibrentasvir. Careful monitoring of heart rate and blood pressure is recommended and dose reduction should be considered if necessary.

**Co-administration of glecaprevir/pibrentasvir + verapamil.** Verapamil is metabolized by several CYPs, including CYP3A4, and is both a substrate and an inhibitor of P-gp. Verapamil levels may be elevated as glecaprevir/pibrentasvir is a weak inhibitor of CYP3A4 and a P-gp inhibitor.

### 1.4.5. Drug interactions between PPLS and lipid-lowering drugs (statins)

**The combined use of ledipasvir / sofosbuvir + rosuvastatin** is contraindicated. Plasma concentrations of rosuvastatin may be markedly increased due to inhibition of P-gp and BRCP by ledipasvir.

**The co-administration of Ombitasvir / Paritaprevir / r + Dasabuvir + Atorvastatin** is contraindicated in the European product label. Atorvastatin is a substrate of CYP3A4 and OATP1B1, and its exposure may be increased due to the inhibition of CYP3A4 by ritonavir and OATP1B1 by paritaprevir.

**The combined use of Ombitasvir / Paritaprevir / r + dasabuvir + lovastatin** is contraindicated. Lovastatin is a substrate of CYP3A4 and OATP1B1. Lovastatin exposure may be increased due to CYP3A4 inhibition by ritonavir, which may lead to serious reactions such as the risk of myopathy, including rhabdomyolysis.

**The combined use of Ombitasvir / paritaprevir / r + dasabuvir + simvastatin** is contraindicated. Exposure to simvastatin may be increased due to OATP/CYP3A4 inhibition by paritaprevir and ritonavir, which may lead to serious reactions such as the risk of myopathy including rhabdomyolysis.

**Co-administration of glecaprevir /pibrentasvir and atorvastatin** (single dose of 10 mg) increased atorvastatin AUC by 8.28-fold and increased Cmax by 22-fold. Co-administration is not recommended due to the increase in atorvastatin levels caused by inhibition of OATP1B1, P-gp and BCRP by glecaprevir/pibrentasvir.

**Co-administration of glecaprevir/pibrentasvir and lovastatin** is not recommended. The simultaneous use of lovastatin and glecaprevir / pibrentasvir did not affect the Cmax of lovastatin and increased AUC by 70%; Cmax and AUC of lovastatin acid increased 5.73 times and 4.10 times. High exposure to lovastatin may increase the risk of myopathy/rhabdomyolysis. With simultaneous use of lovastatin should not exceed a dose of 20 mg / day, and patients should be monitored.

**Co-administration of Glecaprevir/pibrentasvir+simvastatin** is contraindicated due to an increased risk of myopathy/rhabdomyolysis. Co-administration of glecaprevir/pibrentasvir and simvastatin (5 mg once daily) increased simvastatin C and AUC by 99% and 132%; Cmax and AUC of simvastatin acid increased by 10.2 times and 4.48 times.

**Co-administration of ledipasvir/sofosbuvir + atorvastatin** may increase atorvastatin concentrations due to ledipasvir inhibition of P-gp and/or BCRP. Dose reduction of atorvastatin may be required. Adverse events associated with statins, such as myopathy, should be carefully monitored.

**Co-administration of ledipasvir/sofosbuvir + fluvastatin** may increase fluvastatin concentrations due to inhibition of BCRP by ledipasvir. Caution is necessary and close monitoring is recommended. Consideration should be given to reducing the dose of fluvastatin. Importantly, the use of fluvastatin in active liver disease is contraindicated.

**Co-administration of ledipasvir /sofosbuvir and lovastatin** may increase lovastatin concentrations due to ledipasvir's inhibition of P-gp and BCRP. The dose of lovastatin should be carefully titrated and the lowest dose needed should be used with careful monitoring of safety.

**Co-administration of ledipasvir/sofosbuvir + simvastatin** may increase simvastatin concentrations due to ledipasvir's inhibition of P-gp and BCRP. The

dose of simvastatin should be carefully titrated and the lowest dose needed should be used with careful monitoring of safety.

**Ombitasvir / Paritaprevir / r + Dasabuvir + Rosuvastatin.** Rosuvastatin is a substrate of CYP2C9 and CYP3A4, as well as OATP 1B1, 1B3 and 1A2. Simultaneous use increases Cmax and AUC of rosuvastatin by 7.1 and 2.6 times, respectively. The product label in Europe recommends that the maximum daily dose of rosuvastatin be 5 mg, while the product label in the US states that the dose of rosuvastatin should not exceed 10 mg per day. Rosuvastatin is contraindicated in patients with active liver disease and should be used with caution in patients who drink excessive amounts of alcohol and/or have a history of liver disease.

**Co-administration of elbasvir + grazoprevir** (50+200 mg once daily) with atorvastatin (10 mg once daily) increased atorvastatin AUC by 94% and increased Cmax by 4.34 times. The dose of atorvastatin should not exceed a daily dose of 20 mg when co-administered with elbasvir/grazoprevir.

**The co-administration of elbasvir/grazoprevir and fluvastatin** has not been studied. Fluvastatin is a substrate of CYP 2C8, 2C9 and 3A4 as well as OATP 1B1/3 and BCRP. Co-administration may increase fluvastatin concentrations due to BCRP inhibition by elbasvir/grazoprevir and weak inhibition of CYP3A4 by grazoprevir. Adverse events associated with statins, such as myopathy, should be carefully monitored. When co-administered with elbasvir /grazoprevir, the lowest dose required should be used and should not exceed a daily dose of 20 mg. Please note that the use of fluvastatin in active liver disease is contraindicated.

**Glecaprevir / pibrentasvir + rosuvastatin** Co-administration of glecaprevir / pibrentasvir and rosuvastatin (5 mg) increased Cmax and AUC of rosuvastatin by 5.62 times and 2.15 times. The European SPC recommends that the dose of rosuvastatin not exceed 5 mg/day, while the US Prescribing Information recommends that the dose of rosuvastatin not exceed 10 mg/day.

The safety of statins in this patient population is limited, but there were no clinically significant differences in elevated aminotransferase activity or signs of hepatotoxicity in patients with hepatitis C treated with statins compared with those who

did not. The use of statins in advanced end-stage liver disease should still be avoided because safety data are insufficient in these patients and drug metabolism may be seriously impaired [58].

### 1.4.6. Drug interactions between PPLS and lipid-lowering drugs (fibrates)

**Interaction between PPLS and bezafibrate.** Based on metabolism and clearance, a clinically significant interaction is unlikely. Bezafibrate is metabolized by hydroxylation, glucuronidation and renal elimination (~50%). Due to the involvement of several metabolic pathways and renal elimination, a clinically significant interaction with PPLS has not been established.

**Interaction between PPLS and fenofibrate.** And based on metabolism and clearance, a clinically significant interaction is unlikely because fenofibrate is metabolized by several enzymatic pathways (esterases, UGT2B7 and UGT1A1).

To assess the likelihood of reinfection, 597 patients (mean age 44.5 years) were examined, who had SVR after treatment. During follow-up, re-infection occurred in 42 patients (9 women, 33 men). High reinfection rates were associated with homelessness (24.3/100 PY), co-injection drug use (reinfection rate 26.2/100 years per year), and young age (20-24 years). The majority of re-infected patients were successfully treated [59].

Sustained virological response (SVR) currently occurs in 98-99% of HCV-infected patients using 8 or 12 week regimens: sofosbuvir / velpatasvir (SV) + voxilaprevir (SV), glecaprevir / pibrentasvir (GP), elbasvir / grazoprevir (EG). In a retrospective analysis of 2508 patients, the global SVR24 rate was 97.1% (73/2508) [60].

New direct-acting antivirals (DAAs) maintain a virologic response rate of over 90% versus 54% - 70% earlier than shorter treatment times with fewer side effects. Long-term extrapolation shows an estimated cost of €1.9 billion versus 0.9 in other countries for direct costs and €2.4 billion for indirect costs in the absence of DAAs. Treating patients with DAAs will save more than 1 billion euros and is a good investment in the French healthcare system [61].

Sofosbuvir and velpatasvir are available as a fixed dose containing 400 mg of sofosbuvir and 100 mg of velpatasvir per tablet. Velpatasvir is metabolized in vitro by cytochrome P450 (CYP): CYP2B6, CYP2C8 and CYP3A4. Importantly, velpatasvir is transported by P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Excretion with bile of the original drug is the main one. Cirrhosis, including decompensated cirrhosis, does not have a clinically significant effect on velpatasvir [62].

Sofosbuvir should not be administered with known P-gp inducers: rifampicin, carbomazepine, phenobarbital, phenytoin or St. John's wort, as well as with moderate inducers such as: rifabutin, oxcarbazepine, rifapentine and modafinil [63].

Since velpatasvir and voxilaprevir are inhibitors of P-gp, BCRP, OATP1B1 and OATP1B3, co-administration of sofosbuvir, velpatasvir and voxilaprevir with drugs that are substrates of these transporters can increase the concentration and pharmacodynamic effect (clarithromycin, levofloxacin, propafenone, spironolactone, cytostatics) [64].

Chronic hepatitis C (HCV) infection is associated with lower levels of total cholesterol (T-CHOL) and low levels of low-density lipoprotein (LDL-C). In a study of 617 SVR patients with CHC (26.8 months follow-up), it was found that total LDL cholesterol increased significantly from week 4 of treatment and remained elevated until 2 years after treatment. Compared with patients without vascular complications, the proportion of patients with vascular complications had an increase in LDL-C > 40% (80% vs 19.9%, log-rank P = 0.001). Cox regression analysis showed that an increase in LDL-C >40% was the only predictor of vascular complications (HR/CI: 15.44/1.73-138.20, P=0.014) [65].

Dose adjustment or additional monitoring is required when prescribing statins. Rosuvastatin is contraindicated due to a 19-fold increase in the plasma concentration of this drug. BCRP substrates: methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, sulfasalazine and topotecan, dabigatran, which are contraindications for co-administration with sofosbuvir/velpatasvir/voxilaprevir. This is caused by inhi-

bition of P -gp by both velpatasvir and voxilaprevir. Other P-gp substrates may adjust dose or control increased exposure, including digoxin, ticagrelor, and carvedilol [66].

Sofosbuvir-based regimens are contraindicated in patients treated with the antiarrhythmic drug amiodarone due to the risk of life-threatening arrhythmias. Bradycardia has been observed within hours or days of initiation of treatment, but cases have been observed within 2 weeks of initiation of hepatitis C treatment. Due to the long half-life of amiodarone, interaction is possible for several months after amiodarone is discontinued [67].

Alcohol abuse is well known as a disease that accelerates hepatic fibrosis in HCV and often results in delayed initiation of interferon-based treatment. The Hepatitis C Network of Canada (CANUHC) analyzed the efficacy of DAA treatment for HCV at 10 Canadian sites. Since January 2016, out of 725 patients with CHC (mean age: 53 (SD 12.7); 66% men), 37% of patients were found to have been systematically drinking alcohol. Antiviral therapy with DAAs is successful regardless of a history of TIVO in individuals who drink alcohol concomitantly with antiviral treatment [68].

Sofosbuvir/velpatasvir can be administered with most antiretroviral drugs, with the exception of those that induce P-gp activity. Efavirenz, etravirine, nevirapine. Efavirenz reduces the effect of velpatasvir by 50% [69].

The solubility of velpatasvir decreases with increasing pH, so the simultaneous use of antacids, H2 receptors and proton pump inhibitors leads to a decrease in its concentration in the blood serum. If necessary, Sofosbuvir/velpatasvir should be taken with food or taken 4 hours before proton pump inhibitors [70].

Voxilaprevir is metabolized in vitro by CYP3A4, with most of the drug in plasma being the parent drug. Velpatasvir and voxilaprevir are P-gp drug transporter inhibitors. Hepatic clearance is the main route of elimination for voxilaprevir. Patients with compensated (Child-Pugh) cirrhosis of the liver have a concentration of voxi-

laprevir 73% higher than in patients without cirrhosis. The combination of sofosbuvir, velpatasvir and voxilaprevir should not be used in patients with moderate (Child-Pugh B) or severe hepatic impairment (Child-Pugh C) [71].

In 748 patients, liver stiffness was measured using Fibroscan 24 weeks after the end of therapy. High T MI and type 2 diabetes were found to be independently associated with fibrosis stage ($p<0.001$). Severe fibrosis was independently associated with older age, male gender, HIV coinfection, HCV genotype 3, BMI, and the presence of diabetes. The impact of higher BMI on fibrosis severity was greater in those without diabetes than in those with diabetes ($p = 0.003$). SVR is adversely affected by male gender, liver cirrhosis, and infection with the 3-HCV genotype, but not by metabolic cofactors. Among those who did not achieve SVR, diabetes and obesity were associated with FIB-4 progression 12 weeks after the end of therapy [72].

# SECTION 2
# MATERIALS AND RESEARCH METHODS

## 2.1. Justification of the expediency of choosing objects and methods of research

After studying and working out theoretical sources, statistical data on the prevalence of CHC and comorbid pathology, which requires the appointment of cardiotropic and lipid-lowering drugs against the background of direct antiviral drugs, it became relevant to study the safety of the combination of the proposed drugs. In recent years, not only infectious disease specialists and gastroenterologists, but also doctors of other specialties have been treating CHC. When using PPLS, a small number of adverse reactions occur, unlike interferon therapy, which creates the illusion for doctors and patients of ease of treatment without taking into account comorbid therapy. This can lead to serious side complications, especially when prescribing cardiotropic and lipid-lowering therapy.

