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Rimegepant

Updated: July 20, 2021.

OVERVIEW

Introduction

Rimegepant is a small molecule inhibitor of the calcitonin gene-related peptide (CGRP) receptor that blocks the action of CGRP, a potent vasodilator believed to play a role in migraine headaches. Rimegepant is approved for treatment of acute migraine attacks. In clinical trials, rimegepant was generally well tolerated with only rare instances of transient serum aminotransferase elevations during therapy and with no reported instances of clinically apparent liver injury.

Background

Rimegepant (ri me' je pant) is a small molecule inhibitor of the receptor for the calcitonin gene-related peptide (CGRP), which is believed to play a role in the pathogenesis of migraine headaches. CGRP is a potent vasodilator and pain-signaling neurotransmitter that is found throughout the central and peripheral nervous system but is particularly common in trigeminal ganglia. Levels of CGRP are elevated during episodes of migraine headache, and administration of the peptide can induce migraines in susceptible patients. For this reason, approaches to inhibition of CGRP signaling were developed as potential therapies for migraine, both as preventive therapies to decrease the rate of migraine as well as for treatment of acute attacks. Several monoclonal antibodies that block CGRP or its receptor are approved for use in prevention of migraines and two small molecule inhibitors of the CGRP receptor (the "gepants": ubrogepant and rimegepant) are available for treatment of acute migraine. In several randomized, placebo controlled trials, rimegepant in doses of 75 mg was found to increase the rate of being free of headache pain by two hours after [20% to 21% vs 11% to 12% with placebo] and free of the most bothersome other symptoms [35% to 38% vs 25% to 27% with placebo]. Rimegepant was approved for treatment of acute migraine in the United States in 2020, the second oral CGRP receptor antagonist approved for this indication. Rimegepant is available in orally disintegrating tablets of 75 mg under the brand name Nurtec-ODT. The recommended dose is 75 mg orally as soon as possible after onset of migraine. The dose should not exceed 75 mg during any 24 hour period. Rimegepant can be used by patients receiving preventive therapy with monoclonal antibodies to CGRP or its receptor. Rimegepant is generally well tolerated with side effects of nausea, dizziness, somnolence and dry mouth that are generally uncommon (<5%), transient and mild to moderate in severity. Hypersensitivity reactions (largely rash and dyspnea) have arisen in rare cases, but more severe adverse events have not been reported.

Hepatotoxicity

In preregistration controlled trials of rimegepant in several thousand patients, mild-to-moderate serum aminotransferase elevations arose in a small percentage of patients (1% to 2%) and overall rates were not

different from those in placebo recipients. In the controlled trials and subsequently with general use, there have been no reports of clinically apparent liver injury attributed to ubrogepant. In contrast, telcagepant, the initial oral CGRP receptor antagonist evaluated as therapy for migraine headaches, was abandoned during development because of several instances of clinically apparent liver injury in recipients that was characterized by marked elevations in serum aminotransferase levels and symptoms of fatigue, nausea and abdominal discomfort arising within 2 to 4 weeks of starting therapy which rapidly resolved with stopping therapy. Similar episodes have not been reported with rimegepant.

Likelihood score: E (unlikely cause of clinically apparent acute liver injury).

Mechanism of Injury

Possible mechanisms of liver injury due to rimegepant are not known. It is metabolized in the liver largely by CYP 3A4 and is susceptible to drug-drug interactions with agents that induced or inhibit this microsomal enzyme.

Outcome and Management

Drug Class: Migraine Headache Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Rimegepant – Nurtec-ODT®

