CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212728Orig1s000

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	212728 and (b) (4)
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OSE RCM #	2019-1378 and 2019-1391
Reviewer Name(s)	Ingrid N. Chapman, PharmD, BCPS
Team Leader	Donella Fitzgerald, PharmD
Deputy Division Director	Jamie Wilkins, PharmD
Review Completion Date	February 24, 2020
Subject	Evaluation of Need for a REMS
Established Name	Rimegepant
Trade Names	(b) (4) and Nurtec ODT
Name of Applicant	Biohaven Pharmaceuticals, Inc
Therapeutic Class	Calcitonin gene-related peptide antagonist
Formulation(s)	75 mg tablet and 75 mg orally disintegrating tablet
Dosing Regimen	75 mg by mouth as needed up to once daily

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (b) (4) and Nurtec ODT (rimegepant) is necessary to ensure the benefits outweigh its risks. Biohaven Pharmaceuticals, Inc submitted two New Drug Applications (NDA (b) (4) and NDA 212728) for rimegepant tablets and rimegepant orally disintegrating tablets respectively with the proposed indication: for the acute treatment of migraine in adults.

The Applicant did not submit a proposed REMS or risk management plan with this application. No serious risks related to the use of rimegepant were identified during this review. The likely prescribers include neurologists and primary care providers. The Division of Risk Management (DRM) and the Division of Neurology I agree that a REMS is not necessary to ensure the benefits of rimegepant outweigh its risk for the proposed indication, acute treatment of migraine in adults.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) (b) (4) and Nurtec ODT (rimegepant) is necessary to ensure the benefits outweigh its risks. Biohaven Pharmaceuticals, Inc submitted two New Drug Applications (NDA (b) (4) and NDA 212728) for rimegepant tablets and rimegepant orally disintegrating tablets respectively with the proposed indication: for the acute treatment of migraine in adults. These applications are under review in the Division of Neurology 1 (DN 1). The Applicant did not submit a proposed REMS or risk management plan with these applications.

2 Background

2.1 PRODUCT INFORMATION

Rimegepant, a new molecular entity, [a] is a calcitonin gene-related peptide receptor (CGRP) antagonist proposed for the acute treatment of migraine with or without aura in adults.[1] Rimegepant is proposed as 75 mg tablets and 75 mg orally disintegrating tablet (ODT) for oral administration. The proposed dose is 75 mg by mouth up to once daily. Treatment is administered as needed.[b] Rimegepant is not currently approved in any jurisdiction. If approved, rimegepant will be the 2nd drug in the pharmacologic class of oral CGRP antagonists. Ubrogepant, the 1st oral CGRP antagonist, was approved without a Boxed Warning or REMS.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 212728 and NDA (b) (4) relevant to this review:

- 06/27/2019: NDA 212728 submission (rimegepant ODT) for acute treatment of migraines in adults received.
- 06/28/2019: NDA (b) (4) submission (rimegepant tablets) for acute treatment of migraines in adults received.

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

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

- 10/01/2019: The agenda for the rimegepant Mid-cycle meeting (combined meeting for both applications) was issued to the Applicant. It stated, "At this time, there are no major safety concerns identified; we do not anticipate the need for a REMS at this time." Subsequently, the Applicant cancelled the Mid-cycle meeting.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

In the U.S., more than 30 million people have 1 or more migraine headaches per year. This corresponds to approximately 18% of females and 6% of males.[2c] Migraine is a primary headache disorder that is classified as either migraine without aura or migraine with aura. The "POUND" mnemonic for the diagnosis of migraine characterizes the following clinical features of migraines: **P**ulsatile quality of headache; **O**ne-day duration of headache (4 to 72 hours if untreated or unsuccessfully treated); **U**nilateral headache; **N**ausea or vomiting; and **D**isabling intensity of headache.[3] Associated migraine symptoms may include nausea, photophobia and phonophobia. For individuals who experience migraine with aura there are unilateral reversible focal neurologic symptoms such as vision impairment or sensory symptoms that usually develop gradually and are usually followed by migraine symptoms.[4] The Global Burden of Disease Study 2015 ranked migraine as the third-highest cause of disability worldwide in both males and females under the age of 50 years.[5d] Estimated annual U.S. direct costs for migraine are more than $17 billion; the costs of lost productivity and reduced quality of life are significantly higher.[3]

3.2 Description of Current Treatment Options

Non-pharmacologic therapies used as adjunct to treat migraine include biofeedback, cognitive-behavioral therapy, relaxation therapy, and nerve stimulation. The Cerena Transcranial Magnetic Stimulator (Cerena TMS) was the first FDA-approved device to relieve pain caused by migraine headache with aura in adults. In January 2018, the FDA approved to expand the indication of the vagus nerve stimulator, gammaCore, to include migraine in adults. It was originally approved to treat episodic cluster headache pain in adults. In May 2019, Nerivio Migra, a neuromodulation device, was approved for the relief of acute migraine pain.[2] Nerivio Migra uses smartphone-controlled electronic pulses to relieve migraine through conditioned pain modulation.