Given the relevance of the problem under consideration, the results of literary sources, as well as previous studies on this topic, the following areas of research were chosen:

- analysis of the interaction of PPLS with groups of antiarrhythmic, antihypertensive, hypolipidemic drugs using the databases "Drug Bank" and "Hep Drug Interactions" with subsequent generation of protocols for each of the combinations;

- identification of the most frequent combinations of PPLS (Sofosbuvir and Velpatasvir) with drugs from the groups: antiarrhythmics, beta-blockers, calcium channel blockers, ACE inhibitors, sartans, statins, fibrates;

- analysis of the frequency of use by doctors of dangerous or potentially dangerous combinations in the treatment of CHC patients with direct antiviral drugs together with cardiotropic and lipid-lowering drugs.

- development of schemes for relatively safe combinations of PPLS with cardiotropic and lipid-lowering drugs in the treatment of patients with chronic hepatitis C.

Conducting research allowed to fulfill the main tasks that were formed at the beginning of writing the master's work.

### 2.2. Methodology and research methods

This section of the work describes the main methods and characteristics of research materials. To achieve the goals and objectives, the appropriate algorithm for conducting a master's study was used (Table).

Table

Algorithm for conducting a master's study

| Research stages | The content of research areas |
|---|---|
| 1. Study of potentially dangerous combinations of PPLS with cardiotropic and lipid-lowering drugs in the treatment of CHC | Creation of interaction protocols for PPLS and cardiotropic drugs using "Drug Bank" and "Hep Drug Interactions" |
| 2. Analysis of the frequency of prescriptions by doctors of dangerous or potentially dangerous combinations of cardiotropic drugs in the treatment of CHC with the help of PPLS. | Analysis of 118 extracts from the case histories of CHC patients who underwent virus elimination with direct antiviral drugs. |

| | |
|---|---|
| 3. Development of safe combinations of combined use of PPLS and cardiotropic and lipid-lowering drugs. | Analysis and selection of relatively safe combinations of Sofosbuvir and Velpatasvir with antiarrhythmic, beta-blockers, calcium channel blockers, ACE inhibitors, sartans. |

The research was carried out using such methods as bibliosemantic, statistics and graphic.

The bibliosemantic method was used to study Internet resources and scientific literature on modern methods of virus elimination in patients with chronic viral hepatitis C, potential side effects when using interferon therapy, direct antiviral drugs and their combinations with cardiotropic and lipid-lowering drugs.

An analytical method for obtaining protocols for the interaction of PPLS with antihypertensive, antiarrhythmic drugs, statins, fibrates using the databases "Drug Bank" and "Hep Drug Interactions" to search for relatively dangerous and safe drug combinations.

The statistical method was used to assess the prevalence of doctors prescribing potentially dangerous combinations of drugs in the treatment of chronic hepatitis C, combined with the appointment of cardiotropic drugs.

Graphical methods were used to display the material and systematize the research results.

Statistical processing of the obtained data was carried out by nonparametric statistics using STASTICA 8.0 (StatSoft, USA), Microsoft Office Excel 2016, and IBM SPSS Statistics Base version 22.0 programs. The following main statistical characteristics were studied: the number of observations (n), the frequency of the trait, the values of the frequency calculator in assessing the differences between the comparison groups.

# SECTION 3. RESULTS OF OUR RESEARCH

## 3.1. Clinical and epidemiological characteristics of patients with chronic hepatitis C, who were analyzed for compatibility with cardiotropic drugs.

Analysis of extracts from the case histories of patients with chronic hepatitis C was carried out in 118 patients aged 27 to 65 years, including 81 (68.6%) men and 37 (31.4%) women. In all observed patients, CHC activity was verified: group 1 included 73 (61.9%) patients with low CHC activity, the second group included 45 patients (38.1%) with moderate hepatitis activity.

When analyzing the duration of CHC, the duration was set from 5 to 12 years. When conducting an epidemiological survey, parenteral interventions as the cause of infection were established in 67 people (56.8%), blood transfusions or blood products - in 15 (12.7%), dental interventions - in 19 patients (16.1%). Possible causes of infection were not established in - 17 patients (14.4%).

In clinical terms, the course of the disease was asymptomatic in most of the examined patients (72 people; 61.0%). When applying, the patients presented the following complaints: general weakness (65; 55.1%), increased fatigue (58; 49.2%), malaise (47; 39.8%), decreased performance (58; 49.2%), loss of appetite (20; 16.9%), heaviness in the right hypochondrium (50; 39.0%), recurrent nausea (44; 37.3%), bitterness in the mouth (27; 22.9%), myalgia (11; 9.3%).

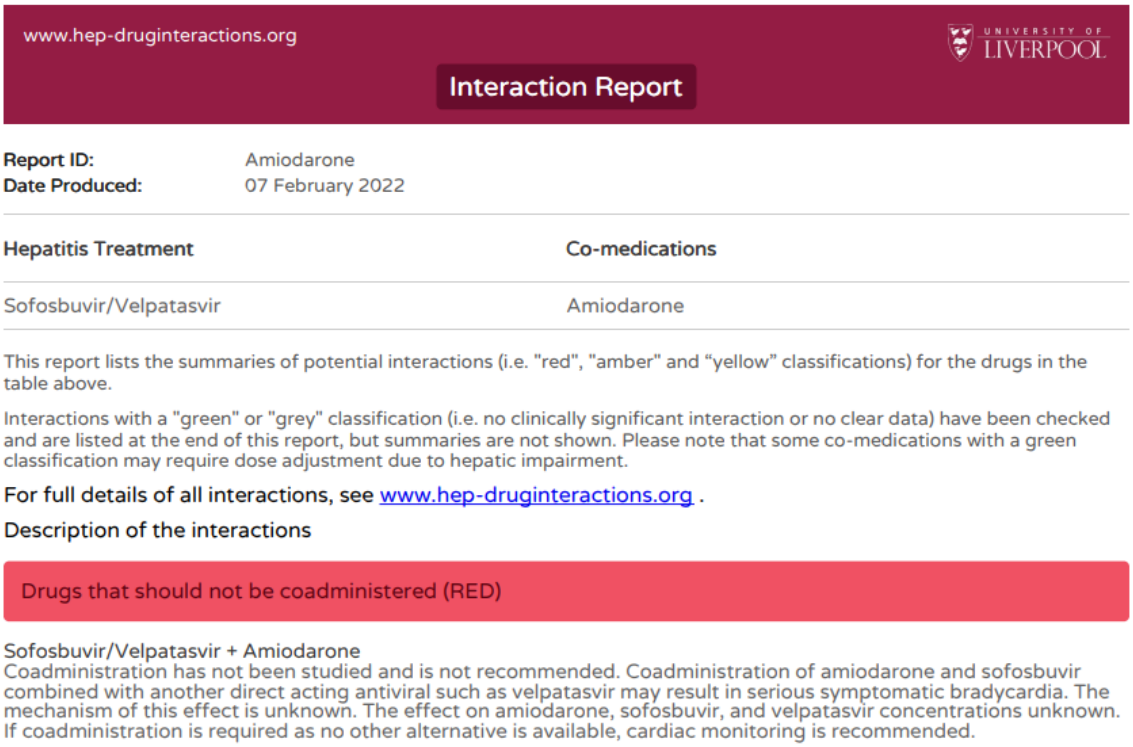
Among the comorbid diseases requiring the appointment of cardiotropic and lipid-lowering drugs were: hypertension (37; 31.4%), symptomatic arterial hypertension (22; 18.6%), rheumatism (7; 5.9%), coronary heart disease (22; 18.6%), postinfarction cardiosclerosis (17; 14.4%), dyslipidemia (55; 46.6%).

## 3.2. Analysis of drug interactions between PPLS against CHC and antiarrhythmic drugs.

We analyzed drug-drug interactions between Amiodarone (an antiarrhythmic drug), which increases the III phase of the action potential of cardiac cells, mainly due to slowing down the current in potassium channels (class III according to the

Vaughan Williams classification) and causes a bradycardia effect as a result of a decrease in the automatism of the sinus node with direct antiviral drug **Sofosbuvir.**

It was established, that the concomitant use of amiodarone and sofosbuvir in combination with another direct-acting antiviral drug such as daclatasvir or simeprevir can lead to severe symptomatic bradycardia and is not recommended (Fig. 1).


www.hep-druginteractions.org

UNIVERSITY OF LIVERPOOL

Interaction Report

**Report ID:** Amiodarone
**Date Produced:** 07 February 2022

| Hepatitis Treatment | Co-medications |
|---|---|
| Sofosbuvir/Velpatasvir | Amiodarone |

This report lists the summaries of potential interactions (i.e. "red", "amber" and "yellow" classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

For full details of all interactions, see www.hep-druginteractions.org .

Description of the interactions

Drugs that should not be coadministered (RED)

Sofosbuvir/Velpatasvir + Amiodarone
Coadministration has not been studied and is not recommended. Coadministration of amiodarone and sofosbuvir combined with another direct acting antiviral such as velpatasvir may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. The effect on amiodarone, sofosbuvir, and velpatasvir concentrations unknown. If coadministration is required as no other alternative is available, cardiac monitoring is recommended.

Fig. 1. Sofosbuvir/velpatasvir combination interaction report with amiodarone based on Hep-Druginteractions.org database (Liverpool).

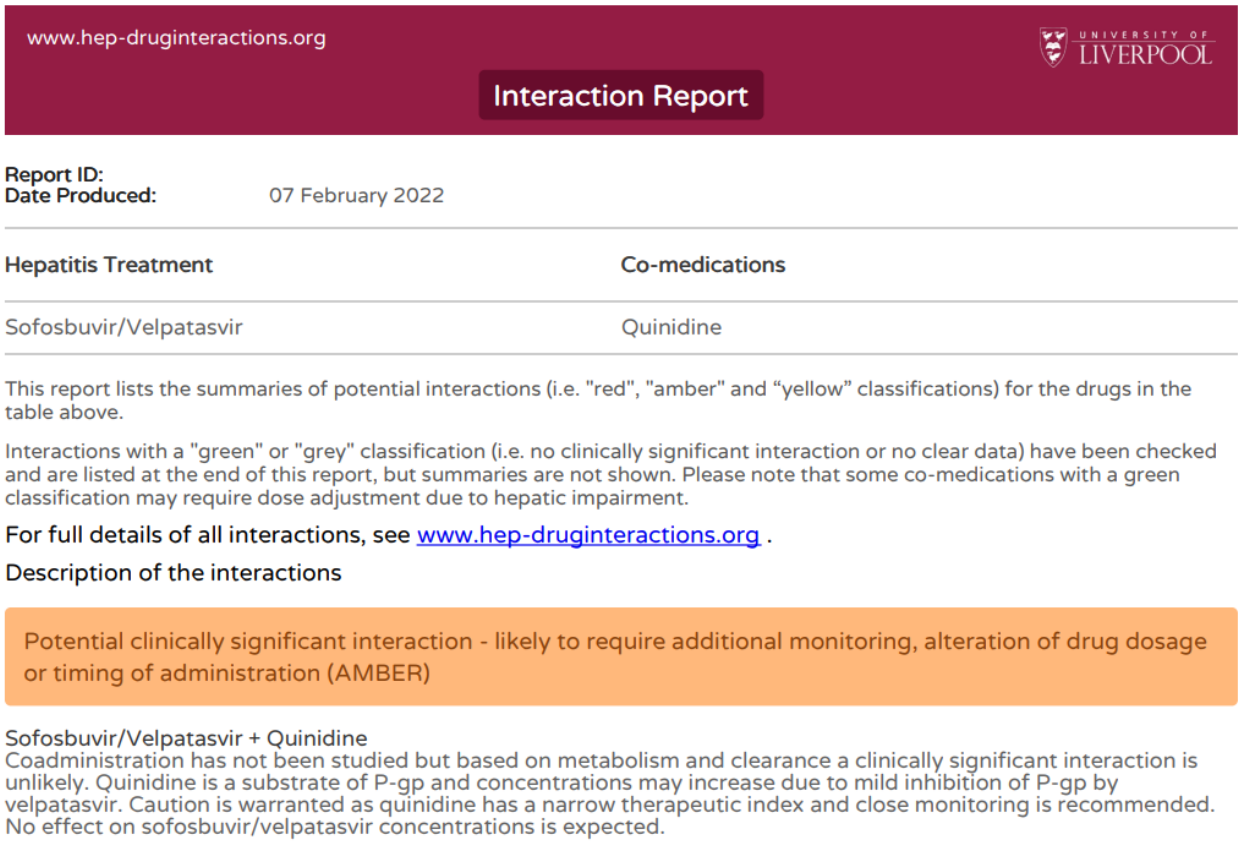
Sofosbuvir/velpatasvir and amiodarone combination in combination with another direct-acting antiviral drug, can lead to severe symptomatic bradycardia. The mechanism of this effect is unknown. The effect on the concentration of amiodarone, sofosbuvir and velpatasvir is not yet known. If co-administration is required because there is no other alternative, continuous cardiac monitoring is recommended.