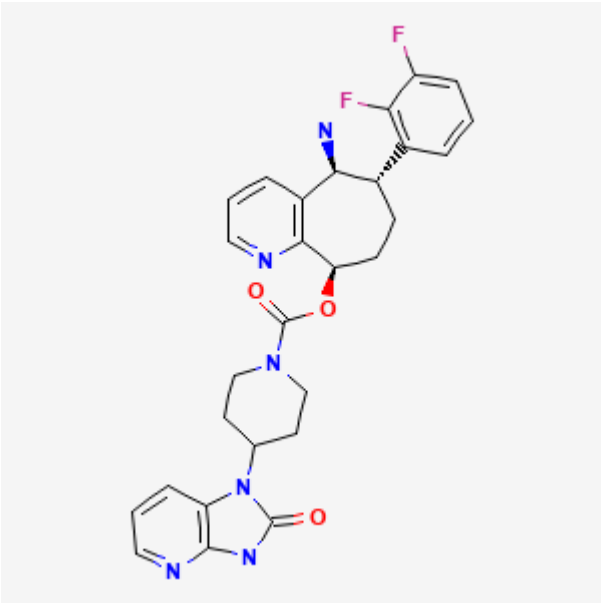
DRUG CLASS

Migraine Headache Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Rimegepant	1289023-67-1	C28-H28-F2-N6-O2	

ANNOTATED BIBLIOGRAPHY

References updated: 20 July 2021

Abbreviations: CGRP, calcitonin gene-related peptide.

Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999.

(Review of hepatotoxicity published in 1999 before the availability of CGRP antagonists).

FDA. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/212728Orig1s000MedR.pdf

(FDA Drug Approvals website that has product labels [package inserts], letters of approval and full FDA multidisciplinary scientific review of the rimegepant application including specific discussion of hepatic adverse events which consisted mainly of mild-to-moderate ALT or AST elevations which were similar in frequency in rimegepant vs placebo recipients and there were no instances of clinically apparent liver injury with jaundice).

Ho TW, Connor KM, Zhang Y, Pearlman E, Koppenhaver J, Fan X, Lines C, et al. Randomized controlled trial of the CGRP receptor antagonist telcagepant for migraine prevention. Neurology. 2014;83:958–66. PubMed PMID: 25107879.

(Among 660 patients with migraine enrolled in a controlled trial of telcagepant [140 or 280 mg] vs placebo twice daily for 12 weeks, 13 patients on telcagepant developed ALT elevations above 3 times ULN, generally between weeks 4 and 6 of treatment, two rising starting at week 2 to as high as 33 and 39 times ULN accompanied by symptoms but not jaundice; discontinuation was followed by full recovery but the episodes led to early termination of the trial because of the risk of significant hepatotoxicity).

Marcus R, Goadsby PJ, Dodick D, Stock D, Manos G, Fischer TZ. BMS-927711 for the acute treatment of migraine: a double-blind, randomized, placebo controlled, dose-ranging trial. Cephalalgia. 2014;34(2):114–25. PubMed PMID: 23965396.

(Among 885 adults enrolled in a randomized controlled dose-finding study of rimegepant [10, 25, 75, 150, 300 or 600 mg] for treatment of a single migraine attack, the proportion of subjects who were headache pain free 2 hours after dosing was 30-33% with 75, 150 and 300 mg of rimegepant vs 35% with sumatriptan and 15% with placebo, while adverse event rates were similar in all groups and there were no "clinically significant changes" in laboratory tests and no ALT elevations above 3 times ULN).

Lipton RB, Croop R, Stock EG, Stock DA, Morris BA, Frost M, Dubowchik GM, et al. Rimegepant, an oral calcitonin gene-related peptide receptor antagonist, for migraine. N Engl J Med. 2019;381:142–9. PubMed PMID: 31291516.

(Among 1186 adults treated for a single migraine attack in a randomized controlled trial, freedom from headache pain at 2 hours was higher with rimegepant [75 mg] than placebo [20% vs 12%] as was resolution of the most bothersome other symptom [38% vs 25%] while adverse event rates were similar, ALT or AST elevations arising in 2.4% vs 2.0% and no elevation being above 3 times ULN).

Croop R, Goadsby PJ, Stock DA, Conway CM, Forshaw M, Stock EG, Coric V, et al. Efficacy, safety, and tolerability of rimegepant orally disintegrating tablet for the acute treatment of migraine: a randomised, phase 3, double-blind, placebo-controlled trial. Lancet. 2019;394:737–45. PubMed PMID: 31311674.