Pharmacologic classes of drugs with the indication to treat acute migraine include ergot derivatives (dihydroergotamine mesylate and ergotamine tartrate) and triptans or 5-$HT_{1b/1d}$ receptor agonists.[e] Of the ergot derivatives, dihydroergotamine is more commonly prescribed than ergotamine. Because of the risks of ischemia and vasospasms, dihydroergotamine is typically reserved for the treatment of intractable severe migraine in the emergency department.[6] Triptans are effective for acute migraines and offer a variety of routes of administration including oral, intranasal, subcutaneous, intramuscular, and transdermal. However, triptans should be avoided in patients with known or suspected coronary

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

[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.*

[e] Triptans (5-HT1b/1d receptor agonists): almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan

artery disease, as they may increase risk of myocardial ischemia, infarction, or other cardiac or cerebrovascular events.[2] Lasmiditan, a 5-HT_{1f} agonist, was approved in October of 2019 for the acute treatment of migraine with or without aura in adults. Its risks include dizziness, sedation, and serotonin syndrome. Lastly, ubrogepant was the most recently approved drug for the treatment of migraine. It has minimal adverse effects. See Table 10.2 in the appendix for detailed risk information.

While there are a number of other treatments for migraines without a specific migraine indication with probable and possible effectiveness including antiemetics, non-steroidal anti-inflammatory agents, steroids, and antiepileptic agents, there is an unmet need for patients with various contraindications.[7]

4 Benefit Assessment

The efficacy and safety of rimegepant was demonstrated in three pivotal studies: BHV3000-303 (rimegepant ODT), BHV3000-302 (rimegepant tablet), and BHV3000-301 (rimegepant tablet).[8] The studies were similar in design. They were Phase 3, double-blind, randomized, placebo-controlled, single-dose efficacy and safety studies of rimegepant 75 mg for the treatment of acute migraine. Patients were randomized in a 1:1 ratio to the rimegepant or placebo treatment groups. Patients were provided the study medication at randomization (baseline visit) and took the study drug at the onset of the moderate or severe pain intensity migraine headache. The Modified Intent-to-Treat (mITT) population included patients randomized only once, took study medication, had a baseline migraine of moderate to severe intensity, and who provided at least 1 post-baseline efficacy data point.

4.1 Co-primary Efficacy Endpoints

The pivotal studies had the same co-primary efficacy endpoints. Results showed statistical significance for both endpoints in all three studies.

1. Freedom from pain at 2 hours post-dose
2. Freedom from the most bothersome symptom (MBS) associated with migraine at 2 hours post-dose

Table 1:[9] Pivotal Studies – Co-primary Efficacy Endpoints

	Study 301		Study 302		Study 303	
	Placebo N= 541	75 mg N= 543	Placebo N=535	75 mg N=537	Placebo N=682	75 mg N=669
Pain Freedom at 2 hours						
Responders, n(%)	77 (14.2)	104 (19.2)	64 (12.0)	105 (19.6)	74 (10.9)	142 (21.2)
Difference from placebo		5%		7.6		10.3
(95% CI)		(0.5, 9.3)		(3.3, 11.9)		(6.5, 14.2)
p-value		0.0298		<0.001		<0.001
Absence of MBS at 2 hours						
Responders, n(%)	150 (27.7)	199 (36.6)	135 (25.2)	202 (37.6)	183 (26.8)	235 (35.1)
Difference from placebo		8.9%		12.4		8.3
(95% CI)		(3.4, 14.4)		(6.9, 17.9)		(3.4, 13.2)
p-value		0.0016		<0.001		0.001

4.2 SECONDARY ENDPOINTS

The secondary endpoints for Studies 301 and 302 included the following (hierarchal testing performed). Results showed that photophobia freedom, phonophobia freedom, and pain relief at 2 hours were statistically significant (*).

1. *Photophobia freedom at 2 hours
2. *Phonophobia freedom at 2 hours
3. *Pain relief (PR) at 2 hours
4. Nausea freedom at 2 hours
5. Probability of requiring rescue medication within 24 hours
6. Sustained pain freedom (SPF) from 2 to 24 hours
7. Sustained pain relief (SPR) from 2 to 24 hours
8. Sustained pain freedom (SPF) from 2 to 48 hours
9. Sustained pain relief from 2 to 48 hours
10. Pain relapse from 2 to 48 hours
11. Proportion of patients able to work or function normally at 2 hours

The secondary endpoints for Study 303 included the following (tested hierarchically after reordering due to the results of Studies 301 and 302). All of the secondary endpoints for Study 303 were significant except for freedom from nausea at 2 hours and pain relapse from 2 to 48 hours (*).

