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2024 Quarter 3 Newsletter

FDA APPROVAL SPOTLIGHT

RezdiffraTM
resmetirom tablets
60mg · 80mg · 100mg

On March 14, 2024, a thyroid hormone receptor-beta (THR- β) partial agonist called Rezdiffra (resmetirom) was approved for the treatment of noncirrhotic metabolic dysfunction-associated steatotic liver disease in adult patients with moderate to advanced liver fibrosis in conjunction with diet and exercise. The stimulation of THR- β leads to a reduction of intrahepatic triglycerides. The dosing for Rezdiffra is weight-based: for patients <100 kg, 80 mg once daily; for patients $\geq$ 100 kg, 100 mg once daily.

Limitations of use for Rezdiffra include concurrent CYP2C8 and/or OATP1B1/B3 inhibitors, concurrent statin therapies, moderate to severe hepatic impairment (Child-Pugh Class B or C), and high risk of cholelithiasis/cholecystitis. There is also no available data on use in patients who are pregnant or breastfeeding. No dose adjustment is required in mild to moderate renal impairment, but its use is recommended to be avoided in severe renal impairment due to the lack of data.

In a 54-month, randomized, double-blind, placebo-controlled trial, Rezdiffra demonstrated a higher rate of steatohepatitis resolution without worsening of liver fibrosis compared to placebo, as well as a higher rate of liver fibrosis improvement without worsening of steatohepatitis compared to placebo, with a dose-dependent response. (See Table 1 for more information). In these clinical trials, the most common adverse drug reactions were gastrointestinal-related (diarrhea, nausea, vomiting, constipation, abdominal pain), as well as pruritus and dizziness.

	Placebo (N=294)	Rezdiffra 80 mg (N=298)	Rezdiffra 100 mg (N=296)
Steatohepatitis resolution without 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)
Response rate, Pathologist B (%)	9	26	24

Difference in response rate vs. placebo (95% CI)		17 (11, 23)	15 (9, 21)
Liver fibrosis improvement without worsening of steatohepatitis			
Response rate, Pathologist A (%)	15	23	28
Difference in response rate vs. placebo (95% CI)		8 (2, 14)	13 (7, 20)
Response rate, Pathologist B (%)	13	23	24
Difference in response rate vs. placebo (95% CI)		11 (5, 17)	11 (5, 17)
	Placebo (N=294)	Rezdiffra 80 mg (N=298)	Rezdiffra 100 mg (N=296)

Currently, evidence-based guidelines support lifestyle changes as first-line therapy approaches to treat nonalcoholic fatty liver disease and mitigate progression. These measures include low-fat diet, increased physical activity, weight loss, etc. Few pharmacological treatments have evidence to support use in these patients. Statin therapy is considered to be one of the safest approaches but not with significant efficacy. Pioglitazone also has some evidence for use in select patients with a comorbidity of diabetes, but further research is needed to determine its true place in recommended treatments.

Rezdiffra is the first medication approved by the Food and Drug Administration (FDA) to treat fibrosis in patients with liver disease. For this patient population, nonalcoholic fatty liver disease can lead to extensive inflammation and scarring, which can result in further comorbidities and dysfunction, such as hepatic portal hypertension, esophageal varices, spontaneous bacterial peritonitis, hepatic encephalopathy, etc. Therefore, this treatment stands to greatly improve morbidity and mortality for this patient population.

References:

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- Leoni S, Tovoli F, Napoli L, Serio I, Ferri S, Bolondi L. Current guidelines for the management of non-alcoholic fatty liver disease: A systematic review with comparative analysis. World J Gastroenterol. 2018 Aug 14;24(30):3361-3373. doi: 10.3748/wjg.v24.i30.3361. PMID: 30122876; PMCID: PMC6092580.