We also analyzed the co-administration of sofosbuvir/velpatasvir/voxilaprevir and amiodarone, in which it was found that the simultaneous use of amiodarone and sofosbuvir in combination with other direct-acting antiviral drugs, such as velpatasvir and voxylaprevir, can lead to serious symptomatic bradycardia. Because the cases are potentially life-threatening, amiodarone should only be used in patients

taking sofosbuvir/velpatasvir/voxilaprevir when other alternative antiarrhythmic drugs are not tolerated or are contraindicated.

Analyzing the frequency of use of Amiodarone with PPLS in a group of 118 patients with CHC who underwent HCV virus elimination, there was not a single case of the use of a combination of this antiarrhythmic drug with Sofosbuvir and Velpatasvir by doctors. This means that doctors are well aware of the special dangers of the combination of these drugs and the need to disseminate this information to doctors.

When conducting a hazard analysis of the combination of sofosbuvir/velpatasvir and quinidine should be taken into account that quinidine is a substrate of P-gp, and its concentration may increase due to the mild inhibition of P-gp by velpatasvir. Caution should be exercised because quinidine has a narrow therapeutic index, and careful observation and cardiac monitoring is recommended (Fig. 2).



www.hep-druginteractions.org

UNIVERSITY OF LIVERPOOL

**Interaction Report**

**Report ID:**
**Date Produced:** 07 February 2022

| Hepatitis Treatment | Co-medications |
|---|---|
| Sofosbuvir/Velpatasvir | Quinidine |

This report lists the summaries of potential interactions (i.e. "red", "amber" and "yellow" classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

**For full details of all interactions, see www.hep-druginteractions.org .**

**Description of the interactions**

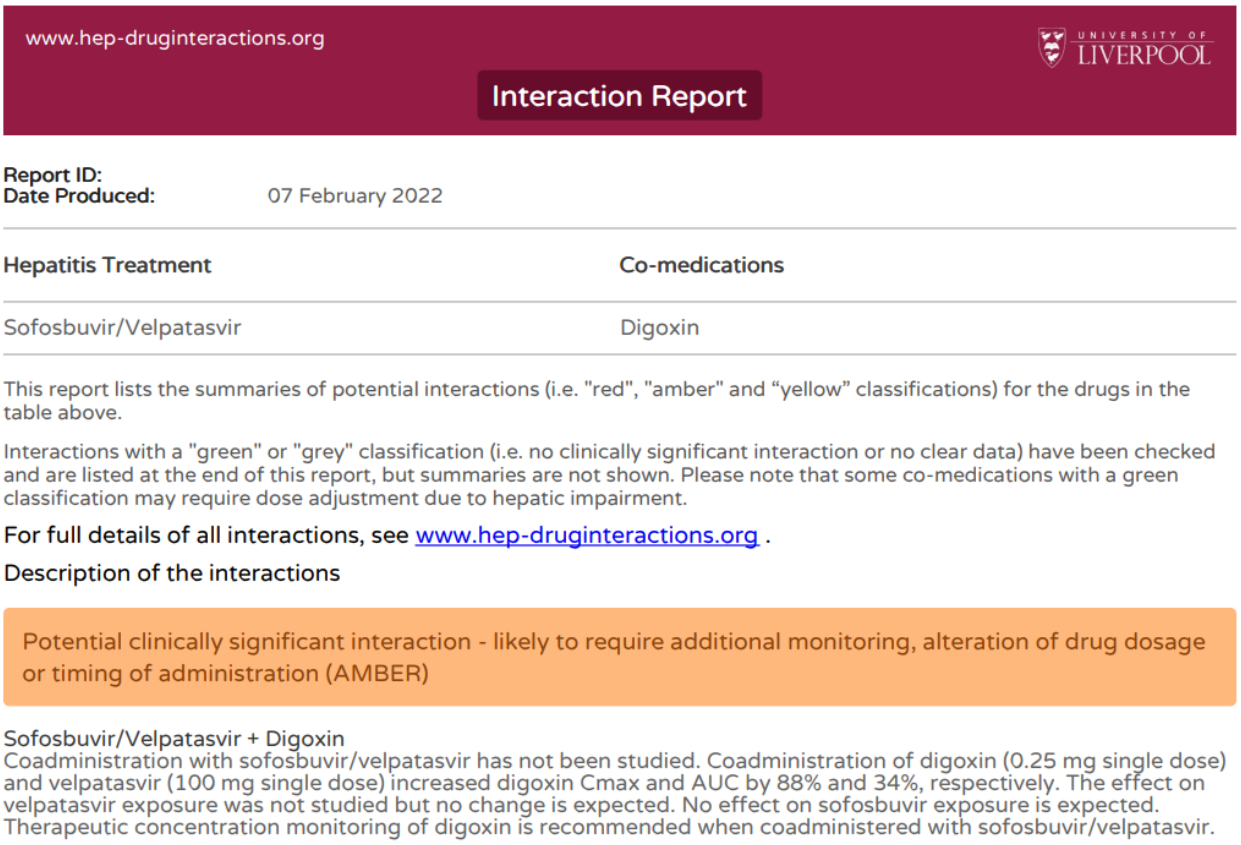
Potential clinically significant interaction - likely to require additional monitoring, alteration of drug dosage or timing of administration (AMBER)

Sofosbuvir/Velpatasvir + Quinidine
Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Quinidine is a substrate of P-gp and concentrations may increase due to mild inhibition of P-gp by velpatasvir. Caution is warranted as quinidine has a narrow therapeutic index and close monitoring is recommended. No effect on sofosbuvir/velpatasvir concentrations is expected.

Fig. 2. Sofosbuvir/velpatasvir combination interaction report with quinidine from the Hep-Druginteractions.org database (Liverpool).

Analyzing the frequency of the use of Quinidine with PPLS in a group of 118 patients with CHC who underwent HCV virus elimination, there was not a single case of doctors using a combination of this antiarrhythmic drug with Sofosbuvir and Velpatasvir. This means that doctors are well aware of the possible adverse effects of this combination on heart function.

When analyzing the effect of the cardioglycoside Digoxin with simultaneous administration with Sofosbuvir / velpatasvir, information was taken into account that the combined administration of digoxin (0.25 mg once) and velpatasvir (100 mg once) increased Cmax and AUC of digoxin by 88% and 34%, respectively. The effect on velpatasvir exposure has not been studied, but no change is expected. When combined with sofosbuvir / velpatasvir, it is recommended to control the therapeutic concentration of digoxin due to the likely development of digitalis intoxication (Fig. 3).



www.hep-druginteractions.org

UNIVERSITY OF LIVERPOOL

**Interaction Report**

**Report ID:**
**Date Produced:** 07 February 2022

| Hepatitis Treatment | Co-medications |
|---|---|
| Sofosbuvir/Velpatasvir | Digoxin |

This report lists the summaries of potential interactions (i.e. "red", "amber" and "yellow" classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

**For full details of all interactions, see www.hep-druginteractions.org .**

**Description of the interactions**

Potential clinically significant interaction - likely to require additional monitoring, alteration of drug dosage or timing of administration (AMBER)

Sofosbuvir/Velpatasvir + Digoxin
Coadministration with sofosbuvir/velpatasvir has not been studied. Coadministration of digoxin (0.25 mg single dose) and velpatasvir (100 mg single dose) increased digoxin Cmax and AUC by 88% and 34%, respectively. The effect on velpatasvir exposure was not studied but no change is expected. No effect on sofosbuvir exposure is expected. Therapeutic concentration monitoring of digoxin is recommended when coadministered with sofosbuvir/velpatasvir.

Fig. 3. Sofosbuvir/velpatasvir combination interaction report with Digoxin based on Hep-Druginteractions.org database (Liverpool).

When making a request for a possible adverse interaction between Sofosbuvir / velpatasvir / voxilaprevir and digoxin, the possible an increase in Cmax and AUC of digoxin by 88% and 34%, respectively. Voxilaprevir is also a P-gp inhibitor, but the additive effect is unknown. Thus, it is recommended to control the therapeutic concentration of digoxin when used simultaneously with sofosbuvir / velpatasvir / voxilaprevir to prevent digitalis intoxication.

Analyzing the frequency of using Digoxin with PPLS in a group of 118 patients with CHC who underwent HCV virus elimination (Sofosbuvir and Velpatasvir), we found that 4 patients had previously undergone digitalization (3.4% of cases). In these patients, the daily dose of Digoxin was moderate and no symptoms of digitalis intoxication were found.

### 3.3. Drug interactions between PPLS against CHC and beta-blockers

We have studied potentially dangerous interactions of sofosbuvir / velpatasvir with beta-blockers, in particular with carvedilol. It should be noted that carvedilol is glucuronidated by UGT 1A1, 2B4 and 2B7 with additional metabolism by CYP2D6 (and to a lesser extent by CYP 2C9 and 1A2), none of which are affected by sofosbuvir/velpatasvir. However, carvedilol is a P-gp substrate and may be elevated due to mild inhibition of P-gp by velpatasvir. Caution should be exercised as carvedilol has a narrow therapeutic index (Figure 4).

www.hep-druginteractions.org

UNIVERSITY OF LIVERPOOL

**Interaction Report**

**Report ID:**
**Date Produced:** 07 February 2022

| Hepatitis Treatment | Co-medications |
|---|---|
| Sofosbuvir/Velpatasvir | Carvedilol |

This report lists the summaries of potential interactions (i.e. "red", "amber" and "yellow" classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

**For full details of all interactions, see** www.hep-druginteractions.org .

**Description of the interactions**

Potential clinically significant interaction - likely to require additional monitoring, alteration of drug dosage or timing of administration (AMBER)

Sofosbuvir/Velpatasvir + Carvedilol
Coadministration has not been studied. Carvedilol is glucuronidated by UGTs 1A1, 2B4 and 2B7 with additional metabolism by CYP2D6 (and to a lesser extent CYPs 2C9 and 1A2), none of which is affected by sofosbuvir/velpatasvir. However, carvedilol is substrate of P-gp and concentrations may increase due to mild inhibition of P-gp by velpatasvir. Caution is warranted as carvedilol has a narrow therapeutic index. [Note, the US Prescribing Information contraindicates carvedilol in patients with severe liver impairment and the European SmPC contraindicates it in patients with hepatic dysfunction.]

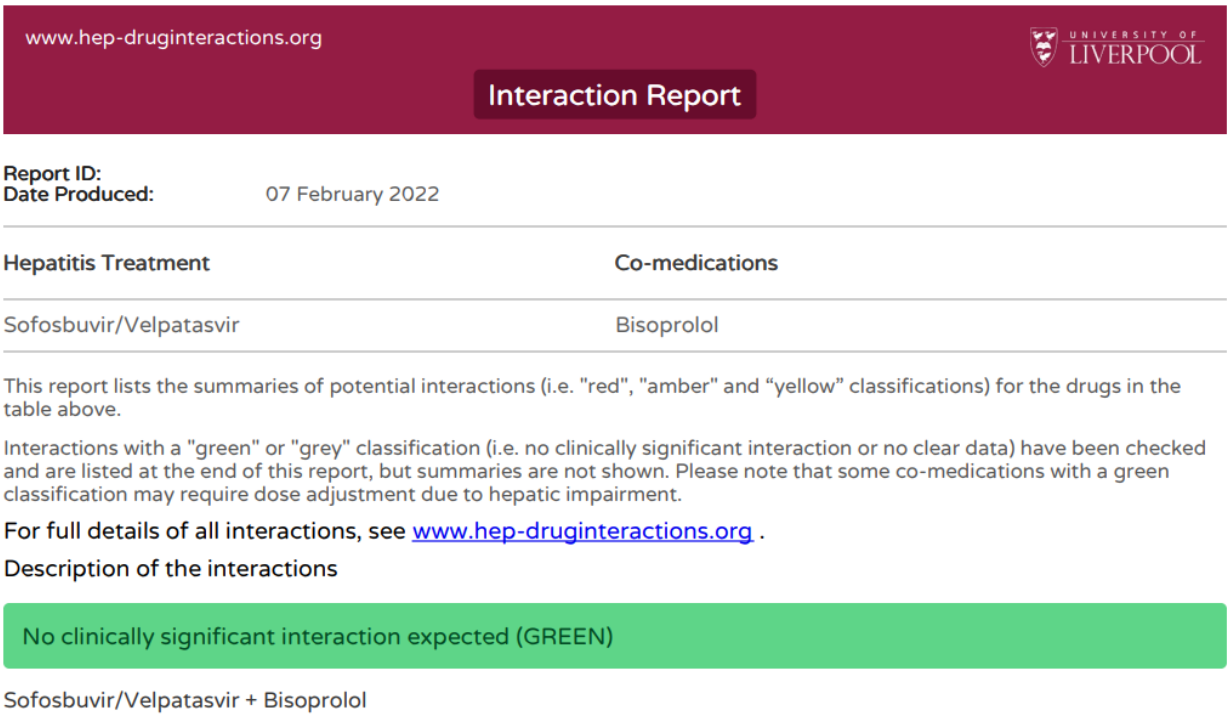
Fig. 4. Sofosbuvir/velpatasvir combination interaction report with Carvedilol based on Hep-Druginteractions.org database (Liverpool).

