

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209394Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	209394
PDUFA Goal Date	August 14, 2017
OSE RCM #	2017-13/15
Reviewer Name(s)	Elizabeth Everhart, MSN
Team Leader	Doris Auth, Pharm D
Division Director	Cynthia LaCivita, Pharm D
Review Completion Date	May 11, 2017
Subject	Evaluation of Need for a REMS
Established Name	Glecaprevir and Pibrentasvir
Trade Name	Mavyret (proposed)
Name of Applicant	Abbvie, Inc.
Therapeutic Class	Glecaprevir is a nonstructural (NS) protein 3/NS protein 4A (NS3/NS4A) protease inhibitor; pibrentasvir is a NS protein 5a (NS5A) inhibitor
Formulation(s)	Fixed Dose Combination (FDC) tablet; 100 mg glecaprevir/40 mg pibrentasvir
Dosing Regimen	3 tablets once daily

Table of Contents

EXECUTIVE SUMMARY3

1 Introduction.....3

2 Background4

 2.1 Product Information.....4

 2.2 Regulatory History4

3 Therapeutic Context and Treatment Options4

 3.1 Description of the Medical Condition.....4

 3.2 Description of Current Treatment Options5

4 Benefit Assessment.....5

5 Risk Assessment & Safe-Use Conditions.....6

 5.1 [Serious Adverse Reaction]7

6 Expected Postmarket Use7

7 Risk Management Activities Proposed by the Applicant.....7

8 Discussion of Need for a REMS.....7

9 Conclusion & Recommendations8

10 Materials Reviewed8

11 References8

12 Appendices..... 10

 12.1 Appendix 1..... 10

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Mavyret (glecaprevir and pibrentasvir) is necessary to ensure the benefits outweigh its risks. Abbvie submitted a New Drug Application (NDA) 209394 for Mavyret with the proposed indication of the treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A^a). The risks associated with Mavyret include the risk of HBV reactivation in patients co-infected with HBV and HCV, as well as drug–drug interactions (DDIs) associated with Mavyret. The applicant did not submit a REMS with this application and did not propose risk management activities for Mavyret beyond routine and enhanced pharmacovigilance (PV) activities and labeling; a voluntary pharmacovigilance plan describing planned pharmacovigilance activities was submitted. [REDACTED] (b) (4)

[REDACTED] The applicant also proposes additional PV activities related to the safety and efficacy of Mavyret in pediatric patients as agreed in their Pediatric Study Plan.

DRISK and the Division of Antiviral Products agree that a REMS is not needed to ensure the benefits of Mavyret outweigh its risks. Chronic HCV is a serious condition that can lead to the development of cirrhosis and hepatocellular carcinoma. Eradicating chronic hepatitis C with direct acting anti-viral medications (DAAs) such as Mavyret decreases morbidity and mortality from advanced liver disease.¹ Mavyret has been shown to be efficacious in achieving high rates of SVR 12 and has a safety profile similar to other DAAs currently approved with risks that can be handled via professional labeling and routine and enhanced pharmacovigilance.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Mavyret (glecaprevir and pibrentasvir) is necessary to ensure the benefits outweigh its risks. Abbvie submitted a New Drug Application (NDA) 209394 for Mavyret with the proposed indication of the treatment of the treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5 or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A). This application is under review in the Division of Antiviral Products (DAVP). The applicant did not submit a REMS with this application but did submit a pharmacovigilance plan.

^a Child-Turcotte-Pugh Classification for Severity of Cirrhosis

2 Background

2.1 PRODUCT INFORMATION

Mavyret (glecaprevir/pibrentasavir), a new molecular entity (NME)^b, is a fixed dose combination (FDC) direct active antiviral (DAA) proposed for the treatment of HCV. Mavyret is proposed as 100 mg glecaprevir/40 mg pibrentasavir, three tablets by mouth once daily for 8 to 16 weeks^c, depending upon prior treatment status and HCV genotype. Glecaprevir is an inhibitor of the HCV nonstructural 3/4 A (NS3/4A) protein protease and pibrentasavir is an inhibitor of the HCV nonstructural 5 A (NS5A) protein. Both of these proteins are involved in HCV viral replication.

