CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217785Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
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	217785
PDUFA Goal Date	March 14, 2024
Nexus TTT #	2023-5597
Reviewer Name(s)	Leah Hart, PharmD
Team Leader	Carolyn Tieu, PharmD, MPH
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	March 08, 2024
Subject	Evaluation of Need for a REMS
Established Name	Resmetirom
Trade Name	Rezdiffra
Name of Applicant	Madrigal Pharmaceuticals, Inc.
Therapeutic Class	Thyroid Hormone Receptor Beta selective agonist
Formulation	Tablets
Dosing Regimen	< 100 kg, 80 mg orally once daily
	≥ 100 kg, 100 mg taken orally once daily

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Rezdiffra (resmetirom) is necessary to ensure the benefits outweigh its risks. Madridgal Pharmaceuticals, Inc. submitted a New Drug Application (NDA) 217785 for Rezdiffra with the proposed indication of, in combination as an adjunct to diet and exercise for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis with moderate (stage 2[F2]) to advanced liver fibrosis stage 3[F3]). If approved, the indication will be in conjunction with diet and exercise for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis). The risks associated with Rezdiffra include drug-induced hepatoxicity, drug interactions with certain statins, and gallbladder-related adverse reactions. The applicant did not submit a proposed REMS or risk management plan with this application.

DRM has determined that a REMS is not needed to ensure the benefits of Rezdiffra outweigh its risks. The statistical reviewer has determined that Rezdiffra showed benefit for the treatment of noncirrhotic nonalcoholic steatohepatitis with moderate to advanced liver fibrosis and the clinical reviewer determined that the benefit risk profile was favorable. The likely prescribers such as gastroenterologists and hepatologists, are likely familiar with each of these risks and the management of them. All three risks will be included in the Warnings and Precautions section of the Prescribing Information. (b) (4)

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Rezdiffra (resmetirom) is necessary to ensure the benefits outweigh its risks. Madridgal Pharmaceuticals, Inc. submitted a New Drug Application (NDA) 217785 for Rezdiffra with the proposed indication of, in conjunction with diet and exercise for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis). This application is under review in the Division of Hepatology and Nutrition. The applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Rezdiffra (resmetirom), a new molecular entity[a], is a liver-directed, orally active, partial agonist for the thyroid hormone receptor beta (THR-Beta), proposed under the accelerated approval pathway (Subpart H) based on a surrogate endpoint reasonably likely to predict clinical benefit for the treatment of adults

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

with nonalcoholic steatohepatitis (NASH) with liver fibrosis. Rezdiffra was granted breakthrough therapy, fast track designation and priority review. Rezdiffra is proposed as a 60 mg, 80 mg, or 100 mg tablet by oral administration. The proposed dose of Rezdiffra is 100 mg once daily with or without food if patient is ≥ 100 kg. Below 100 kg the recommended dosage is 80 mg orally. Rezdiffra is to be taken chronically for the treatment of NASH.[b] Rezdiffra is not currently approved in any jurisdiction.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 217785 relevant to this review:

- 10/18/2019: Fast track designation granted.
- 04/11/2023: Breakthrough therapy designation granted.
- 05/22/2023 Rolling review status granted.
- 06/09/2023: NDA 217785 Part 1 submission for the treatment of NASH received.
- 06/28/2023: NDA 217785 Part 2 submission received.
- 07/14/2023: NDA 217785 Part 3 completed submission received.
- 09/12/2023: Priority designation granted.
- 11/02/2023: 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 Rezdiffra.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Nonalcoholic steatohepatitis (NASH) is a category of nonalcoholic fatty liver disease (NAFLD) with the presence of ≥5% hepatic steatosis and inflammation with hepatocyte injury, with or without any fibrosis.[1] NASH can progress to cirrhosis, liver failure, and rarely liver cancer.[c] The amount of liver fibrosis identified histologically in patients with NAFLD has been strongly linked to the development of liver-related outcomes and death.[2] NAFLD is strongly associated with obesity, insulin resistance or type 2 diabetes mellitus, and dyslipidemia and may be considered the hepatic manifestation of the metabolic syndrome.[3] A recent meta-analysis found that the overall prevalence of combined dyslipidemia in patients with NASH was estimated to be 72%.[4] NASH is projected to be the leading indication for liver transplant within a decade.[5] The Meta-analysis of Histological Data in Viral Hepatitis (METAVIR) score is

