Rezdiffra™ (resmetirom) – New drug approval

- On March 14, 2024, Madrigal Pharmaceuticals announced the FDA approval of Rezdiffra (resmetirom), 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 indication is approved under accelerated approval based on improvement of NASH and fibrosis. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.
    - Use of Rezdiffra should be avoided in patients with decompensated cirrhosis.
- NASH, also referred to as metabolic dysfunction associated steatohepatitis (MASH), is a result of the progression of nonalcoholic fatty liver disease (NAFLD) where liver inflammation, over time, can lead to liver scarring and liver dysfunction. NASH is often associated with other health problems such as high blood pressure and type 2 diabetes.
    - Approximately 6 to 8 million people in the U.S. have NASH with moderate to advanced liver scarring, with that number expected to increase. However, not all patients have been diagnosed with the disease.
    - Madrigal estimates that approximately 1.5 million patients have been diagnosed with NASH in the U.S., of which approximately 525,000 have NASH with moderate to advanced liver fibrosis.
- Rezdiffra is the first FDA approved treatment for NASH.
    - Rezdiffra is a partial agonist of the thyroid hormone receptor-beta (THR-β). THR-β is the major form of THR in the liver, and stimulation of THR-β in the liver reduces liver fat accumulation.
- The efficacy of Rezdiffra was based on an efficacy analysis at month 12 in a randomized, double-blind, placebo-controlled study in 888 patients who had metabolic risk factors and a baseline or recent liver biopsy showing NASH with fibrosis stage 2 or 3 and a NAFLD Activity Score (NAS) of at least 4. Patients were randomized to placebo, Rezdiffra 80 mg once daily, or Rezdiffra 100 mg once daily. Efficacy determination was based on the effect of Rezdiffra on resolution of steatohepatitis without worsening of fibrosis and one stage improvement in fibrosis without worsening of steatohepatitis, on post-baseline liver biopsies collected at 12 months. Two pathologists, Pathologist A and Pathologist B, independently read the liver biopsies for each patient.
    - Both the 80 mg and the 100 mg dosages of Rezdiffra demonstrated improvement on these histopathology endpoints at month 12 compared to placebo.

	Placebo	Rezdiffra 80 mg	Rezdiffra 100 mg
Resolution of steatohepatitis and no worsening of liver fibrosis			
Response rate, Pathologist A (%)	13	27	36
Difference in response rate vs. placebo (95% CI)	--	14 (8, 20)	23 (16, 30)
Difference in response rate vs. placebo (95% CI)	9	26	24

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Difference in response rate vs. placebo (95% CI)	--	17 (11, 23)	15 (9, 21)
Resolution of steatohepatitis and no worsening of liver fibrosis			
Response rate, Pathologist A (%)	15	23	28
Difference in response rate vs. placebo (95% CI)	--	8 (2, 14)	13 (7, 20)
Difference in response rate vs. placebo (95% CI)	13	23	24
Difference in response rate vs. placebo (95% CI)	--	11 (5, 17)	11 (5, 17)

- Warnings and precautions for Rezdiffra include hepatotoxicity, gallbladder-related adverse reactions, and drug interaction with certain statins.
- The most common adverse reactions (≥ 5% of patients and higher compared to placebo) with Rezdiffra use were diarrhea, nausea, pruritus, vomiting, constipation, abdominal pain, and dizziness.
- The recommended dose of Rezdiffra is based on actual body weight. For patients weighing:
  - < 100 kg, the recommended dosage is 80 mg orally once daily
  - ≥ 100 kg, the recommended dosage is 100 mg orally once daily.
- The wholesale acquisition cost (WAC) for Rezdiffra is $47,400 per year.
- Madrigal Pharmaceuticals plans to launch Rezdiffra in April 2024. Rezdiffra will be available as 60 mg, 80 mg, and 100 mg tablets.

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