If approved, Mavyret will have a Box Warning that is part of DAA class labeling for the risk of reactivation of hepatitis B in patients treated with DAAs who also have a history of infection with hepatitis B; additionally, it will have a contraindication for use in patients with severe hepatic impairment (Child-Pugh C). Because of the increased concentration of one or both components of Mavyret when co-administered with rifampin or atazanavir, rifampin co-administration with Mavyret will be contraindicated as will atazanavir. Mavyret is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for [Application/Number] relevant to this review:

- 04/21/2016: Breakthrough designation granted under IND 127416 for GT1 DAA-experienced patients
- 12/14/2016: NDA 209394 submission for the treatment of Hepatitis C received
- 03/15/2017: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for Mavyret

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Hepatitis C (HCV) is a blood-borne virus that affects the liver. The virus may be silent for many years after infection, as 70-85% of people with HCV develop chronic infection. Of the estimated 2.7 – 3.9 million people in the United States with chronic HCV, the majority are unaware of the infection. When left untreated, HCV can lead to chronic liver disease, including cirrhosis and decompensated liver disease, hepatocellular carcinoma, and death^d; according to the Centers for Disease Control and

^b Section 505-1 (a) of the FD&C Act: FDAAA factor (F): *Whether the drug is a new molecular entity.*

^c Section 505-1 (a) of the FD&C Act: FDAAA factor (D): *The expected or actual duration of treatment with the drug.*

^d Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

Prevention, for every 100 persons infected with HCV, 75-85 will develop chronic infection^e, 60-70 will develop chronic liver disease, 5-20 will then go on to develop cirrhosis over 20-30 years, and 1-5 will die from consequences of HCV (i.e., hepatocellular carcinoma and/or complications of cirrhosis). HCV is also the leading indication for liver transplantation in the United States.²

Hepatitis C has currently six known genotypes; they are numbered 1-6 and have further delineation into subtypes (genotype 1a and genotype 1b, for example).³ In the US, genotype 1 is the most common genotype (70%), followed by genotype 2 (15-20%), GT 3 (10-12%), and GT 4 (1%); genotypes 5 and 6 are quite uncommon (roughly \leq 1%) in the US.⁴

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Treatment for chronic HCV has evolved dramatically over the past 5 years from pegylated interferon + ribavirin-based therapy with high toxicity and low efficacy to all-oral direct acting anti-viral (DAA) treatments. There are currently nine brand name DAAs approved, many are in combination; Table 1 (see Appendix 1) summarizes the currently approved DAAs. As the treatment of HCV has moved to all-oral DAA treatment with a better understanding of the virus and the non-structural proteins the DAAs target (i.e., NS3/4A protease inhibitors, NS5B nucleoside polymerase inhibitors, NS5B non-nucleoside polymerase inhibitors, and NS5A inhibitors), HCV eradication is achieved in the majority of patients receiving treatment. There remains an unmet medical need for patients who have failed treatment with a DAA.

4 Benefit Assessment

The goal of HCV treatment is sustained virologic response at 12 weeks post-treatment (SVR 12), defined as undetectable HCV RNA 12 weeks post-treatment; SVR 12 is considered a virologic cure.⁵ Eradicating the virus reduces progression to end-stage liver disease and the complications of cirrhosis, including the development of hepatocellular carcinoma; all-cause mortality is also decreased.⁶ In the eight pivotal clinical trials submitted by the applicant and described in the sections below, high SVR 12 rates were seen across all treatment arms of the trials.^f

Overall Results in Treatment-Naïve and peginterferon, ribavirin and/or sofosbuvir Treatment-Experienced Subjects

In subjects who are treatment-naïve or treatment-experienced to combinations of peginterferon, ribavirin and/or sofosbuvir (PRS) who received the recommended duration, 98% (1150/1178) achieved SVR 12 overall (among which 98% (274/281) subjects with compensated cirrhosis achieved SVR 12), while <1% (3/1178) experienced on-treatment virologic failure and <1% (11/1161) experienced post-treatment relapse.

^e Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

^f Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

Subjects with CKD Stage 4 and 5 without Cirrhosis or with Compensated Cirrhosis

EXPEDITION-4 was an open-label, single-arm, multicenter phase 3 trial to evaluate safety and efficacy in subjects with severe renal impairment including those on dialysis (CKD Stages 4 and 5) with or without cirrhosis. There were 104 subjects enrolled, 53%, 15%, 11%, 19%, 1% and 1% with genotypes 1, 2, 3, 4, 5 and 6; respectively. Overall, 19% of subjects had compensated cirrhosis and 81% of subjects were non-cirrhotic; 58% and 42% of subjects were treatment-naïve and PRS treatment-experienced, respectively. The SVR₁₂ rate was 98%. The presence of renal impairment did not affect efficacy; no dose-adjustments were required.