When co-administering sofosbuvir/velpatasvir/voxilaprevir and carvedilol, be aware that carvedilol is glucuronidated by UGT 1A1, 2B4 and 2B7 with additional metabolism by CYP2D6 (and to a lesser extent by CYP 2C9 and 1A2), none of which are affected by sofosbuvir/velpatasvir/voxilaprevir. However, carvedilol is a P-gp substrate and concentrations may be elevated due to moderate P-gp inhibition by velpatasvir and voxilaprevir. Caution should be exercised as carvedilol has a narrow therapeutic distance. It should be noted that according to US prescribing information, carvedilol is contraindicated in patients with severe hepatic insufficiency, and European Standards do not recommend carvedilol in patients with hepatic dysfunction.

When analyzing the interaction of a group of beta-blockers with PPLS, Carvedilol has the greatest potential danger, the concentration of which can increase uncontrollably when administered simultaneously with a powerful inhibitor of CYP3A4 and P-glycoprotein Velpatasvir. We identified 11 cases (out of 118 extracts, 9.3%) of the simultaneous appointment of Carvedilol and PPLS. This problem

is relevant for patients with severe stages of fibrosis (F3-F4), since Carvedilol is included in the standards for the prevention of variceal bleeding in patients with HCV cirrhosis.

Relatively safe alternatives to Carvedilol are Atenolol, Bisoprolol, Proprano-lol, Metoprolol, which do not have dangerous consequences when administered sim-ultaneously with PPLS (Figure 5, 6, 7, 8).


www.hep-druginteractions.org

UNIVERSITY OF LIVERPOOL

Interaction Report

**Report ID:**
**Date Produced:** 07 February 2022

| Hepatitis Treatment | Co-medications |
|---|---|
| Sofosbuvir/Velpatasvir | Bisoprolol |

This report lists the summaries of potential interactions (i.e. "red", "amber" and "yellow" classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

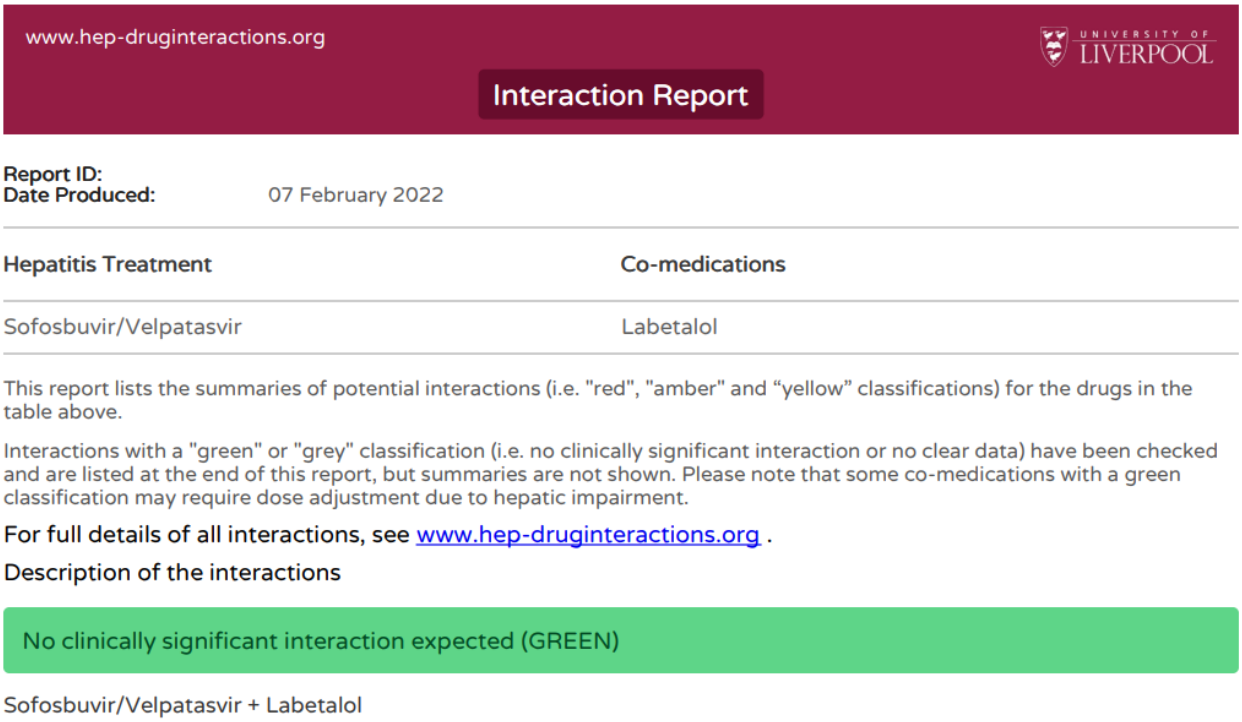
For full details of all interactions, see www.hep-druginteractions.org .

Description of the interactions

No clinically significant interaction expected (GREEN)

Sofosbuvir/Velpatasvir + Bisoprolol

Fig. 5. Sofosbuvir/velpatasvir combination interaction report with bisoprolol from the Hep-Druginteractions.org database (Liverpool).


www.hep-druginteractions.org

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Interaction Report

**Report ID:**
**Date Produced:** 07 February 2022

| Hepatitis Treatment | Co-medications |
|---|---|
| Sofosbuvir/Velpatasvir | Labetalol |

This report lists the summaries of potential interactions (i.e. "red", "amber" and "yellow" classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

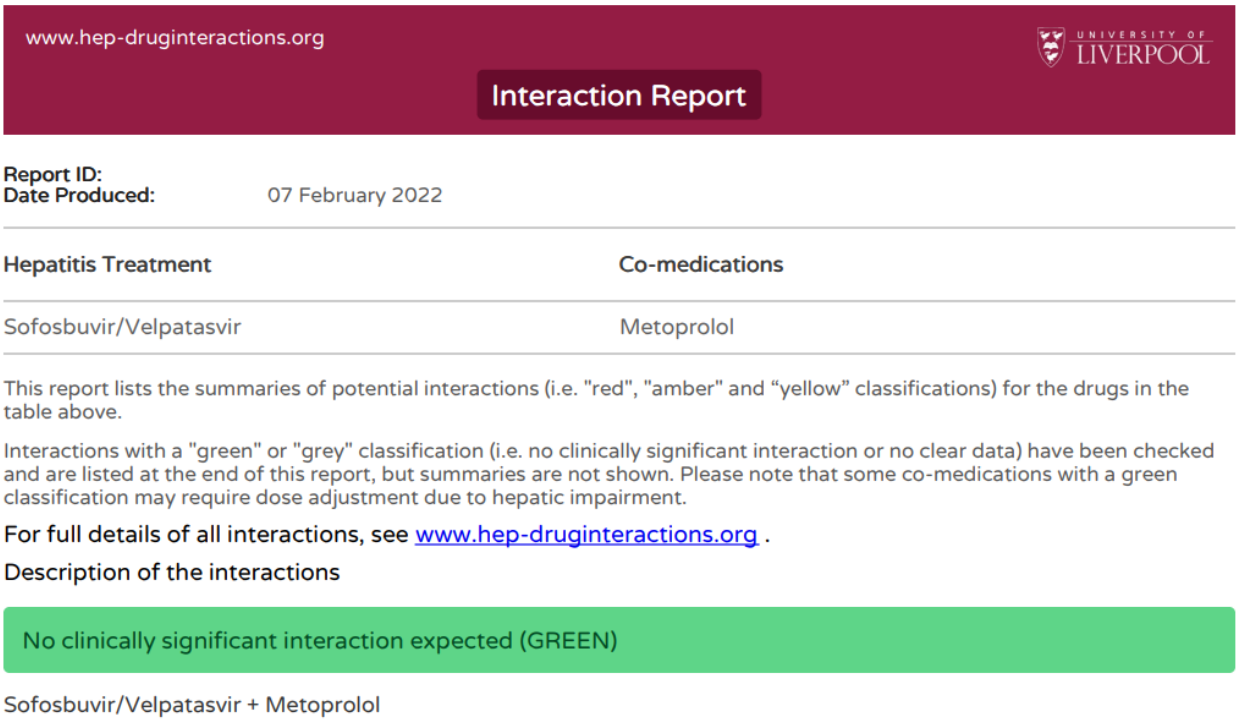
**For full details of all interactions, see www.hep-druginteractions.org .**

**Description of the interactions**

No clinically significant interaction expected (GREEN)

Sofosbuvir/Velpatasvir + Labetalol

Fig. 6. Sofosbuvir/velpatasvir combination interaction report with Labetalol based on Hep-Druginteractions.org database (Liverpool).


www.hep-druginteractions.org

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Interaction Report

**Report ID:**
**Date Produced:** 07 February 2022

| Hepatitis Treatment | Co-medications |
|---|---|
| Sofosbuvir/Velpatasvir | Metoprolol |

This report lists the summaries of potential interactions (i.e. "red", "amber" and "yellow" classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

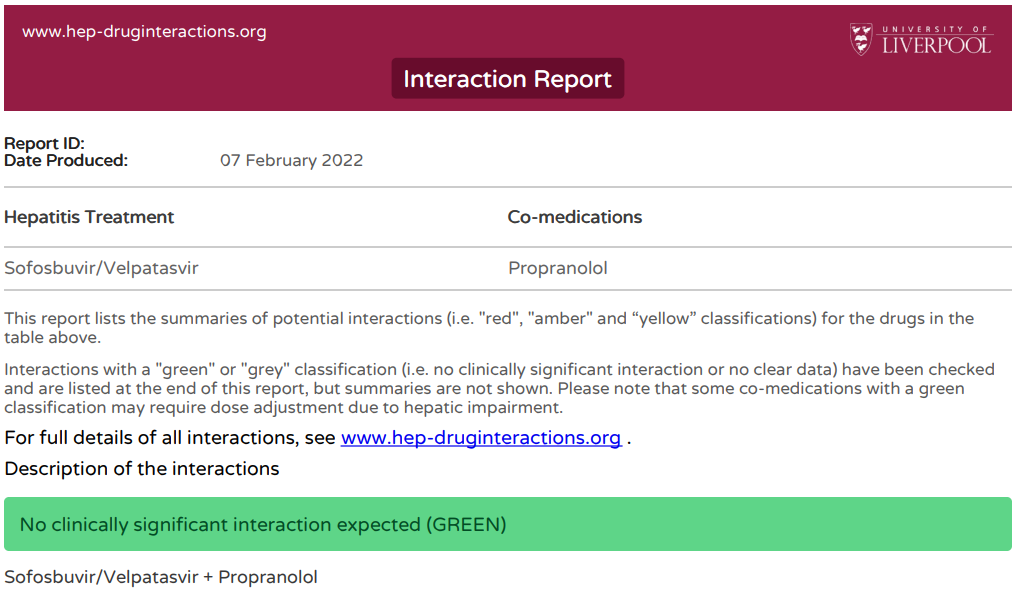
**For full details of all interactions, see www.hep-druginteractions.org .**

**Description of the interactions**

No clinically significant interaction expected (GREEN)

Sofosbuvir/Velpatasvir + Metoprolol

Fig. 7. Sofosbuvir/velpatasvir combination interaction report with metoprolol based on Hep-Druginteractions.org database (Liverpool).


www.hep-druginteractions.org

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Interaction Report

Report ID:
Date Produced: 07 February 2022

| Hepatitis Treatment | Co-medications |
|---|---|
| Sofosbuvir/Velpatasvir | Propranolol |

This report lists the summaries of potential interactions (i.e. "red", "amber" and "yellow" classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

For full details of all interactions, see www.hep-druginteractions.org .