1. *Pain relief at 2 hours post dose
2. *Ability to function normally at 2 hours post dose
3. *Sustained pain relief from 2 to 24 hours
4. *Sustained freedom from MBS from 2 to 24 hours
5. *Probability of requiring rescue medication within 24 hours
6. *Sustained ability to function at a normal level from 2 to 24 hours
7. *Sustained pain relief from 2 to 48 hours
8. *Sustained freedom from MBS from 2 to 48 hours
9. *Sustained ability to function at a normal level from 2 to 48 hours
10. *Freedom from photophobia at 2 hours post dose
11. *Functional disability at 90 minutes
12. *Pain relief at 90 minutes post dose
13. *Sustained pain freedom from 2 to 24 hours
14. *Freedom from MBS at 90 minutes post dose
15. *Pain freedom at 90 minutes post dose
16. *Freedom from phonophobia at 2 hours post dose
17. *Sustained pain freedom from 2 to 48 hours
18. *Pain relief at 60 minutes post dose
19. *Ability to function normally at 60 minutes post dose
20. Freedom from nausea at 2 hours post dose
21. Pain relapse from 2 to 48 hours

The Clinical Reviewer concluded that the applicant has submitted enough evidence to meet the statutory evidentiary standard. Studies 301, 302, and 303 all provide evidence that 75 mg of rimegepant is an effective dose for the acute treatment of migraine. Studies 301 and 302 (b) (4) , and study 303 demonstrated the efficacy of the ODT formulation.[9]

5 Risk Assessment & Safe-Use Conditions

The safety database for rimegepant is comprised of the three pivotal studies and Study BHV3000-201. Study 201 is an ongoing, Phase 2/3, multicenter, multiple-dose, long-term, open-label, study in patients with migraine (no placebo group).[10] The objective of this study is to assess the safety and tolerability of long-term use of rimegepant 75 mg (n = 1784), taken up to one tablet (one dose) per calendar day.

Common adverse events in the pivotal studies that occurred in ≥ 1% of rimegepant-treated patients included various infections (e.g. upper respiratory tract infections and urinary tract infections), dyspepsia, and nausea.[9] No serious risks related to the use of rimegepant were identified during this review.[f] Additionally, there were no deaths in the clinical development program for rimegepant.

6 Expected Postmarket Use

Rimegepant will likely be prescribed primarily in the outpatient setting. The likely prescribers include neurologists and primary care providers. These prescribers are likely to be familiar with the management of the common adverse events associated with rimegepant including infections, dyspepsia, and nausea.

7 Risk Management Activities Proposed by the Applicant

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

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of rimegepant 75 mg (b) (4) ODT formulation based on the efficacy and safety information currently available.

Migraine is ranked as the third-highest cause of disability worldwide in those under age 50. The loss of productivity and decreased quality of life for individuals experiencing migraines is significant and costs the U.S. more than $17 billion dollars annually. Rimegepant offers an additional option to treat acute migraine with a different mechanism of action and no known serious risks. Healthcare providers

[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.*

prescribing rimegepant are likely to be familiar with managing the common adverse events of rimegepant including infections, dyspepsia, and nausea. DRM recommends that, should rimegepant be approved, a REMS is not necessary to ensure its benefits outweigh its risk for the acute treatment of migraine in adults.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for rimegepant 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

1. Biohaven Pharmaceuticals, Inc. Rimegepant. NDA 212728 and NDA (b) (4) Prescribing information, draft. June 27, 2019.
2. Chawla J. Migraine Headache. *Medscape.* October 21, 2019. Accessed October 30 , 2019.
3. Mayans L, Walling A. Acute Migraine Headache: Treatment Strategies. *American family physician.* 2018;97(4):243-251.
4. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. 2018;38(1):1-211.
5. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia.* 2018;38(1):1-211.
6. Smith JH. Acute treatment of migraine in adults. *UpToDate.* November 15, 2019. Accessed November 21, 2019.
7. Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: the american headache society evidence assessment of migraine pharmacotherapies. *Headache.* 2015;55(1):3-20.
8. Biohaven Pharmaceuticals, Inc. Rimegepant. NDA 212728 and NDA (b) (4) Module 2.7.3 - Summary of Clinical Efficacy. June 27, 2019.
9. Jawidzik L. Food and Drug Administration. Division of Neurology I. Rimegepant. NDA (b) (4) and NDA 212728. Draft Review. Clinical Reviewer. January 13, 2020.
10. Biohaven Pharmaceuticals, Inc. Rimegepant. NDA 212728 and NDA (b) (4) Module 2.7.4 - Summary of Clinical Safety. June 27, 2019.
11. Drugs@FDA: FDA Approved Drug Products. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed February 4, 2020.