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

[c] 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.*

a semiquantitative classification system used to stage fibrosis with a fibrosis score of F0 (no fibrosis), F1 (portal fibrosis without septa), F2 (few septa), F3 (numerous septa without cirrhosis), F4 (cirrhosis).

The global prevalence of NASH is estimated at 1.5-6.45% in the general population. Using a Markov model with 1-year cycles and 20-year horizon to estimate the burden of NASH with Type 2 DM in the United States, the model estimates that 6.4 people in the United States are living with NASH and Type 2 DM.[6,d] The 20-year cost of NAFLD was $55.8 billion and over the next 20 years, NASH with Type 2 DM will account for 65,000 transplants, 1.37 million cardiovascular related deaths, and 812,000 liver-related deaths.

3.2. Description of Current Treatment Options

There are no FDA-approved pharmacologic treatment for NASH. One general measure that applies to all patients with NAFLD is to refrain from alcohol as heavy alcohol use is associated with disease progression.[7] Weight loss is a recommended primary therapy for those patients who are overweight or have obesity. In a 2015 study, all patients who lost ≥10% of their weight had reductions NAFLD activity score (NAS), 90% had resolution of NASH, and 45% had regression of fibrosis.[8]

Oxidative stress is one of the key factors in the onset and development of NASH, vitamin E has been thought to act as an antioxidant reducing oxidative stress.[9,10] A meta-analysis including NAFLD and NASH in child and adult patients shows that vitamin E therapy significantly improves serum AST, ALT, and ALP levels, without significant change in BMI.[11]

Currently the Glucagon-like peptide-1 receptor agonists (GLP-1 RA) are being studied in NASH due to the biological effects of GLP-1RAs on lipids, glucose metabolism, weight loss, and cardiovascular outcomes.[12] Liraglutide has been the most widely studied GLP-1RA in NAFLD in patients with type 2 diabetes.[13,14]

With no FDA-approved treatment, there is an unmet medical need in this patient population.

4. Benefit Assessment

The pivotal trial (MGL-3196-11) supporting this application consisted of an ongoing multi-center, randomized, double-blind, placebo-controlled, study which evaluated a total of 1,050 participants enrolled and randomized on or before July 31, 2021, across 172 sites and 14 countries. The efficacy analysis focuses on the analysis population defined as all F2 and F3 participants as determined by eligibility read who were randomized on or before July 31, 2021. A total of 888 participants were included (resmetirom 80 mg group=298, resmetirom 100 mg group = 296, placebo group=294) in the analysis. Patients were randomized 1:1:1 to receive resmetirom 80 mg, resmetirom 100 mg, or placebo taken orally once daily. This trial will continue through 54 months to evaluate clinical outcomes in the pivotal trial population.

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

Trial 11 had dual primary endpoints at Week 52. The first measured the proportion of patients who achieved a NASH resolution associated with a 2-point reduction in NAS with no worsening of fibrosis by liver biopsy as assessed independently by 2 central reader pathologists at Week 52 on the primary glass slide read. At Week 52, the percentage of NASH resolution responders in the 100 mg resmetirom treatment group was 29.9% compared with 9.7% for placebo patients, with a LS mean between-group difference (95% CI) of 20.7% (15.3%, 26.2%) (p<0.0001). The 80 mg resmetirom treatment group had 25.9% of patient showing NASH resolution and an LS mean between-group difference (95% CI) with placebo of 16.4% (11.0, 21.8%) (p<0.0001).

