# Swiss Summary of the Risk Management Plan (RMP)

# Maviret®

## (Glecaprevir / Pibrentasvir)

100 mg/40 mg

Film-coated tablets

Version 5.0 (February 2020)

AbbVie AG

***Disclaimer***

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary of Maviret® is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of Maviret® in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. AbbVie AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Maviret®.

# Part VI: Summary of the Risk Management Plan

## Summary of risk management plan for Glecaprevir/Pibrentasvir

This is a summary of the risk management plan (RMP) for glecaprevir/pibrentasvir. The RMP details important risks of glecaprevir/pibrentasvir, how these risks can be minimized, and how more information will be obtained about glecaprevir/pibrentasvir's risks and uncertainties (missing information).
Glecaprevir/pibrentasvir's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how glecaprevir/pibrentasvir should be used.
This summary of the RMP for glecaprevir/pibrentasvir should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which are part of the European Public Assessment Report (EPAR).
Important new concerns or changes to the current ones will be included in updates of glecaprevir/pibrentasvir's RMP.

## I The Medicine and What it Is Used For

Glecaprevir/pibrentasvir is authorized for the treatment of chronic hepatitis C virus (HCV) infection in adults and adolescents (12 to less than 18 years old; see SmPC for the full indication). It contains glecaprevir/pibrentasvir as the active substance and it is given by mouth.
Further information about the evaluation of glecaprevir/pibrentasvir's benefits can be found in glecaprevir/pibrentasvir's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:
*http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004430/h uman_med_002151.jsp&mid=WC0b01ac058001d124.*

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

Important risks of glecaprevir/pibrentasvir, together with measures to minimize such risks and the proposed studies for learning more about glecaprevir/pibrentasvir's risks, are outlined below.
Measures to minimize the risks identified for medicinal products can be:

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

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.
If important information that may affect the safe use of glecaprevir/pibrentasvir is not yet available, it is listed under "missing information" below.

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

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

| **List of Important Risks and Missing Information** | |
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| Important identified risks | HBV reactivation |
| | Resistance development |
| Important potential risks | Recurrence of hepatocellular carcinoma |
| | Emergence of hepatocellular carcinoma |
| | Drug-drug interactions:<br>– Concomitant use with other drugs that are strong inhibitors of OATP1B1 or OATP1B3 (e.g., ciclosporin 400 mg, darunavir with or without ritonavir, and lopinavir/ritonavir)<br>– Concomitant use with drugs that are moderate inducers of P-gp/CYP3A (e.g., efavirenz, oxcarbazepine, eslicarbazepine, lumacaftor, crizotinib)<br>– Concomitant use with drugs that are sensitive substrates of P-gp (e.g., digoxin)<br>– Concomitant use with drugs that are sensitive substrates of OATP1B1 or OATP1B3 (e.g., lovastatin, pravastatin, rosuvastatin) |
| Missing information | Safety in patients with moderate hepatic impairment (Child-Pugh B) |
| | Safety in pregnant and breastfeeding patients |
| | Safety in patients with previous hepatocellular carcinoma |

## II.B Summary of Important Risks

| **Important identified risk: Hepatitis B Virus (HBV) reactivation** | |
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| Evidence for linking the risk to the medicine | Procedure EMEA/H/A-20/1438 under Article 20 of Regulation (EC) No 726/2004.<br>Cases of HBV reactivation have been reported in the literature during treatment with HCV DAAs, similar to those observed in the setting of immunosuppression due to chemotherapy (Wahle 2015, Hoofnagle 2009, Pattullo 2015, Tohme 2013, Mimms 1993).<br>Current data from the literature appear to demonstrate a potential association between HBV reactivation and treatment with DAAs.<br>During the Article 20 procedure the MAHs of DAAs in Europe analysed data from their clinical trial safety databases, literature and observational cohorts and concluded that the frequency of HBV reactivation during treatment for HCV is low. Currently, the information is scarce to adequately characterize the risk in the population of HCV/HBV co-infected patients in terms of demographic or clinical characteristics.<br>No reports of HBV reactivation were identified in the GLE/PIB clinical dataset because patients with HBV coinfection were excluded from clinical trials. |
| Risk factors and risk groups | Risk factors for HBV co-infection and potentially, reactivation, include background prevalence/incidence of the country of residence, hepatotropic insults (drugs, alcohol), cessation of antiviral agents, and route of transmission (e.g., blood contaminated needles). Disease-related risk factors are those with HBV genotype C, male sex, continued elevated ALT (≥ 5 × ULN), older age (≥ 40 years) at seroconversion, advanced liver disease, HBsAg ≥ 1000 IU/mL, presence of HBsAg in serum and chronic HBsAg carriers, and superimposed infections with other hepatotropic viruses (Bessone 2016, Sarin 2016).<br>Other risk factors for re-activation include: pregnancy, chemotherapy, use of immunomodulators, autoimmune conditions, HIV infection, solid organ transplantation, and stem cell transplantation. HBV genotype B may be associated with a higher |