(Among 1811 adults treated for a single attack of migraine in a randomized controlled trial, freedom from headache pain 2 hours after dosing was higher after rimegepant [75 mg] vs placebo [21% vs 11%] as was freedom from the most bothersome other symptom [35% vs 27%], while the most common adverse event was nausea [2% vs 1%] and ALT elevations above 3 times ULN occurred in 0.1% of both groups and there were no instances of liver injury with jaundice).

Tfelt-Hansen P, Loder E. The Emperor's new gepants: are the effects of the new oral CGRP antagonists clinically meaningful? Headache. 2019;59:113–7. PubMed PMID: 30451300.

(Commentary on the relative efficacy of two oral CGRP receptor antagonists, ubrogepant and rimegepant, which show only modest efficacy in acute migraine [therapeutic gain of 5-8%] and only when compared to placebo as compared to well-known effective therapies such as aspirin and other nonsteroidal antiinflammatory agents [8-14%] and the triptans [16-32%]).

Lasmiditan (Reyvow) and ubrogepant (Ubrelvy) for acute treatment of migraine. Med Lett Drugs Ther. 2020;62(1593):35–9. PubMed PMID: 32555120.

(Concise review of the mechanism of action, clinical efficacy, safety and costs of ubrogepant and lasmiditan as therapy of acute migraine shortly after their approval for this indication in the US, mentions side effects of ubrogepant being nausea and somnolence but does not mention ALT elevations or hepatotoxicity).

Rimegepant (Nurtec ODT) for acute treatment of migraine. Med Lett Drugs Ther. 2020;62(1597):70–2. PubMed PMID: 32555113.

(Concise review of the mechanism of action, pharmacology, clinical efficacy, safety and cost of rimegepant shortly after its approval in the US as therapy of acute migraine in adults, mentions that it "was generally well tolerated in clinical trials; nausea was the most common adverse event [~2%]").

Berman G, Croop R, Kudrow D, Halverson P, Lovegren M, Thiry AC, Conway CM, et al. Safety of rimegepant, an oral CGRP receptor antagonist, plus CGRP monoclonal antibodies for migraine. Headache. 2020;60:1734–42. PubMed PMID: 32799325.

(Description of 13 patients taking CGRP monoclonal antibodies for prevention of migraine [erenumab, galcanezumab or fremanezumab] who used rimegepant tablets to treat a total of 224 acute attacks of migraine, with no serious adverse events and no elevations in ALT above 3 times ULN or episodes of liver injury with jaundice).

Croop R, Lipton RB, Kudrow D, Stock DA, Kamen L, Conway CM, Stock EG, et al. Oral rimegepant for preventive treatment of migraine: a phase 2/3, randomised, double-blind, placebo-controlled trial. Lancet. 2021;397:51–60. PubMed PMID: 33338437.

(Among 747 patients with migraine headaches enrolled in a 12-week randomized controlled trial, those treated with rimegepant [75 mg] every other day had a greater decrease in monthly number of days with migraine vs those on placebo [-4.3 vs -3.5 days], while overall adverse event rates were similar [both 36%] as were ALT or AST elevations above 3 times ULN [both 1%] and there were no instances of liver injury with jaundice, although 1 patient receiving rimegepant had an asymptomatic and transient elevation in ALT above 10 times ULN).

Drugs for migraine. Med Lett Drugs Ther. 2020;62(1608):153–60. PubMed PMID: 33434187.

(Concise summary of the relative clinical efficacy, safety and costs of drugs to treat acute migraine headache [such as analgesics, opiates, triptans, ergots and oral CGRP receptor antagonists] and to prevent migraines [such as anticonvulsants, beta blockers, antidepressants and the monoclonal antibodies to CGRP and its receptor]).

Robbins MS. Diagnosis and management of headache: a review. JAMA. 2021;325:1874–85. PubMed PMID: 33974014.

(Review of the diagnosis and management of headache including use of calcitonin gene-related peptide antagonists for acute migraine attacks which has uncommon side effects of dry mouth and dizziness; no mention of ALT elevations or hepatotoxicity).