The second primary endpoint measured the proportion of patients with at least a 1-point improvement in fibrosis stage with no worsening of NASH by liver biopsy as assessed by 2 pathologists at Week 52. At Week 52, the percentage of fibrosis responders in the 100 mg resmetirom treatment group was 25.9% compared with 14.2% for placebo patients, with an LS mean between-group difference (95% CI) of 11.8% (6.4%, 17.2%) (p<0.0001). The 80 mg resmetirom treatment group had 24.2% of patients showing fibrosis improvement and an LS mean between-group difference (95% CI) with placebo of 10.2% (4.8%, 15.7%) (p=0.0002).

The clinical reviewer has concluded that both dosages of resmetirom (80 mg and 100 mg daily) demonstrated superiority compared to placebo on both histologic surrogate endpoints, 1) resolution of NASH and no worsening of liver fibrosis and 2) improvement of fibrosis and no worsening of NASH evaluated at the 52-week interim analysis.[e,15]

The primary composite clinical benefit endpoint will be evaluated upon trial completion and is measured as the time to first occurrence of any of the following adjudicated events:

- Death (all cause)
- Liver transplant
- Significant hepatic events including hepatic decompensation events:
    - Ascites
    - Encephalopathy
    - Gastroesophageal variceal hemorrhage
- Histological progression to cirrhosis
- Confirmed increase of model of end-stage liver disease (MELD) score from <12 to ≥15

5. Risk Assessment & Safe-Use Conditions

The safety database includes data from two phase three randomized placebo-controlled trials, Trial 11 and 14.[16] Trial 14 was a phase 3, multicenter, randomized, double-blind, placebo-controlled study with

[e] 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.*

an open-label arm in patients with NAFLD (presumptive NASH) and a parallel-enrolling open label arm with patients with compensated NASH cirrhosis. There are two safety populations: those in Trial 11 with noncirrhotic NASH with stages F2 or F3 liver fibrosis and the pooled population from all patients in Trial 11 and including Trial 14. The most frequent adverse event was diarrhea in both the 100 mg arm and the 80 mg arm across both study populations.

In trial 11, a total of 888 subjects with F2 and F3 fibrosis were randomized 1:1:1 to receive placebo (n=294), 80 mg (n=298), or 100 mg (296). In the pooled analysis (Trials 11 and 14), a total of 2019 patients were enrolled in placebo (n=667), 80 mg (679), and 100 mg (673).

There were 6 deaths in the clinical development program. In Trial 11, there were two in the 100 mg arm for the F2 and F3 population, no deaths in the 80 mg group and one in the placebo arm. In the pooled analysis population, there were three Serious Adverse Events (SAEs) with fatal outcomes, two in the 80 mg arm and one in the placebo. One subject had a significant history of cardiac disease and on day 180 was hospitalized with acute left ventricular failure, acute myocardial infarction, and prosthetic cardiac valve thrombosis. The subject did not discontinue the study drug and the patient died on study day 213 and no autopsy was performed. The clinical reviewer agrees that this subject's death was not related to the study drug.[14] The subject on placebo died on day 263 with no cause of death provided and no autopsy. The clinical reviewer agrees that this subject's death was not related to the study drug.[14]One patient in the 80 mg group died due to a road traffic accident and one subject in the resmetirom 80 mg group due to COVID 19 infection and cardiac arrest. One subject receiving resmetirom 100 mg died due to hepatic cholestasis and Hodgkin's disease. The clinical reviewer agrees that these subjects' deaths were not related to the study drug.[14]

One subject had a significant cardiac past medical history and on day 143, a CT of her abdomen, showed a partly calcified stone on the gallbladder neck and a follow up HIDA scan was abnormal. She underwent a cholecystectomy on day 207 with no complications. On day 348 she experienced an episode of generalized pruritus, and the study drug was interrupted. On study day 365, the subject overexerted herself and had a myocardial infarction (MI) and pronounced dead. The clinical reviewer does not agree with the Applicant that the event of cholelithiasis was not related to study drug; however, the MI is unlikely related to the study drug.[14]