Description of the interactions

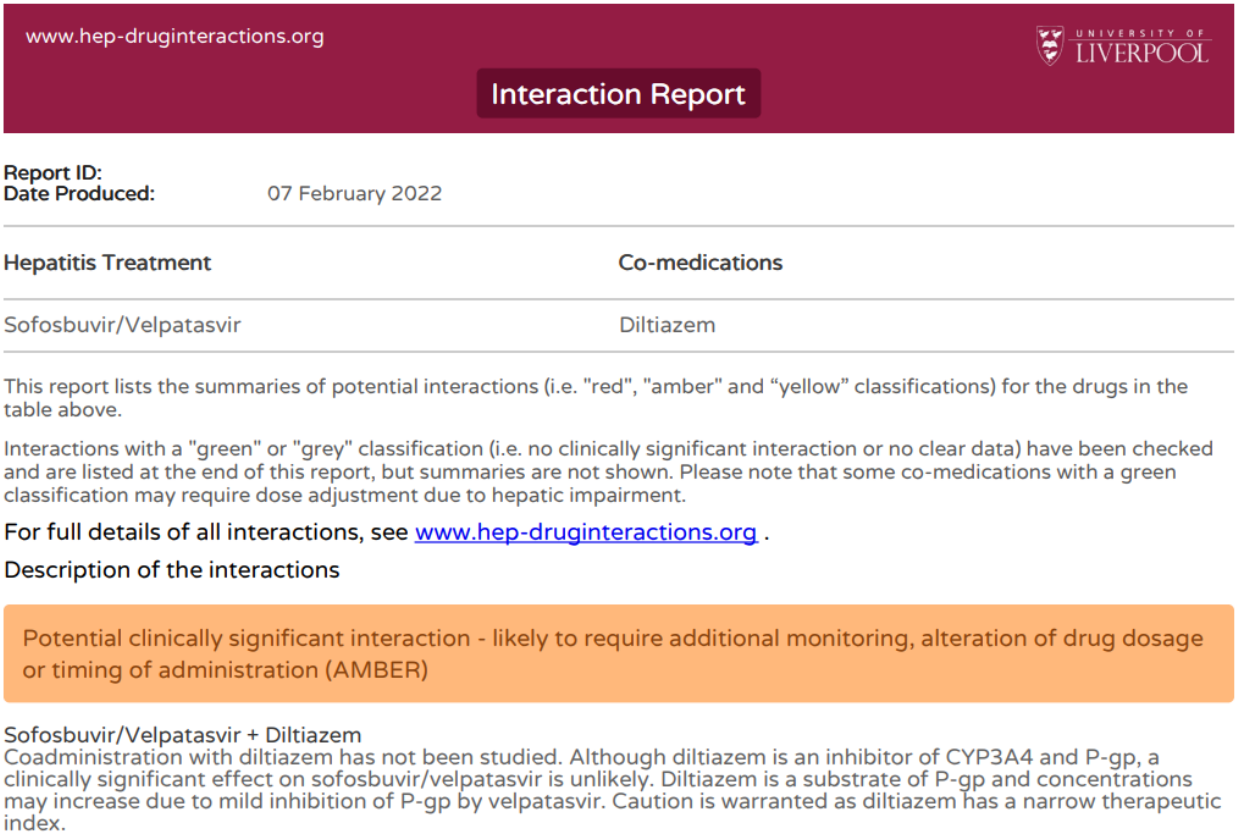
No clinically significant interaction expected (GREEN)

Sofosbuvir/Velpatasvir + Propranolol

Fig. 8. Sofosbuvir/velpatasvir combination interaction report with Propranolol from the Hep-Druginteractions.org database (Liverpool).

### 3.4. Analysis of drug interactions between PPLS against CHC and calcium channel blockers.

When considering the combination of Sofosbuvir/Velpatasvir and Diltiazem, it should be taken into account that although Diltiazem is an inhibitor of CYP3A4 and P-gp, a clinically significant effect on sofosbuvir/velpatasvir is unlikely. Diltiazem is a P-gp substrate and concentrations may be elevated due to the strong inhibition of P-gp by velpatasvir. Caution should be exercised in this clinical setting as diltiazem has a narrow therapeutic index (Figure 9).


www.hep-druginteractions.org

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Interaction Report

Report ID:
Date Produced: 07 February 2022

| Hepatitis Treatment | Co-medications |
|---|---|
| Sofosbuvir/Velpatasvir | Diltiazem |

This report lists the summaries of potential interactions (i.e. "red", "amber" and "yellow" classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

For full details of all interactions, see www.hep-druginteractions.org .

Description of the interactions

Potential clinically significant interaction - likely to require additional monitoring, alteration of drug dosage or timing of administration (AMBER)

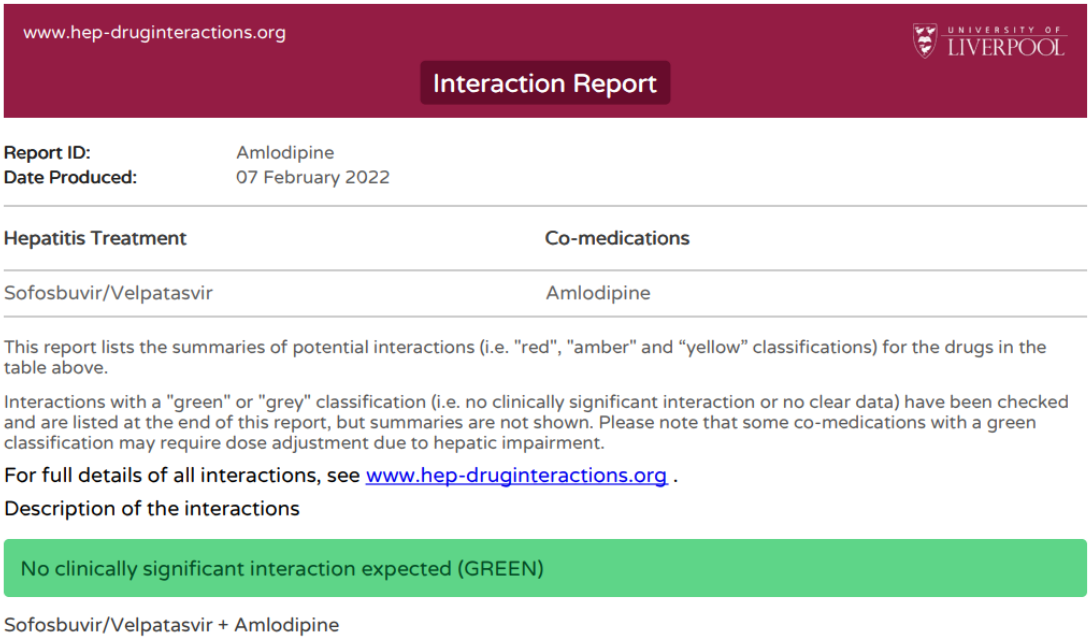
Sofosbuvir/Velpatasvir + Diltiazem
Coadministration with diltiazem has not been studied. Although diltiazem is an inhibitor of CYP3A4 and P-gp, a clinically significant effect on sofosbuvir/velpatasvir is unlikely. Diltiazem is a substrate of P-gp and concentrations may increase due to mild inhibition of P-gp by velpatasvir. Caution is warranted as diltiazem has a narrow therapeutic index.

Fig. 9. Sofosbuvir/velpatasvir combination interaction report with Diltiazem based on Hep-Druginteractions.org database (Liverpool).

When prescribing the combination Sofosbuvir / Velpatasvir / Voxilaprevir + Diltiazem, it is significant that Diltiazem is a P-gp substrate, and its concentration may increase due to inhibition of P-gp by velpatasvir and voxilaprevir. Special care should be taken with this combination of drugs, since diltiazem has a narrow therapeutic index.

When prescribing Sofosbuvir / Velpatasvir / Voxilaprevir + Verapamil, it should be taken into account that Verapamil is metabolized by several CYPs, including CYP3A4, and is a P-gp substrate and inhibitor. Verapamil levels may be elevated because Velpatasvir and Voxilaprevir are P-gp inhibitors. Inhibition of CYP3A4 and P-gp by verapamil may also increase sofosbuvir/velpatasvir/voxilaprevir concentrations, but this is unlikely to be clinically significant. Patients should be monitored for side effects such as hypotension, bradyarrhythmias, and lactic acidosis.

Relatively safe is the combination of Sofosbuvir / Velpatasvir with other calcium channel blockers, such as Amlodipine (Fig. 10) and nifedipine (Fig. 11).


www.hep-druginteractions.org

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Interaction Report

**Report ID:** Amlodipine
**Date Produced:** 07 February 2022

| Hepatitis Treatment | Co-medications |
|---|---|
| Sofosbuvir/Velpatasvir | Amlodipine |

This report lists the summaries of potential interactions (i.e. "red", "amber" and "yellow" classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

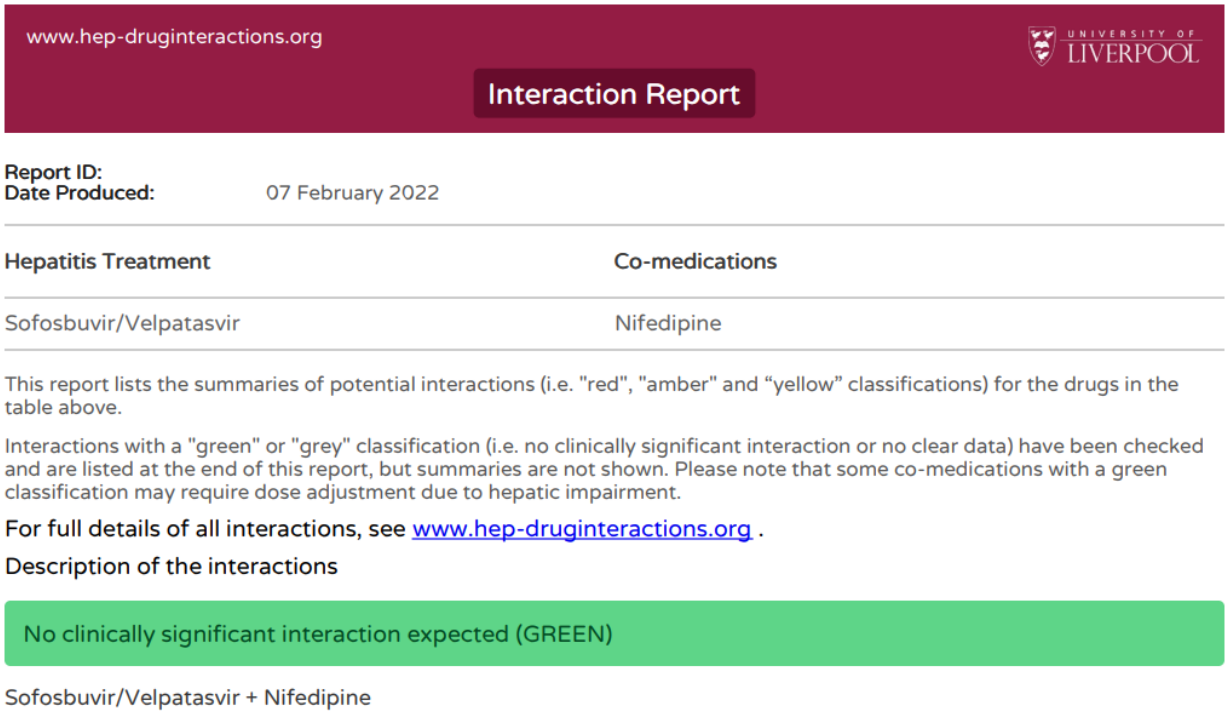
For full details of all interactions, see www.hep-druginteractions.org .

Description of the interactions

No clinically significant interaction expected (GREEN)

Sofosbuvir/Velpatasvir + Amlodipine

Fig.10. Sofosbuvir/velpatasvir combination interaction report with amlodipine based on Hep-Druginteractions.org database (Liverpool).


www.hep-druginteractions.org

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Interaction Report

**Report ID:**
**Date Produced:** 07 February 2022

| Hepatitis Treatment | Co-medications |
|---|---|
| Sofosbuvir/Velpatasvir | Nifedipine |

This report lists the summaries of potential interactions (i.e. "red", "amber" and "yellow" classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

For full details of all interactions, see www.hep-druginteractions.org .

Description of the interactions

No clinically significant interaction expected (GREEN)

Sofosbuvir/Velpatasvir + Nifedipine

Fig. 11. Sofosbuvir/velpatasvir combination interaction report with Nifedipine based on Hep-Druginteractions.org database (Liverpool).

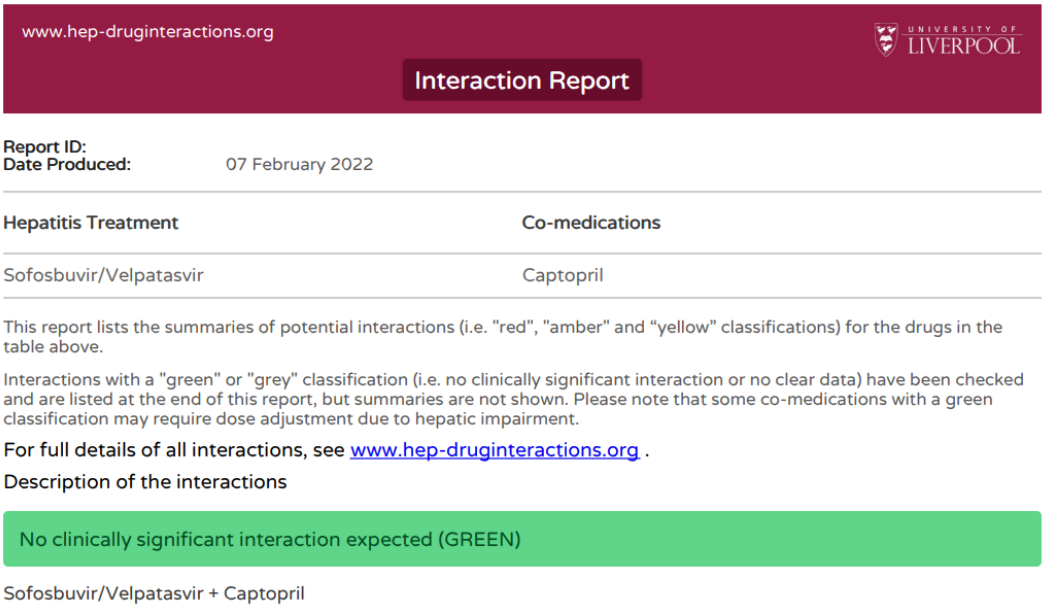
Thus, when prescribing calcium channel blockers amlodipine, according to the results of the Drug Bank (https: // go.drugbank.com / ) and Hep Drug Interactions (https: // www.hep-druginteractions.org / checker) analysis, it was found that these

combinations potentially dangerous as a result of the development of negative inotropic and chronotropic effects with the development of hypotension.