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| | likelihood of viral clearance, but may also be associated with a higher risk of hepatic decompensation during the hepatitis flare (Lee 2015). There is limited information regarding the frequency of and attendant risk factors for HBV reactivation in DAA-treated HCV co-infected patients. While the risk of reactivation in DAA treated patients is currently unknown, patients with occult HBV infection (HBsAg negative, anti-HBs negative, and anti-HBc positive) are at risk for reactivation and should therefore be followed and managed according to current clinical practice guidelines. |
| Risk minimization measures | Routine risk minimization measures:<br>• SmPC Section 4.4 - Special warnings and precautions for use, includes information on HBV/HCV co-infected patients at risk, and recommendation for monitoring of patients for HBV reactivation.<br>• PIL Section 2 - What you need to know before you take Maviret.<br>• HBV screening should be performed in all patients before initiation of treatment.<br>• HBV/HCV co-infected patients should be monitored and managed per current clinical guidelines.<br>• Restricted medical prescription.<br>o Use of treatment should be initiated and supervised by specialists.<br>• Pack size.<br>Additional risk minimization measures:<br>None. |

| **Important identified risk: Resistance development** | |
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| Evidence for linking the risk to the medicine | Clinical trial dataset = Integrated Resistance Report (R&D16/0492). Treatment-emergent substitutions in NS3 and/or NS5A were detected in 26 of the 32 patients who experienced virologic failure in the GLE/PIB Phase 2/3 registrational studies. |
| Risk factors and risk groups | Certain groups of patients are at increased risk of virologic failure, and if virologic failure occurs, there is a high likelihood that virus harboring resistance to GLE and PIB will be present at the time of virologic failure.<br>Patients experienced to both a PI and an NS5A |

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| | inhibitor may be at risk of resistance development. In MAGELLAN-1 16-week arm, the $SVR_{12}$ rate in PI + NS5A inhibitor-experienced patients with GT1 or GT4 HCV with/without cirrhosis was 81.3% (13/16). Furthermore, in terms of baseline resistance profile, the presence of NS5A substitutions combined with NS3 substitutions at key amino acid positions (155, 156, and 168) was associated with treatment failure (including breakthrough) while the presence of NS5A substitutions alone was not.<br>In addition, patients infected with GT3 who have the A30K polymorphism in NS5A at baseline may be at risk of resistance development; the $SVR_{12}$ rate in those receiving the recommended regimen of GLE/PIB who had A30K in NS5A at baseline was 75% (15/20).<br>As with other anti-viral agents, off-label use, poor compliance and medication errors (e.g., inappropriate schedule of drug administration) may result in suboptimal GLE/PIB exposures that may lead to treatment failure and subsequent to resistance development. |
| Risk minimization measures | Routine risk minimization measures:<br>• SmPC Section 4.2 - Posology and method of administration, includes information on dosage and duration of treatment for patients without prior HCV therapy or patients with failed prior HCV therapies.<br>• PIL Section 3 - How to take Maviret, advise to patients on appropriate dosing and administration to achieve maximal efficacy.<br>• SmPC Section 5.1 - Pharmacodynamic properties, provides information on HCV resistance-associated substitutions.<br>• Maviret is not recommended for patients who failed a prior regimen containing an NS5A inhibitor and/or an NS3/4A PI.<br>• Restricted medical prescription.<br>o Use of treatment should be initiated and supervised by specialists.<br>• Pack size.<br>Additional risk minimization measures:<br>None |
| Additional pharmacovigilance | Additional pharmacovigilance activities: Study with |