5.1. Drug-Induced Hepatotoxicity

In addition to the pooled population, Drug Induced Liver Injury (DILI) assessment was also assessed in the open label arms of Trial 14 and even though trial 18 did not have a comparator arm, relevant cases concerning for DILI were also assessed. In Trial 11, eleven percent of subjects in the Rezdiffra 80 mg arm and 13% in the 100 mg arm experienced alanine aminotransferase (ALT) elevations greater than 3 times the upper limit of normal compared with 10% of placebo. Two percent in both the Rezdiffra 80 mg and 100 mg experienced ALT elevations greater than 5 times the upper limit of normal. For aspartate aminotransferase (AST), 9% of subjects in the Rezdiffra 80 mg arm and 12% of patients in the 100 mg arm had AST greater than 3 times the upper limit of normal compared to 10% of placebo subjects. In Rezdiffra treated subjects, 1% in the 80 mg arm and 4% in the 100 mg arm experienced elevations of

AST greater than 5 times the upper limit of normal compared to 2% of placebo patients. The elevations in AST and ALT increased in the first 4 weeks after initiating treatment with resmetirom and returned to baseline around 8 weeks after treatment initiation.

There was a total of 10 cases that qualified as potential Hy's Law cases in both drug arms across the two trials compared to only one case in the placebo arm. Of those 10 cases, only one case was assessed as probable DILI. This subject had serum markers suggestive of possible autoimmune liver disease (AILD) with normal liver tests at baseline and started on resmetirom 80 mg. At approximately 57 days after starting resmetirom, the subject developed elevated aminotransferases and the resmetirom was suspended on day 64. The patient was tested for autoimmune markers and both the Antimitochondrial Antibody test (AMA), and Antinuclear Antibody test (ANA) were positive; however, there was no baseline AMA and ANA to compare to. By day 197, the subject's AST and ALT were back to baseline and the patient was rechallenged on day 253. On day 281 (day 28 for rechallenge), the patient again had an elevation in ALT, AST, and total bilirubin (TB) levels that were consistent with drug-induced autoimmune-like hepatitis (DI-ALH) phenotype. An abdominal CT was done on Day 282 that showed gallstones with gallbladder wall thickening, pericholecystic fluid without duct dilation with a high suspicion of acute cholecystitis. After treatment discontinuation, at Day 341; 87 days after rechallenging, the patient's liver tests returned to baseline. The team assessed this case as probable DILI due to resmetirom and meetings Hy's Law criteria and this will be included in the PI in 5.1 of Warnings and Precautions.[16]

There was one case of possible, if not probable DILI due to resmetirom in the open-label arm of Trial 14. The subject had NASH related cirrhosis and developed elevated aminotransferases approximately 140 days after starting 80 mg of resmetirom. She was negative at baseline for any autoimmune markers except for ANA which was not done at baseline. On day 83, the subject's dose was decreased to 60 mg without reason or indication. On day 141 the subject's liver enzymes were increased from baseline with no symptoms mentioned. The study drug was stopped on day 141. An ultrasound showed cirrhosis with no focal lesion on day 166 and liver chemistries peaked on day 196 and remained elevated in the injury onset range for 4 months, but then decreased. On day 201 the patient's anti smooth muscle antibody (ASMA) was weakly positive, and IgG was elevated. All other autoantibodies were negative with ANA not provided. The patient was diagnosed with autoimmune hepatitis (AIH) with no biopsy on day 230 and on day 250 the patient needed to start immunosuppression with azathioprine for 14 days followed by mycophenolate mofetil which is "ongoing". The patient's liver chemistries returned to baseline by day 281. The clinical reviewer concluded that the labs are suggestive of a mild DILI with AIH features rather than de novo AIH.[14]

At the time of this review, one additional case of is being reviewed by the Agency's DILI team for possible DILI. This subject was reported in the Study 11 (F1- pooled analysis). The subject was randomized to receive resmetirom 80 mg and while in the study was diagnosed with moderate stage 1 indolent multiple myeloma. On study day 111 the subject experienced transaminase elevation and the study drug was discontinued on day 113. The subject was removed from the study on day 141 at which time transaminases had returned to normal. The investigator's assessment was that the transaminase increase is related to the study drug and the Applicant disagreed.