In our study, the appointment of Amlodipine was established in 14 of 118 cases (11.9%). A reasonable alternative in this clinical situation is Amlodipine and Nifedipine, which do not have dangerous interactions with Sofosbuvir and Velpatasvir.

### 3.5. Analysis of drug interactions between PPLS against CHC and angiotensin-converting enzyme inhibitors.

Analyzing possible unsafe interactions between PPLS and drugs of the ACE inhibitor group, it was found that no significant interactions are predicted when prescribing sofosbuvir / velpatasvir with captopril, enalapril, lisinopril (Fig. 12, 13, 14).


www.hep-druginteractions.org

UNIVERSITY OF LIVERPOOL

Interaction Report

Report ID:
Date Produced: 07 February 2022

| Hepatitis Treatment | Co-medications |
|---|---|
| Sofosbuvir/Velpatasvir | Captopril |

This report lists the summaries of potential interactions (i.e. "red", "amber" and "yellow" classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

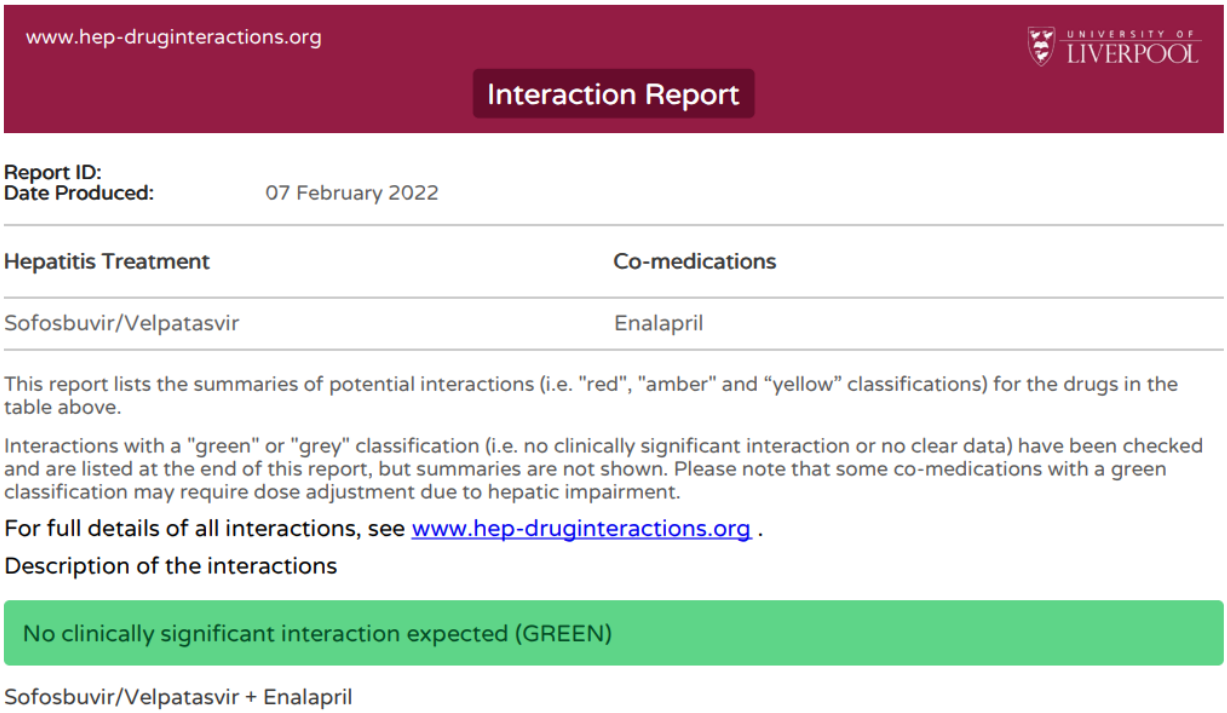
For full details of all interactions, see www.hep-druginteractions.org .

Description of the interactions

No clinically significant interaction expected (GREEN)

Sofosbuvir/Velpatasvir + Captopril

Fig. 12. Sofosbuvir/velpatasvir combination interaction report with Captopril based on Hep-Druginteractions.org database (Liverpool).


www.hep-druginteractions.org

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Interaction Report

**Report ID:**
**Date Produced:** 07 February 2022

| Hepatitis Treatment | Co-medications |
|---|---|
| Sofosbuvir/Velpatasvir | Enalapril |

This report lists the summaries of potential interactions (i.e. "red", "amber" and "yellow" classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

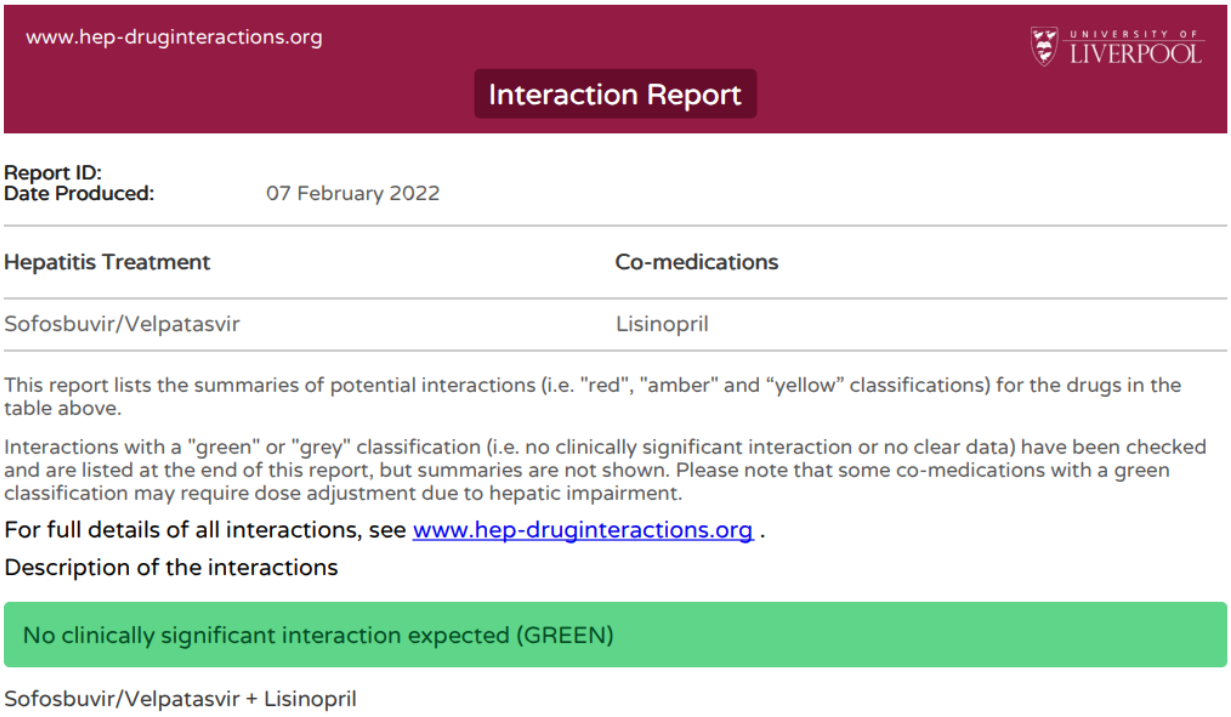
For full details of all interactions, see www.hep-druginteractions.org .

Description of the interactions

No clinically significant interaction expected (GREEN)

Sofosbuvir/Velpatasvir + Enalapril

Fig.13. Sofosbuvir/velpatasvir combination interaction report with Enalopril based on Hep-Druginteractions.org database (Liverpool).


www.hep-druginteractions.org

UNIVERSITY OF LIVERPOOL

Interaction Report

**Report ID:**
**Date Produced:** 07 February 2022

| Hepatitis Treatment | Co-medications |
|---|---|
| Sofosbuvir/Velpatasvir | Lisinopril |

This report lists the summaries of potential interactions (i.e. "red", "amber" and "yellow" classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

For full details of all interactions, see www.hep-druginteractions.org .

Description of the interactions

No clinically significant interaction expected (GREEN)

Sofosbuvir/Velpatasvir + Lisinopril

Fig. 14. Sofosbuvir/velpatasvir combination interaction report with Lisinopril based on Hep-Druginteractions.org database (Liverpool).

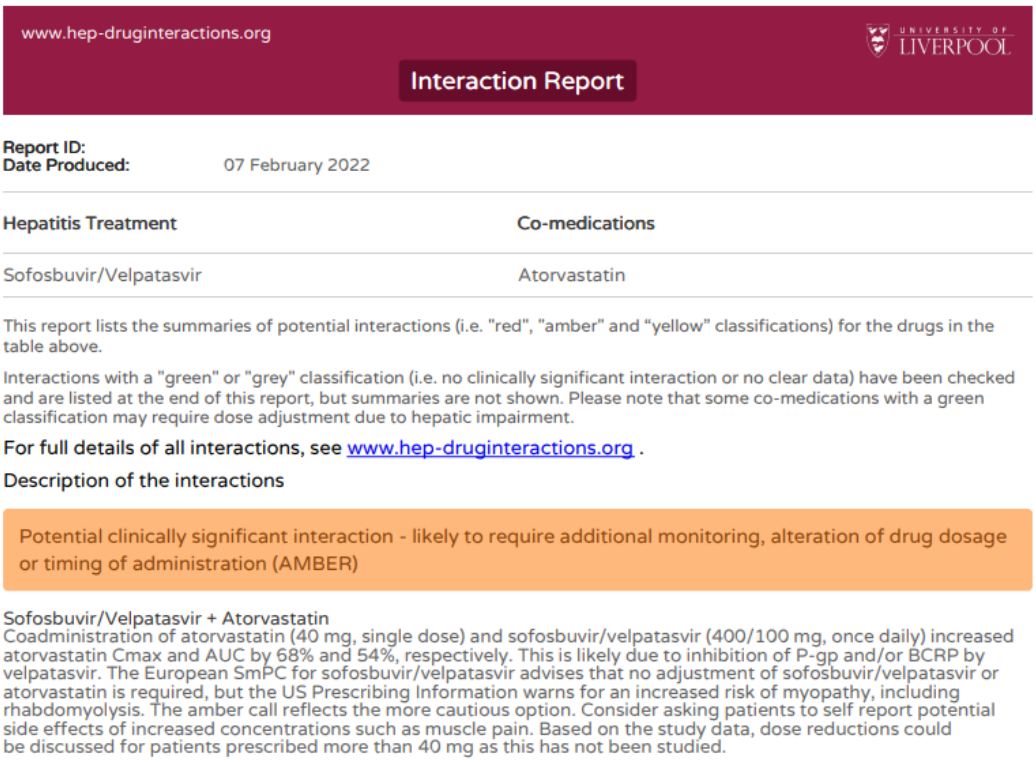
In our study, the appointment of angiotensin-converting enzyme blockers (Captopril, Enalopril, Lisinopril) was established in 32 out of 118 cases (27.1%)

against the background of the use of direct antiviral drugs. There were no significant side effects in patients with CHC with virus elimination.

Especially in the mature age group, the appointment of drugs from the group of angiotensin-converting enzyme inhibitors and sartans was relevant, respectively, in 15 patients (12.7%) and 11 (9.3%), respectively. Potentially dangerous pharmacokinetic and pharmacodynamic interactions between these groups of antihypertensive drugs and PPLS have not been established.

### 3.6. Analysis of drug interactions between PPLS against CHC and lipid-lowering drugs.

**With the combined use of sofosbuvir/velpatasvir and atorvastatin,** judging by metabolism and clearance, atorvastatin exposure may increase due to inhibition of OATP1B1, which leads to an increase in side effects. Co-administration of these drugs is not recommended in Europe, but the US recommends using the lowest approved dose of drugs after assessing the risk/benefit ratio (Figure 15).



www.hep-druginteractions.org

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**Interaction Report**

**Report ID:**
**Date Produced:** 07 February 2022

| Hepatitis Treatment | Co-medications |
|---|---|
| Sofosbuvir/Velpatasvir | Atorvastatin |

This report lists the summaries of potential interactions (i.e. "red", "amber" and "yellow" classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

For full details of all interactions, see www.hep-druginteractions.org .