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| activities | long-term follow-up (36 months): Study M13-576 is evaluating durability of response (SVR) and development and/or persistence of resistance among subjects who do not achieve SVR in previous trials. See Section II.C of this summary for an overview of the post-authorization development plan. |

| **Important potential risk: Recurrence of hepatocellular carcinoma** | |
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| Evidence for linking the risk to the medicine | Clinical trial dataset. Patients with a history of HCC within 5 years of screening were excluded from clinical trials. There are no cases of recurrence of HCC in the clinical trial database.<br>Procedure EMEA/H/A-20/1438 under Article 20 of Regulation (EC) No 726/2004.<br>During Article 20 procedure, the MAHs of DAAs in the European Union Europe analyzed data from their clinical trial safety databases, literature and observational cohorts and concluded that the frequency of recurrent HCC is low and within the expected range of 1 – 8% in cirrhotic patients, with no notable occurrences in non-cirrhotic patients. Some small studies have reported an increased risk recurrence of HCC after DAA treatment in patients who underwent prior HCC treatment including liver transplantation (Conti 2016, Reig 2016). An established risk factor for HCC is cirrhosis, either compensated or decompensated. |
| Risk factors and risk groups | History of prior HCC treatment is the strongest predictor of HCC recurrence in persons with HCV infection (OR: 12.41, 95% CI: 5.19 – 29.65); younger age, Child-Pugh B class; and severe liver fibrosis (liver stiffness > 21.3 kPa) are also significantly associated with the development of HCC recurrence (Conti 2016). |
| Risk minimization measures | Routine risk minimization measures:<br>• Restricted medical prescription.<br>o Use of treatment should be initiated and supervised by specialists.<br>Additional risk minimization measures:<br>None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities: The MAHs shall conduct and submit the results of a joint prospective, observational PASS, "DAA-PASS: A Post-Authorisation Safety Study of Early Recurrence of Hepatocellular Carcinoma in HCV-Infected |

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| | Patients after Direct-Acting Antiviral Therapy" that will estimate the risk of early HCC recurrence associated with DAA therapy exposure relative to no DAA therapy exposure during routine clinical care of HCV-infected patients with previous successfully treated HCC. See Section II.C of this summary for an overview of the post-authorization development plan. |

| **Important potential risk: Emergence of hepatocellular carcinoma** | |
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| Evidence for linking the risk to the medicine | Clinical trial dataset;<br>In total, there are 6 reports of emergent HCC in the clinical trial dataset (6/2,369 subjects; 0.25%; 95% CI: 0.12% to 0.55%).<br>The demographic characteristics of the 6 patients are as follows: 3 males and 3 females, age range 52 to 66 years (median 57.5 years). Five subjects were Caucasian, and 1 subject was Asian; 5 out of the 6 cases had cirrhosis at baseline. The range of Fibroscan score at baseline was 6.1 to 29.5 kPa (median 16.0 kPa). The time to onset ranged from 40 to 189 days (median 107 days). The time since diagnosis of HCV ranged from 2 to 36 years. In total, 4 patients were treatment experienced, and 2 were treatment naïve.<br>Procedure EMEA/H/A-20/1438 under Article 20 of Regulation (EC) No 726/2004.<br>During the Article 20 procedure the MAHs of DAAs in Europe analyzed data from their clinical trial safety databases, literature and observational cohorts and concluded that the frequency of emergent and recurrent HCC is low and within the expected range of 1 – 8% in cirrhotic patients, with no notable occurrences in noncirrhotic patients. An established risk factor for HCC is cirrhosis, either compensated or decompensated. |
| Risk factors and risk groups | Risk factors for development of HCC include older age, increased fibrosis, presence of cirrhosis, high viral load, and ALT at baseline. Both increasing age and increasing level of fibrosis are associated with a significantly higher risk of HCC. The elderly (65+ years) are at risk even without progression of liver fibrosis (Maruoka 2012). |
| Risk minimization measures | Routine risk minimization measures:<br>• Restricted medical prescription.<br>o Use of treatment should be initiated |

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| | and supervised by specialists.<br>Additional risk minimization measures:<br>None. |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>Proposed retrospective Cohort Study, "A study to evaluate the risk of de novo hepatocellular carcinoma in patients with compensated cirrhosis treated with direct-acting antivirals for chronic hepatitis C."<br>See Section II.C of this summary for an overview of the post-authorization development plan. |