10.2 TABLE:[11] TREATMENT OPTIONS FOR MIGRAINE

Drug (Approval Date)	Indication(s)	Important Safety and Tolerability Issues	Risk Management Approaches
Dihydroergotamine mesylate (1946- injection & 1997- nasal)	Acute treatment of cluster headaches Acute treatment of migraine headaches with or without aura	**Boxed Warning** **Concurrent drug therapy** Serious or life-threatening peripheral ischemia has been associated with the coadministration of dihydroergotamine with potent CYP3A4 inhibitors, including protease inhibitors and macrolide antibiotics. Because CYP3A4 inhibition elevates the serum levels of dihydroergotamine, the risk for vasospasm leading to cerebral ischemia or ischemia of the extremities is increased. Hence, concomitant use of these medications is contraindicated. **Warning and Precautions** Cardiovascular effects Cardiac valvular fibrosis Cerebrovascular events Cardiovascular disease Pleural/retroperitoneal fibrosis **Contraindications** Hypersensitivity to dihydroergotamine or any component of the formulation; uncontrolled hypertension, ischemic heart disease, angina pectoris, history of MI, silent ischemia, or coronary artery vasospasm including Prinzmetal angina; hemiplegic or basilar migraine; peripheral vascular disease; sepsis; severe hepatic or renal dysfunction; following vascular surgery; avoid use within 24 hours of 5-hydroxytryptamine-1 (5HT1) receptor agonists (triptans), other serotonin agonists, or ergot-like agents; concurrent use of peripheral and central vasoconstrictors; concurrent use of potent inhibitors of CYP3A4 (includes protease inhibitors, azole antifungals, and some macrolide antibiotics); pregnancy, breastfeeding.	**Labeling** – Boxed Warning, Warning & Precautions, and Contraindications
Ergotamine tartrate (1983 - oral)	As therapy to abort or prevent vascular headache (e.g., migraine, migraine variants or a so-called "histaminic cephalalgia")	**Boxed Warning:** same as dihydroergotamine **Warning and Precautions** Cardiovascular effects (vasospasm or vasoconstriction) Coadministration with CYP3A4 inhibitors Fibrotic complications Ergotism (intense arterial vasoconstriction, producing signs and symptoms of peripheral vascular ischemia) **Contraindications** Peripheral vascular disease; coronary heart disease; hypertension; hepatic or renal function impairment; sepsis; hypersensitivity to any component of the product; pregnancy; potent CYP3A4 inhibitors (e.g., ritonavir, nelfinavir, indinavir, erythromycin, clarithromycin, troleandomycin).	**Labeling** – Boxed Warning, Warning & Precautions, and Contraindications
Triptans Almotriptan (2001) Eletriptan (2002) Frovatriptan (2001) Naratriptan (1998) Rizatriptan (1998) Sumatriptan (1992) Zolmitriptan (1997)	Acute treatment of migraine with or without aura in adults; acute treatment of migraine headache pain in children 12 years and older with a history of migraine attacks with or without aura usually	**Warnings and Precautions (rizatriptan)** Myocardial ischemia, myocardial infarction, and Prinzmetal's angina Arrhythmias Chest/throat/neck/jaw pain, tightness, pressure, or heaviness Cerebral hemorrhage, subarachnoid hemorrhage, and stroke: Gastrointestinal ischemic events, peripheral vasospastic reactions: Medication overuse headache: Serotonin syndrome: **Contraindications (rizatriptan)** Ischemic heart disease or coronary artery vasospasm	**Labeling** – Warning & Precautions, and Contraindications

	lasting 4 hours or more when untreated **(almotriptan only)**; acute treatment of migraine with or without aura in pediatric patients 6 to 17 years of age **(rizatriptan only).**	Cardiovascular disease (including uncontrolled hypertension) Coronary artery vasospasm History of stroke or transient ischemic attack Peripheral vascular disease Ischemic bowel disease Hemiplegic or basilar migraine Recent history or concurrent use with ergotamine derivatives, other triptans, monoamine oxidase inhibitor (MAOI) therapy, and potent CYP3A4 inhibitors	
Lasmiditan (October 2019)	Acute treatment of migraine with or without aura in adults	**Warnings and Precautions** Driving Impairment Central Nervous System (CNS) Depression Serotonin Syndrome Medication Overuse Headache	**Labeling** – Warning & Precautions
Ubrogepant (December 2019)	Acute treatment of migraine with or without aura in adults	**Adverse Reactions** Central nervous system – Drowsiness (2% to 3%) Gastrointestinal – Nausea (4%) and xerostomia (2%)	**Labeling** – Adverse Reactions

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