[redacted] The concern is that the only way to know if the patient has autoimmune liver disease is through invasive biopsy; [redacted]

The warning and precautions of draft labeling states that patients must be monitored during treatment with Rezdiffra for elevations in liver function tests and for the development of liver-related adverse reactions. Hepatologists and gastroenterologists are familiar with the diagnosis of hepatotoxicity include drug-induced given their specialty. The Patient Counseling section of labeling states to inform patients of the risks of [redacted] hepatotoxicity and to instruct patients to immediately report any signs or symptoms of sever liver injury which could include fatigue, nausea, vomiting, right upper quadrant pain or tenderness, jaundice, fever, rash, and/or eosinophilia. The prescriber will likely counsel patients on these signs and symptoms and the importance of calling their prescriber. The Patient Package Insert (PPI) will inform patients of the risk of drug-induced hepatotoxicity, the signs and symptoms of hepatoxicity and to inform their healthcare provider right away if they develop signs and/or symptoms.[17] There will be enhanced pharmacovigilance for DILI for two years post approval.

5.2. Drug Interaction with Certain Statins

Approximately 49% of subjects were concomitantly on statins in the pooled 80 mg and 100 mg groups with about a third using moderate to high intensity statins. Rezdiffra is metabolized by CYP2C8 and is not metabolized by other CYP enzymes in vitro. Increased exposure of atorvastatin, pravastatin, rosuvastatin, and simvastatin was observed with concomitantly administered with Rezdiffra in drug interaction studies. This increased exposure could increase the risk of adverse reactions related to these drugs including myopathy and rhabdomyolysis, and hepatic dysfunction. The Prescribing Information (PI) states to monitor for statin relation side effects including but not limited to elevation of liver tests, myopathy, and rhabdomyolysis. In addition to the Warnings and Precaution section of the label, the drug interaction between statins and Rezdiffra is included in the Drug Interactions section. Specifically, there are dosing recommendations in the Drug Interaction section of the PI for limiting the daily dose of atorvastatin (40 mg), pravastatin (40 mg), rosuvastatin (20 mg), and simvastatin (20 mg).[16]

5.3. Gallbladder-Related Adverse Reactions

In the pooled safety population, the incidence of gallstones was higher for the resmetirom treated patients (0.9 per 100 patient-years for 80 mg and 0.8 per 100 patient-years for 100 mg). Also, the incidence of newly reported cholelithiasis-related events was higher in the resmetirom 80 mg (0.9%) and 100 mg (0.8%) versus placebo (0.3%). Although not significant, there was an increase in bile duct stone, cholecystitis, and obstructive pancreatitis in the treatment arms compared to placebo.

The background incidence of gallbladder disease (GD), also called gallstone disease, varies by ethnicity and geographic location with an estimated 20.5 million persons in the United States with gallbladder

disease. [18,f] A recent study found that the prevalence of NAFLD is 3.3% in patients with GD, which includes both the presence of gallstones and history of cholecystectomy, and 1% in those without GD concluding that GD and cholecystectomy may be risk factors for NAFLD.[19] Given the association between GD and NAFLD, as well as the association between thyroid hormones and the development of GD, gallbladder-related adverse reactions will be included in the PI. The Warnings and Precautions section of the PI instructs that if cholelithiasis is suspected, gallbladder diagnostic studies and appropriate clinical follow-up are indicated and that if an acute event such as acute cholecystitis is suspected, resmetirom should be interrupted until the event is resolved.[16]

6. Expected Postmarket Use

Rezdiffra is most likely to be used both inpatient and outpatient on a chronic basis. Prescribers will most likely be both inpatient and office-based gastroenterologists or hepatologists who are familiar with treating NASH as well as diagnosing any drug-induced hepatotoxicity possibly associated with the drug. It is likely that both inpatient and outpatient pharmacies will dispense Rezdiffra. The drug will be self-administered by the patient and both the prescriber and patient will need to monitor for adverse events.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for Rezdiffra beyond routine pharmacovigilance and labeling.