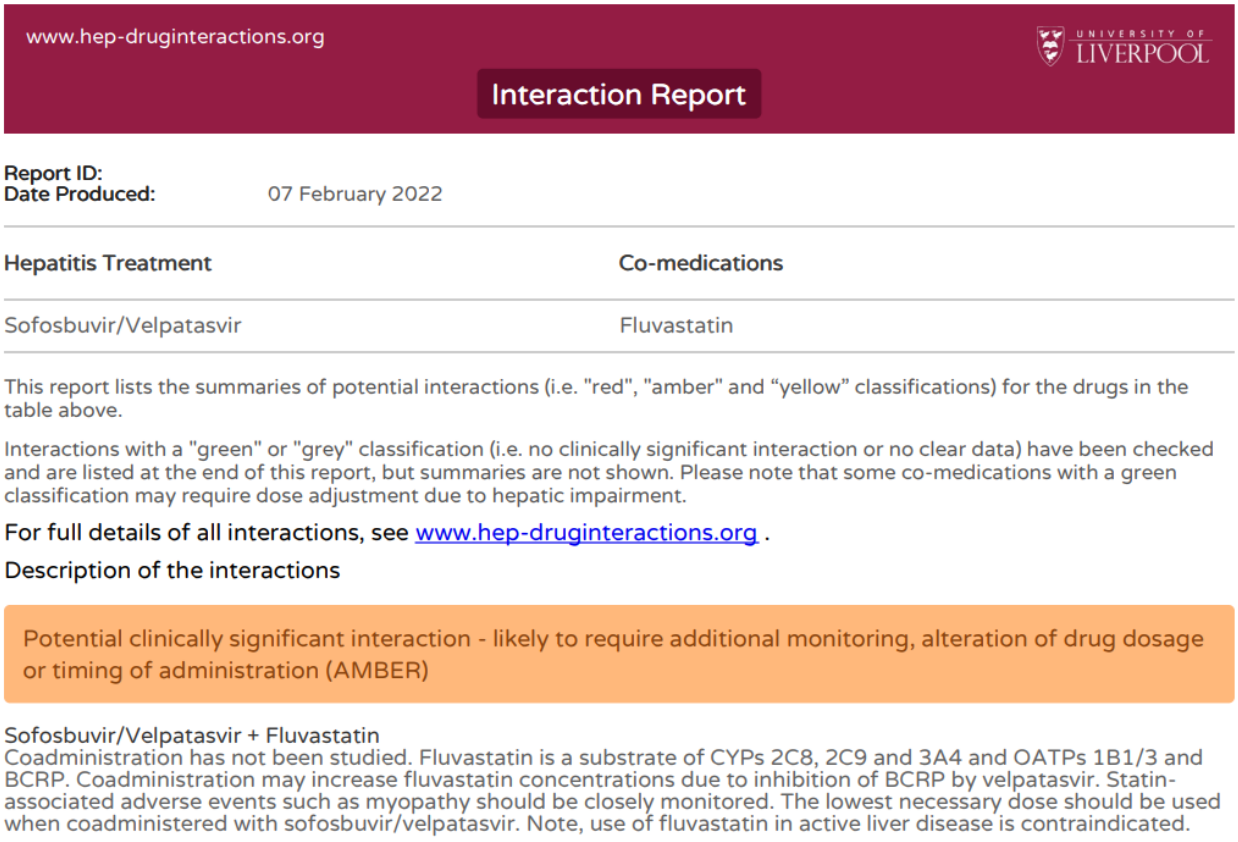
Description of the interactions

Potential clinically significant interaction - likely to require additional monitoring, alteration of drug dosage or timing of administration (AMBER)

Sofosbuvir/Velpatasvir + Atorvastatin
Coadministration of atorvastatin (40 mg, single dose) and sofosbuvir/velpatasvir (400/100 mg, once daily) increased atorvastatin Cmax and AUC by 68% and 54%, respectively. This is likely due to inhibition of P-gp and/or BCRP by velpatasvir. The European SmPC for sofosbuvir/velpatasvir advises that no adjustment of sofosbuvir/velpatasvir or atorvastatin is required, but the US Prescribing Information warns for an increased risk of myopathy, including rhabdomyolysis. The amber call reflects the more cautious option. Consider asking patients to self report potential side effects of increased concentrations such as muscle pain. Based on the study data, dose reductions could be discussed for patients prescribed more than 40 mg as this has not been studied.

Fig. 15. Sofosbuvir/velpatasvir combination interaction report with atorvastatin from the Hep-Druginteractions.org database (Liverpool).

**When co-administering sofosbuvir/velpatasvir and fluvastatin,** it should be taken into account that fluvastatin is a substrate of CYP 2C8, 2C9 and 3A4, as well as OATP 1B1/3 and BCRP. The simultaneous use of this combination may increase the concentration of fluvastatin due to inhibition of BCRP and OATP by velpatasvir and voxilaprevir. European standards of treatment do not recommend their combined use. The prescribing information for the combination of these drugs in the US states that statin-related adverse events, such as myopathy, should be carefully monitored. When co-administered with sofosbuvir/velpatasvir/voxilaprevir, the lowest required dose should be used. In clinical practice, it should be taken into account that the use of fluvastatin in active liver disease is contraindicated (Fig. 16).


www.hep-druginteractions.org

UNIVERSITY OF LIVERPOOL

Interaction Report

**Report ID:**
**Date Produced:** 07 February 2022

| Hepatitis Treatment | Co-medications |
|---|---|
| Sofosbuvir/Velpatasvir | Fluvastatin |

This report lists the summaries of potential interactions (i.e. "red", "amber" and "yellow" classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

For full details of all interactions, see www.hep-druginteractions.org .

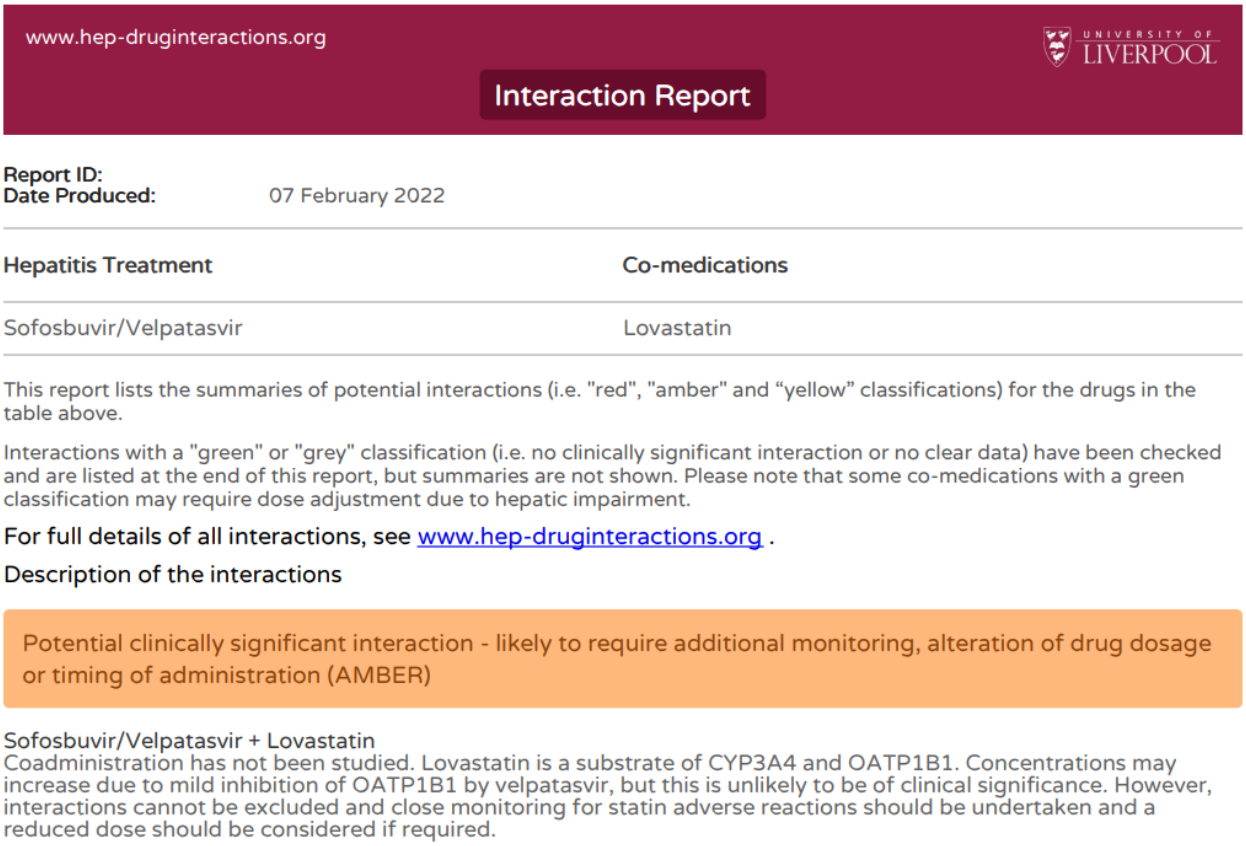
Description of the interactions

Potential clinically significant interaction - likely to require additional monitoring, alteration of drug dosage or timing of administration (AMBER)

Sofosbuvir/Velpatasvir + Fluvastatin
Coadministration has not been studied. Fluvastatin is a substrate of CYPs 2C8, 2C9 and 3A4 and OATPs 1B1/3 and BCRP. Coadministration may increase fluvastatin concentrations due to inhibition of BCRP by velpatasvir. Statin-associated adverse events such as myopathy should be closely monitored. The lowest necessary dose should be used when coadministered with sofosbuvir/velpatasvir. Note, use of fluvastatin in active liver disease is contraindicated.

Fig. 16. Sofosbuvir/velpatasvir combination interaction report with fluvastatin from the Hep-Druginteractions.org database (Liverpool).

**Features of the co-administration of sofosbuvir / velpatasvir and lovastatin** is that lovastatin is a substrate of CYP3A4 and OATP1B1. Concentrations may be elevated due to inhibition of OATP1B1 by velpatasvir and voxilaprevir. European guidelines for the treatment of liver pathology indicate that their co-administration is not recommended. The US Standards of Care for HCV information states that statin-related adverse events, such as myopathy, should be carefully monitored (Fig. 17).



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UNIVERSITY OF LIVERPOOL

Interaction Report

**Report ID:**
**Date Produced:** 07 February 2022

| Hepatitis Treatment | Co-medications |
|---|---|
| Sofosbuvir/Velpatasvir | Lovastatin |

This report lists the summaries of potential interactions (i.e. "red", "amber" and "yellow" classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

For full details of all interactions, see www.hep-druginteractions.org .

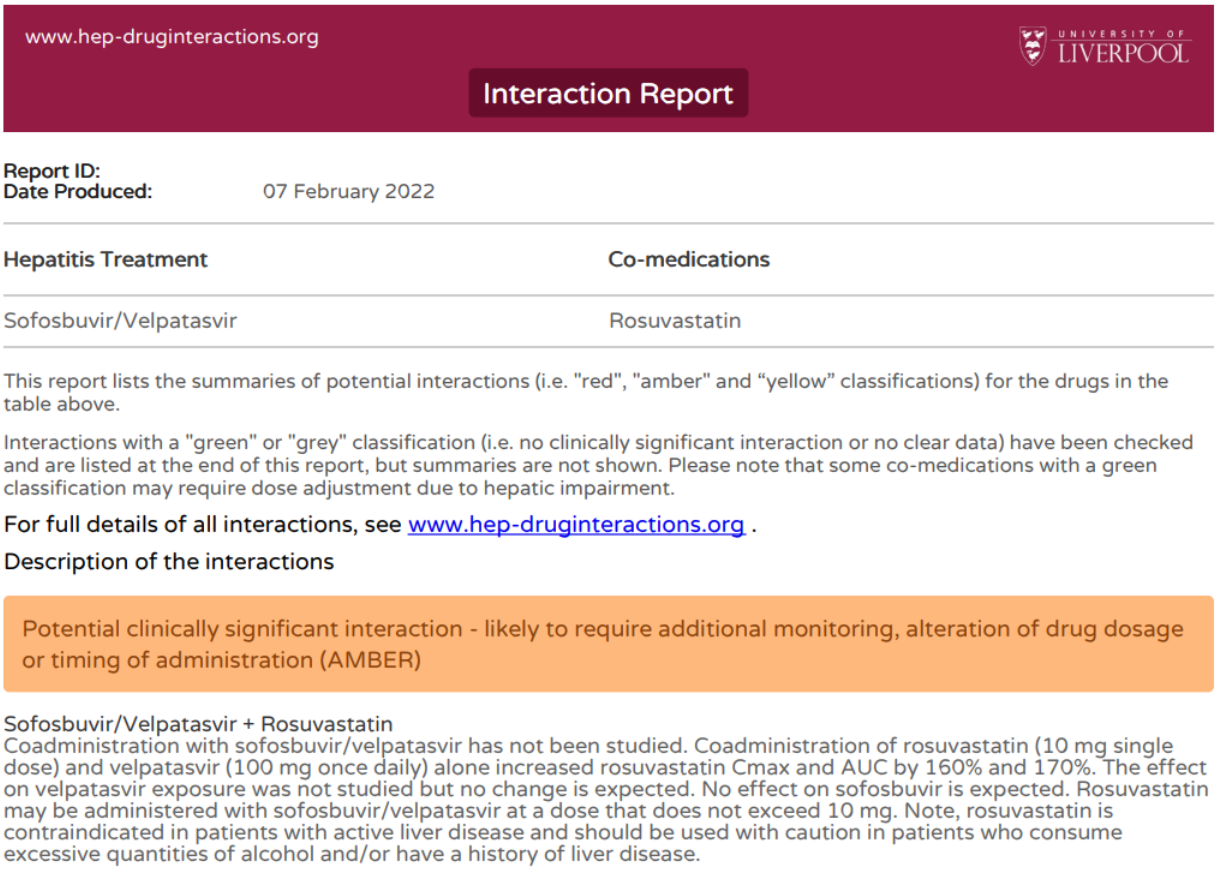
Description of the interactions

Potential clinically significant interaction - likely to require additional monitoring, alteration of drug dosage or timing of administration (AMBER)

Sofosbuvir/Velpatasvir + Lovastatin
Coadministration has not been studied. Lovastatin is a substrate of CYP3A4 and OATP1B1. Concentrations may increase due to mild inhibition of OATP1B1 by velpatasvir, but this is unlikely to be of clinical significance. However, interactions cannot be excluded and close monitoring for statin adverse reactions should be undertaken and a reduced dose should be considered if required.