| **Important potential risk: Drug-drug interactions:**<br>**– Concomitant use with other drugs that are strong inhibitors of OATP1B1 or OATP1B3 (e.g., ciclosporin 400 mg, darunavir with or without ritonavir, and lopinavir/ritonavir)**<br>**– Concomitant use with drugs that are moderate inducers of P-gp/CYP3A (e.g., efavirenz, oxcarbazepine, eslicarbazepine, lumacaftor, crizotinib)**<br>**– Concomitant use with drugs that are sensitive substrates of P-gp (e.g., digoxin)**<br>**– Concomitant use with drugs that are sensitive substrates of OATP1B1 or OATP1B3 (e.g., lovastatin, pravastatin, rosuvastatin)** | |
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| Evidence for linking the risk to the medicine | Mechanism-based DDIs may occur with the GLE/PIB regimen when they are coadministered with drugs that interfere with their metabolism and transport, or are coadministered with drugs that are substrates for transporters inhibited by GLE/PIB.<br>The frequencies of clinically significant DDIs that could result in adverse events and subsequent safety concerns could not be determined based on Phase 2 and 3 clinical trial data as concomitant medications with the potential for interaction are either not given with GLE/PIB or are dose-reduced. However, the relative frequencies of the DDIs could be estimated from information regarding the most frequently used concomitant medications during the Phase 2 and 3 clinical trials.<br>Concomitant use of these drugs with the DAA regimen may result in serious outcomes and/or AEs due to increased exposures of these drugs, increased exposure of the DAAs, or decreased exposures of the DAAs leading to reduced efficacy and resistance development. |
| Risk factors and risk groups | Patients at risk would be those who receive the most frequent concomitant medications which may be impacted by the GLE/PIB regimen. This may include patients receiving concomitant medications for |

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| | treatment of conditions such as hypercholesterolemia or HIV coinfection, or patients receiving immunosuppressives in the post-transplant setting. |
| Risk minimization measures | Routine risk minimization measures:<br>• SmPC Section 4.5 - Interaction with other medicinal products and other forms of interaction, provides information on drug – drug interactions with moderate and strong P-gp/CYP3A inducers or substrates; and OATP1B1 or OATP1B3 strong inhibitors and substrates.<br>• SmPC Section 4.4 - Special warnings and precautions for use, and PIL Section 2 - What you need to know before you take Maviret, provide information on medicines patients should not take when on Maviret.<br>• Medicinal products that are contraindicated with Maviret are listed in SmPC Section 4.3.<br>• Specific dose adjustment and/or monitoring recommendations per SmPC Section 4.5.<br>• Medicinal products not recommended for co-administration with Maviret as detailed in SmPC Section 4.5.<br>• List of medicines not to be taken with Maviret is included in PIL Section 2 - What you need to know before you take Maviret.<br>• Restricted medical prescription.<br>o Use of treatment should be initiated and supervised by specialists<br>Additional risk minimization measures:<br>None. |

| **Missing information: Safety in patients with moderate hepatic impairment (Child-Pugh B)** | |
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| Risk minimization measures | Routine risk minimization measures:<br>• SmPC Section 4.2 - Posology and method of administration, hepatic impairment section, provides information that advises that the use of GLE/PIB is not recommended in patients with moderate hepatic impairment (Child Pugh B).<br>• SmPC Section 4.4 - Special warnings and precautions for use, advises that the use of Maviret is not recommended in patients with |

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| | moderate hepatic impairment (Child-Pugh B).<br>• Restricted medical prescription.<br>o Use of treatment should be initiated and supervised by specialists.<br>Additional risk minimization measures:<br>None. |

| **Missing information: Safety in pregnant and breastfeeding patients** | |
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| Risk minimization measures | Routine risk minimization measures:<br>• SmPC Section 4.6 - Fertility, pregnancy and lactation and PIL Section 2 - What you need to know before you take Maviret, advise that the use of Maviret is not recommended in pregnancy.<br>• Per SmPC Section 4.6, Maviret is not recommended for use in pregnancy and the decision to continue or discontinue Maviret in the lactating mother should consider the benefit of breastfeeding for the child and the benefit of therapy for the woman.<br>• Per PIL Section 2, the use of Maviret during pregnancy is not recommended, and patients should consult with their doctor before taking Maviret if they are breast-feeding.<br>• Restricted medical prescription.<br>o Use of treatment should be initiated and supervised by specialists.<br>Additional risk minimization measures:<br>None. |

| **Missing information: Safety in patients with previous hepatocellular carcinoma** | |
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| Risk minimization measures | Routine risk minimization measures:<br>• Restricted medical prescription.<br>o Use of treatment should be initiated and supervised by specialists.<br>Additional risk minimization measures:<br>None. |
| Additional pharmacovigilance activities | Additional Pharmacovigilance Activity:<br>The MAHs shall conduct and submit the results of a joint prospective, observational PASS, "DAA-PASS: A Post-Authorisation Safety Study of Early Recurrence of Hepatocellular Carcinoma in HCV-Infected Patients after Direct-Acting Antiviral Therapy" that will estimate the risk of early HCC |