2024 GUIDELINE UPDATES



Cannabinoid hyperemesis syndrome (CHS) is a recently described collection of symptoms distinct from other vomiting disorders, such as chemotherapy-induced vomiting, hyperemesis gravidarum, and cyclic vomiting syndrome. The exact pathophysiology has not been fully elucidated, but it is thought to involve multiple cannabinoid receptors along neurologic and endocrinologic pathways. While the overall prevalence of CHS is 0.1%, some studies estimate that up to 33% of marijuana smokers have experienced CHS at some point, although it is typically thought to only affect chronic, heavy users of marijuana (i.e. those with cannabis use disorder). As it was first described in 2004, the diagnosis and treatment of CHS has been inconsistent due to the lack of robust research.

In May of 2024, the American Gastroenterological Association (AGA) released a clinical practice update on the diagnosis and management of CHS. In these guidelines, the AGA classifies CHS as a subtype of cyclic vomiting syndrome with the unique caveat that patients may have paradoxical effects, whereby cannabis use may cause and alleviate symptoms.

The guidelines give several diagnostic criteria for CHS, which include the following:

- Cannabis use ≥ 1 year prior to symptom onset
- Cannabis use > 4 times per week
- Vomiting episodes ≥ 3 times annually
- Symptom resolution after ≥ 6 month cannabis abstinence or equal to 3 typical vomiting cycles

To treat CHS, the AGA recommends amitriptyline 75-100 mg by mouth daily at bedtime as the first-line therapy. Additionally, they acknowledge benefit for topical capsaicin 0.1% cream applied to the upper abdomen, as well as anti-emetics, for symptomatic relief. The AGA strongly recommends counseling for marijuana cessation but the avoidance of immediate cessation (e.g. stopping “cold-turkey”) to avoid withdrawals and worsening of symptoms.

Further research is currently being undertaken as to the best anti-emetics, as well as unique treatment modalities, for CHS. As new data becomes available, it is likely that the AGA will update their recommendations further to support the larger body of evidence.

References:

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- Richards JR, Lapoint JM, Burillo-Putze G. Cannabinoid hyperemesis syndrome: potential mechanisms for the benefit of capsaicin and hot water hydrotherapy in treatment. *Clin Toxicol (Phila)*. 2018 Jan;56(1):15-24. doi: 10.1080/15563650.2017.1349910. Epub 2017 Jul 21. PMID: 28730896.

LEGISLATIVE NEWS



The Non-Opioids Prevent Addiction in the Nation (NOPAIN) Act was introduced in the Senate on March 4, 2021 and approved on December 29, 2022 with plans to go into effect on January 1, 2025. As stated, this bill serves to temporarily establish “separate payments for certain non-opioid pain management treatments that are able to replace or reduce opioid consumption under the Medicare prospective payment system for hospital outpatient department services and the payment system for ambulatory surgical center services.” As a response to the opioid crisis and high costs of branded pain management therapies, this bipartisan bill targets specific non-opioid therapies and directs the Center for Medicare and Medicaid Services (CMS) to make a separate, additional payment to hospital outpatient departments for each utilization of these therapies for postsurgical pain relief.

To do this, several factors were considered. Specific rates for these “separate, additional payments” were clarified and set and a new J code for Exparel (bupivacaine) was approved, for example. Additionally, CMS is required to report to Congress by January 1, 2028 to identify areas for improvement in terms of patient’s access to care, budgetary limitations, gaps in coverage, etc. This report will also include a comparison of opioids utilized prior to and following the implementation of this legislation to determine its efficacy.

As this legislation is only a temporary measure through January 1, 2028, the resulting CMS report should prove insightful for government healthcare spending, as well as overall improvement of prescribing/ordering practices when limitation for using non-opioid pain management are decreased. Medicare, Medicaid, and private insurance plan will benefit from the knowledge received from this report. As the opioid epidemic continues to be addressed, both with legislative measures and with individual prescribing and dispensing improvements, patient welfare will improve as pain can be robustly managed via a multimodal approach that is both safe and effective.

References:

- S.586 - 117th Congress (2021-2022): NOPAIN Act. (2021, March 4). <https://www.congress.gov/bill/117th-congress/senate-bill/586>