Fig. 17. Sofosbuvir/velpatasvir combination interaction report with lovastatin from the Hep-Druginteractions.org database (Liverpool).

**The combined use of Sofosbuvir / Velpatasvir and Rosuvastatin is** contraindicated due to increased concentrations and side effects of Rosuvastatin due to inhibition of BCRP by Velpatasvir. The simultaneous use of rosuvastatin (10 mg once a day) and sofosbuvir / velpatasvir / voxilaprevir (400/100/100 mg once a day) and voxilaprevir (100 mg once a day) increased Cmax and AUC of rosuvastatin by 18.9 and 7.4 times (Fig. 18).



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UNIVERSITY OF LIVERPOOL

Interaction Report

**Report ID:**
**Date Produced:** 07 February 2022

| Hepatitis Treatment | Co-medications |
|---|---|
| Sofosbuvir/Velpatasvir | Rosuvastatin |

This report lists the summaries of potential interactions (i.e. "red", "amber" and "yellow" classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

For full details of all interactions, see www.hep-druginteractions.org .

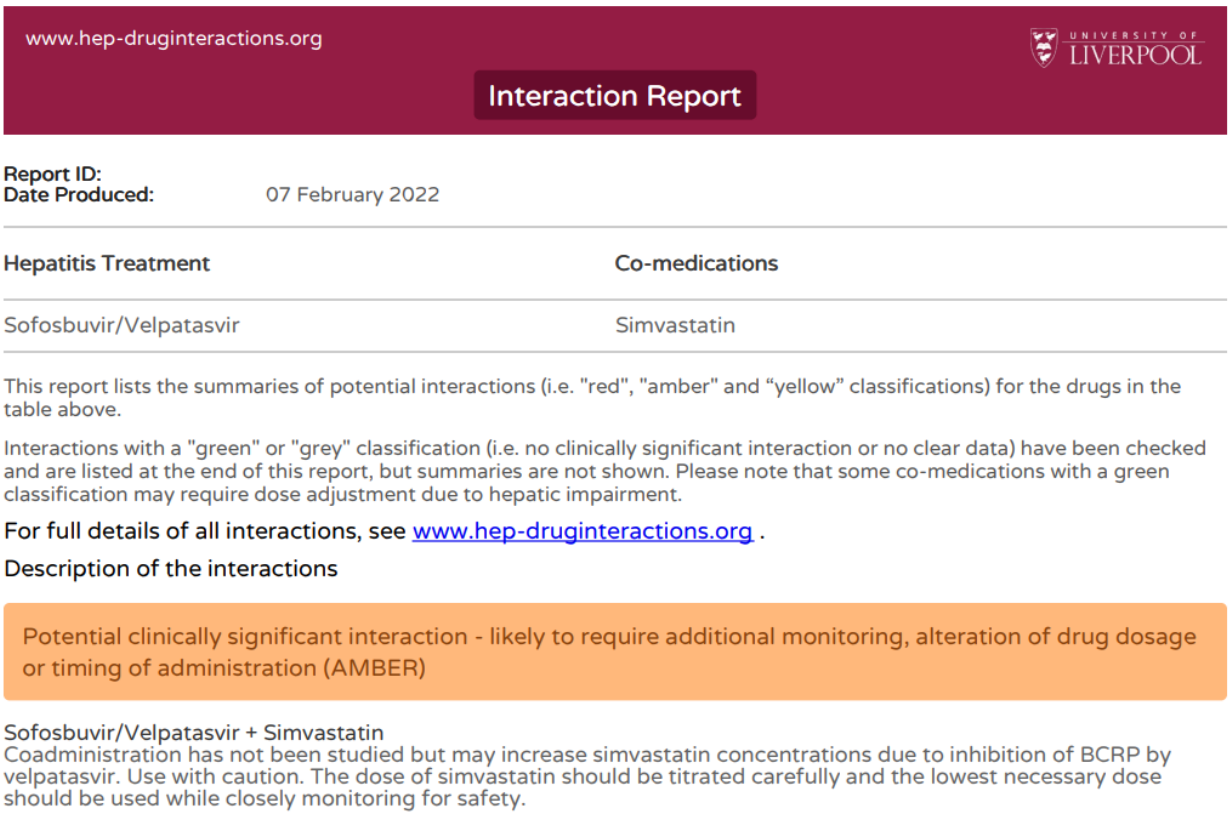
Description of the interactions

Potential clinically significant interaction - likely to require additional monitoring, alteration of drug dosage or timing of administration (AMBER)

Sofosbuvir/Velpatasvir + Rosuvastatin
Coadministration with sofosbuvir/velpatasvir has not been studied. Coadministration of rosuvastatin (10 mg single dose) and velpatasvir (100 mg once daily) alone increased rosuvastatin Cmax and AUC by 160% and 170%. The effect on velpatasvir exposure was not studied but no change is expected. No effect on sofosbuvir is expected. Rosuvastatin may be administered with sofosbuvir/velpatasvir at a dose that does not exceed 10 mg. Note, rosuvastatin is contraindicated in patients with active liver disease and should be used with caution in patients who consume excessive quantities of alcohol and/or have a history of liver disease.

Fig. 18. Sofosbuvir/velpatasvir combination interaction report with Rosuvatstatin based on Hep-Druginteractions.org database (Liverpool).

The combination of Sofosbuvir/Velpatasvir + Simvastatin increased the concentration of Simvastatin due to inhibition of BCRP by Velpatasvir. Co-administration is not recommended in Europe and the US, as elevated concentrations of statins may increase the risk of myopathy, including rhabdomyolysis. If high doses of statins are needed, the lowest required dose of statins should be given based on a risk/benefit assessment (Figure 19).


www.hep-druginteractions.org

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Interaction Report

Report ID:
Date Produced: 07 February 2022

| Hepatitis Treatment | Co-medications |
|---|---|
| Sofosbuvir/Velpatasvir | Simvastatin |

This report lists the summaries of potential interactions (i.e. "red", "amber" and "yellow" classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

For full details of all interactions, see www.hep-druginteractions.org .

Description of the interactions

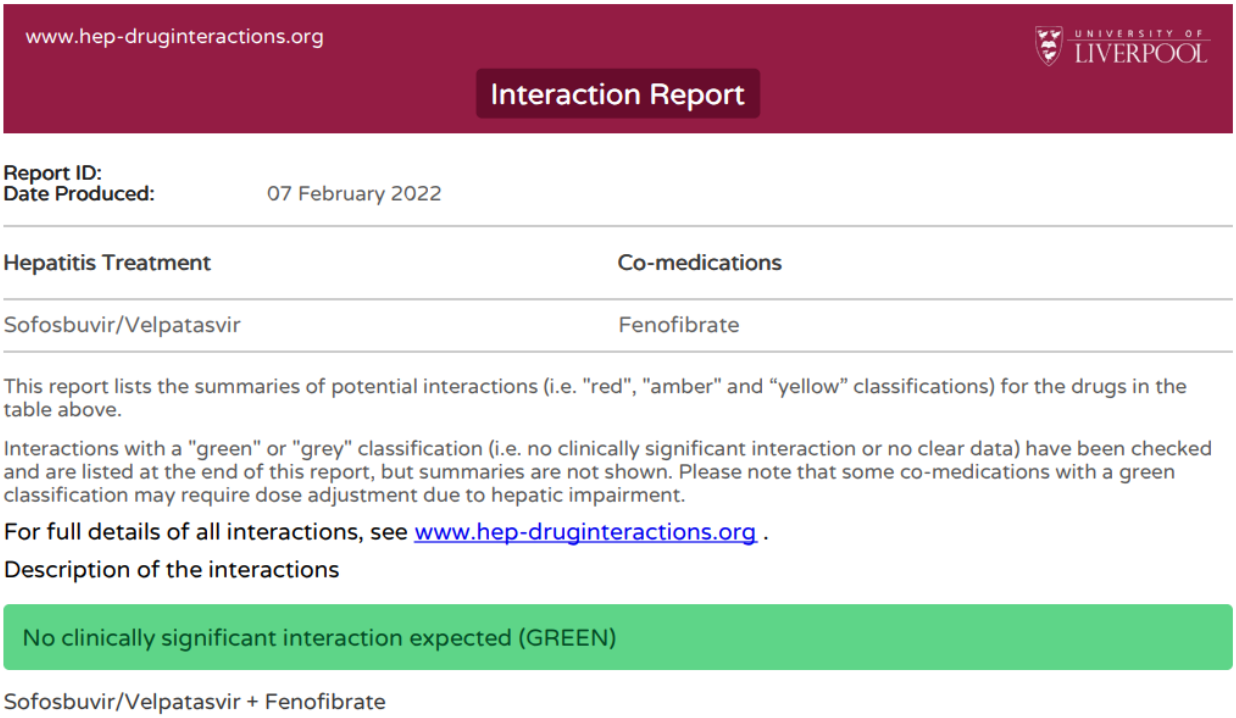
Potential clinically significant interaction - likely to require additional monitoring, alteration of drug dosage or timing of administration (AMBER)

Sofosbuvir/Velpatasvir + Simvastatin
Coadministration has not been studied but may increase simvastatin concentrations due to inhibition of BCRP by velpatasvir. Use with caution. The dose of simvastatin should be titrated carefully and the lowest necessary dose should be used while closely monitoring for safety.

Fig. 19. Sofosbuvir/velpatasvir combination interaction report with simvastatin from the Hep-Druginteractions.org database (Liverpool).

26 patients (22.0%) from a total group of 118 CHC patients who underwent virus-eliminating therapy also took drugs from the statin group (Simvastatin, Atorvastatin, Rosuvastatin). Of these, 7 (26.9%) had signs of myalgia, an increase in the level of creatinine phosphokinase, 5 of these patients were referred for a consultation with a rheumatologist to rule out an autoimmune complication of CHC - dermatomyositis. After a thorough analysis of the results of the ANA profile (blot analysis), the autoimmune nature of myalgias was excluded. The most likely cause of muscle pathology was a significant increase in the concentration of statins after the start of Velpatasvir, a potent inhibitor of CYP3A4. After stopping the use of statins and replacing them with drugs in the fibrate group, all the symptoms of myalgia disappeared during the intake of virus-eliminating therapy.

An alternative to prescribing statins for direct antiviral therapy for CHC is the use of fibrates, which do not have dangerous drug interactions with Sofosbuvir and Velpatasvir (Fig. 20).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UNIVERSITY OF LIVERPOOL

Interaction Report

Report ID:
Date Produced: 07 February 2022

| Hepatitis Treatment | Co-medications |
|---|---|
| Sofosbuvir/Velpatasvir | Fenofibrate |

This report lists the summaries of potential interactions (i.e. "red", "amber" and "yellow" classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

For full details of all interactions, see www.hep-druginteractions.org .

Description of the interactions

No clinically significant interaction expected (GREEN)

Sofosbuvir/Velpatasvir + Fenofibrate

Fig. 20. Sofosbuvir/velpatasvir combination interaction report with Fenofibrate based on Hep-Druginteractions.org database (Liverpool).

## FINDINGS

1. The most clinically significant side effects of the combined use of PPLS (Sofosbuvir and Velpatasvir) in the treatment of CHC is the prescription of statins, which induced the development of myalgia symptoms in 26.9%, which decreased when statins were replaced with drugs from the fibrate group. Almost all statins are contraindicated for combined use with PPLS in CHC (Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Rosuvastatin, Simvastatin). In the case of dyslipidemia in patients with CHC, it is advisable to prescribe fibrates that are compatible with direct antiviral drugs for CHC (Bezafibrate, Ezetimibe, Fenofibrate).

2. According to the results of the analysis of the databases Drug Bank (https: // go.drugbank.com / ) and Hep Drug Interactions (https: // www.hep-druginteractions.org / checker ), the most dangerous co-administration of Sofosbuvir and Velpatasvir with Amiodarone and Digoxin. In the analyzed extracts from the case histories, doctors avoided the simultaneous prescription of these drugs. Relatively safe in cardiac arrhythmias, the appointment of PPLS together with Vernacalant or Flecainide can be recognized.

3. In 9.3% of cases (11 out of 118) of CHC treatment with PPLS, Carvedilol was prescribed mainly in patients with severe liver fibrosis (stages F3-F4), which is potentially dangerous for these patients. The drugs of choice in this group of patients may be beta-blockers: Atenolol, Bisoprolol, Propranolol.

4. In 11.9% (14 out of 118 patients with CHC), Amplodipine was taken as part of antihypertensive therapy, which is a potentially dangerous prescription along with PPLS. A reasonable alternative in this clinical situation is Nifedipine, which can be taken instead of Amlodipine.

5. The use of ACE inhibitors and angiotensin II receptor inhibitors (sartans) in HCV virus-eliminating therapy is quite safe and does not require additional adjustment of pharmacotherapy regimens. The safety of the simultaneous appointment of PPLS with Enalapril, Losartan has been proven.

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