Subjects who are NS5A Inhibitor or NS3/4A-Protease Inhibitor-Experienced, with or without Compensated Cirrhosis

MAGELLAN-1 was a randomized, multipart, open-label trial in 141 genotype 1- or 4-infected subjects who failed a previous regimen containing NS5A and/or NS3/4A protease inhibitors (PI). Part 1 (n=50) was a randomized trial using 12 weeks of glecaprevir 200 mg and pibrentasvir 80 mg, glecaprevir 300 mg and pibrentasvir 120 mg, with and without ribavirin (glecaprevir 300 mg plus pibrentasvir 120 mg without ribavirin only is included in the analysis). Part 2 (n=91) randomized genotype 1 or 4-infected subjects with or without compensated cirrhosis to 12- or 16-weeks of treatment with Mavyret. The SVR 12 in subjects who were experienced to NS5A inhibitors only was 94% (16/17); the SVR 12 in patients who were experienced to NS3/4A protease inhibitors only was 92% (23/25).⁷

5 Risk Assessment & Safe-Use Conditions

The safety assessment for Mavyret in subjects without cirrhosis or with compensated cirrhosis (Child-Pugh A) was derived from Phase 2 and 3 trials which evaluated 2369 subjects. In clinical trials with Mavyret, adverse reactions observed in greater than or equal to 5% of subjects receiving 8, 12, or 16 weeks of treatment with Mavyret were headache (13%), fatigue (11%), and nausea (8%). In subjects receiving Mavyret who experienced adverse reactions, 80% had an adverse reaction of mild severity (Grade 1). In the placebo-controlled trial, these adverse reactions occurred with similar frequency in subjects treated with placebo compared to those treated with Mavyret.⁸

A concern for hepatotoxicity seen in some patients, mainly with advanced liver disease, in the approved DAAs, Technivie and Viekira Pak/Viekira Pak – XR, prompted FDA to require updates to those drugs' labels.⁹ As part of the clinical development of Mavyret, an Expert Hepatic Panel (EHP) of hepatologists was convened to review all cases of potential hepatotoxicity identified in the clinical trial safety populations. There were 33 potential cases identified, with 1 case being identified as possibly drug-induced liver injury (DILI). This case occurred 20 days after the end of treatment and, while listed as possibly being DILI, the patient was found to have gallstones and the so case appeared to be more related to biliary obstruction, rather than DILI.¹⁰

In addition to the contraindication for use of rifampin with Mavyret described earlier in this review, there are several drug-drug interactions (DDI) with Mavyret. These DDIs will be described in Section 7 (Drug Interactions) of the label.

The main serious risk with Mavyret is the risk of hepatitis B reactivation, which is discussed in the section below.

5.1 RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS CO-INFECTED WITH HCV AND HBV

Hepatitis B virus (HBV) reactivation has occurred in patients taking DAAs who are co-infected with HCV and HBV and who are not receiving HBV antiviral therapy. HBV reactivation is characterized by rapidly increasing HBV DNA (marker of viral activity) which can be accompanied by increases in liver aminotransferase levels (e.g., AST and ALT elevations) and, in severe cases, increases in bilirubin levels, liver failure, and death.

To mitigate this risk, all DAA labels were updated with a Box Warning for risk of HBV reactivation in patients co-infected with HBV and HCV.¹¹ If approved, Mavyret will include the same Boxed Warning. The label includes a recommendation for testing all patients for evidence of current or prior HBV infection. If a patient has evidence of serologically of HBV infection, the label recommends monitoring the patient both clinically and via labs for any signs of HBV reactivation during treatment with Mavyret and during post-treatment follow-up.

6 Expected Postmarket Use

If approved, Mavyret will be used in the outpatient clinic setting by healthcare providers, mainly hepatologists and gastroenterologists, who typically see and treat patients with HCV. Patients will be prescribed the medication to take at home.

7 Risk Management Activities Proposed by the Applicant

The applicant did not propose any risk management activities for Mavyret beyond routine and enhanced pharmacovigilance activities and labeling; a voluntary pharmacovigilance (PV) plan describing planned PV activities was submitted. (b) (4)

The applicant also proposes additional PV activities related to the safety and efficacy of Mavyret in pediatric patients as agreed in their Pediatric Study Plan.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of Mavyret on the basis of the efficacy and safety information currently available. Chronic HCV is a serious condition that can lead to the development of cirrhosis and hepatocellular carcinoma. Eradicating chronic hepatitis C with DAAs such as Mavyret decreases morbidity and mortality from advanced liver disease. Mavyret has been shown to be efficacious in achieving high rates of SVR 12 and has a safety profile similar to other DAAs currently approved with risks that can be handled via professional labeling and routine pharmacovigilance.