7.1. Other Proposed Risk Management Activities

At the time of this review, the review team is discussing the need for additional postmarket safety activities that will be needed if approved. The first two are Pediatric Research Equity Act (PREA) postmarketing requirement for use in post-pubertal pediatric patients ages 12 through 17 years and pre-pubertal pediatric patients ages 6 through 12 years with NASH and moderate to advanced fibrosis (stage F2 and F3). The Agency will also be requesting enhanced pharmacovigilance (EPV) for both drug-induced hepatotoxicity and exposure to Rezdiffra during pregnancy or lactation.

Reviewer's Comments: *We note that these other activities proposed by the applicant are outside of the scope of the REMS program and defer to Division of Pharmacovigilance and Epidemiology for review and input.*

8. Discussion of Need for a REMS

Untreated NASH is a serious condition, which can lead to cirrhosis, liver failure/need for transplantation, hepatocellular carcinoma, and death. With no approved pharmacological treatments for NASH, there is

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

an unmet need for pharmacological treatment. Rezdiffra (resmetirom) is a liver-directed, orally active, partial agonist for the thyroid hormone receptor beta (THR-Beta), proposed under the accelerated approval pathway (Subpart H) based on a surrogate endpoint reasonably likely to predict clinical benefit for the treatment of adults with nonalcoholic steatohepatitis (NASH) with liver fibrosis. Rezdiffra is proposed for the treatment of noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (consistent with states F2 to F3 fibrosis) with diet and exercise. The pivotal trial, Trial 11, supports the efficacy of Rezdiffra as evidenced by a statistically significant percent of subjects achieving NASH resolution and 1-point improvement in fibrosis stage with no worsening of NASH by liver biopsy at Week 52. The Clinical Reviewer recommends approval of Rezdiffra based on the efficacy and safety information currently available.

The risks associated with the use of Rezdiffra are drug-induced hepatoxicity including DILI, drug-interactions with certain statins, and gallbladder-related adverse reactions. This is a novel drug class and the first approval for the treatment of NASH. The risks will be communicated in the Warnings and Precaution section of the PI with clear instructions to providers what to do if the patient experiences any of the risks associated with Rezdiffra. (b) (4) The drug interaction with certain statins is also addressed in the Drug Interaction section of the PI.

The likely prescribers are gastroenterologists and hepatologists who are expected to be familiar with diagnosing and managing drug-induced hepatotoxicity, and gallbladder-related adverse reactions. The PI of Lipitor warns that plasma levels can be significantly increased with concomitant administration several drugs.[20] Given the number of drug interactions between statins and other widely used medications, providers are likely familiar with the need to check for drug interactions for patients using statins. The Rezdiffra PI will warn providers about this interaction, how to monitor, and dosage adjustments necessary for atorvastatin, pravastatin, rosuvastatin, and simvastatin. In addition to the PI, pharmacy management systems would typically check for significant drug interactions in patients who are prescribed Rezdiffra.

This reviewer has determined that a REMS is not necessary to ensure the benefits of Rezdiffra outweigh its risks. The risks will be included in the Warnings and Precautions section of the label with instructions in each section for managing the risk. In addition, the risk of drug interaction with certain statins is included in the Drug Interaction section of the PI with recommendations for dosage adjustments of certain statins while concomitantly on Rezdiffra.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for Rezdiffra to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. Appendices

10.1. References

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