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| | recurrence associated with DAA therapy exposure relative to no DAA therapy exposure during routine clinical care of HCV-infected patients with previous successfully treated HCC. |

## II.C Post-Authorization Development Plan
## II.C.1 Studies Which are Conditions of the Marketing Authorization

The following studies are conditions of the marketing authorization:
**Prospective Safety Study in HCV Infected Patients to Assess Risk of HCC Recurrence Associated with DAA therapy**
DAA-PASS: A Post-Authorisation Safety Study of Early Recurrence of Hepatocellular Carcinoma in HCV-Infected Patients after Direct-Acting Antiviral Therapy.
Purpose of the study:
DAA-PASS is designed to investigate the question: Does DAA therapy for chronic HCV infection increase the risk of early HCC recurrence among a well-characterized group of patients who have received successful HCC treatment interventions, relative to no DAA therapy?
Safety concerns addressed include: Recurrence of hepatocellular carcinoma and the Missing Information for safety in patients with previous hepatocellular carcinoma.
The primary objective is to estimate the risk of early HCC recurrence (within 24 months after the first HCC-free image) associated with DAA therapy exposure relative to no DAA therapy exposure during routine clinical care of HCV-infected patients with successfully treated HCC, in the prospective DAA-PASS cohort.
The secondary objectives are to:

1. Compare the adjusted incidence of early HCC recurrence (within 24 months after the first HCC-free image) associated with DAA therapy exposure relative to no DAA therapy exposure during routine clinical care of HCV-infected patients with successfully treated HCC, in the prospective DAA-PASS cohort;
2. Estimate the risk of early HCC recurrence (within 24 months after the first HCC-free image) associated with DAA therapy exposure relative to no DAA therapy exposure including a historical cohort of HCV patients not exposed to DAA with initial HCC diagnosis and subsequent successful treatment of HCC;
3. Compare the adjusted incidence of early HCC recurrence (within 24 months after the first HCC-free image) associated with DAA therapy exposure relative to no DAA therapy exposure including a historical cohort of HCV patients not exposed to DAA with initial HCC diagnosis and subsequent successful treatment of HCC.

## II.C.2 Other Studies in Post-Authorization Development Plan
**Long-term Follow-Up Phase 2/3 Study M13-576**
A Follow-up Study to Assess Resistance and Durability of Response to AbbVie Direct Acting Antiviral Agent (DAA) Therapy (ABT-493 and/or ABT-530) in Subjects Who

Participated in Phase 2 or 3 Clinical Studies for the Treatment of Chronic Hepatitis C Virus (HCV) Infection.
Purpose of the study:
To address durability of SVR and the risk of resistance development and persistence of any resistance developed upon virologic failure.
The primary objectives are to assess the durability of response for subjects who achieved $SVR_{12}$ with a regimen including ABT-493 and/or ABT-530 and to assess the emergence and persistence of specific HCV amino acid substitutions associated with drug resistance in subjects who experienced virologic failure.
The secondary objectives are to summarize medical events related to progression of liver disease including but not limited to: events of hepatic decompensation, change in Child-Pugh classification, liver transplantation, hepatocellular carcinoma and/or, death; to summarize results of the following laboratory tests and scores: FibroTest, APRI, IP-10, alpha fetoprotein (if collected under a previous protocol version), FibroScan, and liver biopsy.

**Proposed Retrospective Cohort Study in HCV Infected Patients to Assess the Risk of De Novo HCC Associated with DAA Therapy**

A study to evaluate the risk of de novo hepatocellular carcinoma in patients with compensated cirrhosis treated with direct-acting antivirals for chronic hepatitis C.
Purpose of the study:
To evaluate the potential risk of de novo HCC after DAA treatment in HCV-infected patients with compensated cirrhosis without a history of HCC relative to patients treated with IFNcontaining regimens or untreated chronic HCV patients using the US Veterans Health Administration cohort.

The primary objectives are:

1. Estimate the risk of de novo HCC associated with DAA therapy exposure in cirrhotic HCV-infected patients compared to no anti-HCV therapy exposure in cirrhotic HCVinfected patients.
2. Estimate the risk of de novo HCC in cirrhotic HCV patients treated with DAA therapy compared to those treated with IFN-based therapy.

The secondary objective is:
Compare, in a subset of patients with available data recorded in the Veterans Affairs Registries Clinical Case (VA CCR), tumor characteristics (i.e., tumor size, tumor number, tumor stage, tumor type) of the de novo HCC cases observed following initiation of DAA therapy to those of de novo HCC cases observed (a) following initiation of IFN containing regimens and (b) in untreated patients.