9 Conclusion & Recommendations

Based on the available data, DAVP and DRISK have determined that a REMS is not necessary to ensure the benefits of Mavyret outweigh its risks. The safety concerns associated with Mavyret will be communicated via labeling and, in general, healthcare providers who treat chronic hepatitis C should be familiar with the risks of HBV reactivation in patients co-infected with HBV and HCV, as well as the DDIs associated with Mavyret. Labeling negotiations with the applicant were ongoing as of the time of this review. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Materials Reviewed

The following is a list of materials informing this review:

1. Abbvie. Draft Prescribing Information for Mavyret, December, 2016.
2. Abbvie. Clinical Overview for Mavyret, December, 2016.
3. Abbvie. Summary of Clinical Safety for Mavyret, December, 2016.
4. Abbvie. Pharmacovigilance Plan for Mavyret, December, 2016.
5. Stabinski, Larissa. Division of Antiviral Products. Mid-cycle Clinical Review slides for NDA 209394, March 14, 2017.
6. Abbvie. Expert Hepatic Panel (EHP) Assessments; EHP Worksheet for 10 Patients Discussed 12 January 2017 and EHP Worksheet for 23 Patients Discussed 10 February 2017.

11 References

¹ van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, Duarte-Rojo A, Heathcote EJ, Manns MP, Kuske L, Zeuzem S, Hofmann WP, de Knegt RJ, Hansen BE, Janssen HL. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA* 2012;308(24):2584-93; accessed 4/5/17 <https://www.ncbi.nlm.nih.gov/pubmed/23268517>

² Centers for Disease Control and Prevention. Viral Hepatitis – Hepatitis C Information: <https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#section1>, accessed 4/4/17

³ Petruzzello A, Marigliano S, Loquercio G, Cacciapuoti C. Hepatitis C virus (HCV) genotypes distribution: an epidemiological up-date in Europe. *Infectious Agents and Cancer*. 2016;11:53. doi:10.1186/s13027-016-0099-0

⁴ Spach, D. HCV Epidemiology in the United States. Module 1, Lesson 1, from University of Washington; Hepatitis C Online: <http://www.hepatitis-c.uw.edu/go/screening-diagnosis/epidemiology-us/core-concept/all> , accessed 4/18/17

⁵Scott, JD; Kim, HN. Goals for Treatment and Predicting Response. Module 4, Lesson 1, from University of Washington; Hepatitis C Online: <http://www.hepatitisc.uw.edu/go/evaluation-treatment/treatment-goals-predicting-response/core-concept/all> , accessed 4/20/17

⁶van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, Duarte-Rojo A, Heathcote EJ, Manns MP, Kuske L, Zeuzem S, Hofmann WP, de Knegt RJ, Hansen BE, Janssen HL. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA 2012;308(24):2584-93; accessed 4/5/17 <https://www.ncbi.nlm.nih.gov/pubmed/23268517>

⁷Abbvie. Draft Product Label for Mavyret, April, 2017.

⁸Abbvie. Draft Product Label for Mavyret, April, 2017.

⁹FDA. Drug Safety Communication: FDA warns of serious liver injury risk with hepatitis C treatments Viekira Pak and Technivie. October 22, 2015

¹⁰Gilead. Overview of Clinical Safety, page 48. December, 2016

¹¹FDA. Drug Safety Communication: FDA warns about the risk of hepatitis B reactivating in some patients treated with direct-acting antivirals for hepatitis C. October 4, 2016

12 Appendices

12.1 Appendix 1

Table 1 – List of approved DAAs for Hepatitis C

Brand name	Active ingredient(s)	Year Approved
Daklinza	Daclatasvir	2015
Epclusa	sofosbuvir and velpatasvir	2016
Harvoni	ledipasvir and sofosbuvir	2014
Olysio	Simeprevir	2013
Sovaldi	Sofosbuvir	2013
Technivie	ombitasvir and paritaprevir and ritonavir	2015
Viekira Pak	dasabuvir and ombitasvir and paritaprevir and ritonavir	2014
Viekira Pak XR	dasabuvir and ombitasvir and paritaprevir and ritonavir	2016
Zepatier	elbasvir and grazoprevir	2016

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/s/

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