CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216386Orig1s000

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	216386
PDUFA Goal Date	March 9, 2023
OSE RCM #	2022-503
Reviewer Name(s)	Lindsey W. Crist, PharmD, BCPS
Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	March 9, 2023
Subject	Evaluation of Need for a REMS
Established Name	Zavegepant
Trade Name	Zavzpret
Name of Applicant	Biohaven Pharmaceutical Holding Company, Ltd.
Therapeutic Class	Calcitonin gene-related peptide antagonist; Anti-migraine
Formulation(s)	Single-dose nasal spray delivering 10 mg of zavegepant
Dosing Regimen	10 mg given as a single spray in one nostril The maximum dose per 24 hour period is 10 mg

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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 Zavzpret (zavegepant) is necessary to ensure the benefits outweigh its risks. Biohaven Pharmaceutical Holding Company, Ltd. submitted a New Drug Application (NDA) 216386 for zavegepant with the proposed indication for the acute treatment of migraine with or without aura in adults. The Applicant did not submit a proposed REMS or risk management plan with this application.

The benefit for the acute treatment of migraine with or without aura in adults was demonstrated as zavegepant 10 mg nasal spray resulted in a statistically significant difference compared to placebo in the co-primary endpoints of pain freedom at 2 hours post dose and MBS freedom at 2 hours post dose in two pivotal trials.

The risks associated with zavegepant include hypersensitivity. The proposed labeling will include a Section 5, Warning and Precaution for hypersensitivity. This is consistent with other CGRP antagonists currently approved. There are several theoretical safety concerns associated with CGRP antagonism including possible cardiovascular, cerebrovascular, peripheral vascular, and gastrointestinal adverse events. There were no clear safety signals for any of these risks in the clinical trials. Hepatotoxicity is a potential safety concern for this drug class as the clinical development of two early investigational CGRP inhibitors was terminated due to liver toxicity. However, available data for zavegepant does not suggest a significant risk of hepatotoxicity when used as labeled. Overall, the safety profile for zavegepant is comparable to other CGRP antagonists approved for the same indication. Based on the available safety and efficacy data, risk mitigation beyond labeling is not required. The clinical reviewer recommends enhanced pharmacovigilance for myocardial infarction, stroke, and hepatotoxicity to continue to evaluate long-term safety in the real-world population.

DRM has determined that a REMS is not needed to ensure the benefits of zavegepant outweigh its risks.

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) Zavzpret (zavegepant) is necessary to ensure the benefits outweigh its risks. Biohaven Pharmaceutical Holding Company, Ltd. (hereafter referred to as the Applicant) submitted a New Drug Application (NDA) 216386 for zavegepant with the proposed indication for the acute treatment of migraine with or without aura in adults. This application is under review in the Division of Neurology 2. The Applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Zavzpret (zavegepant), 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.[1,2] CGRP is an endogenous neuropeptide that is a potent vasodilator in the cerebral, coronary, and renal vascular beds.[3] CGRP has been shown to have a role in migraine pathophysiology. Plasma CGRP levels increase during migraine attacks and infusion of CGRP induces migraine-like attacks in susceptible people.[4]

Zavegepant is proposed as a ready-to-use, unit-dose nasal spray delivering 10 mg. The proposed dose is 10 mg given as a single spray in one nostril with a maximum dose of 10 mg (one spray) in a 24 hour period.[1,2] It is intended for acute treatment of migraines and will most likely be administered as needed and primarily in the outpatient setting.[b] The safety of treating more than 8 migraines in a 30-day period has not been established. Zavegepant is not indicated for the preventative treatment of migraine.

If approved, zavegepant would be the first CGRP antagonist available as a nasal spray; however, other CGRP antagonists are available for acute treatment of migraines and for migraine prevention. None of the currently approved CGRP antagonists were approved with a Boxed Warning or REMS. Zavegepant is not currently approved in any jurisdiction.

2.2. Regulatory History

The following is a summary of the regulatory history for 216386 relevant to this review:

- **03/09/2022:** NDA 216386 submission for the acute treatment of migraine with or without aura in adults received.
- **08/24/2022:** A Mid-cycle Communication was issued to the Applicant. The Agency informed the Applicant that "no major safety concerns have been identified; we do not anticipate a need for a REMS at this time." Subsequently, the Applicant canceled the planned Mid-Cycle teleconference with the Agency.
- **12/13/2022:** A late-cycle meeting was held between the Agency and Applicant via teleconference. No safety concerns were discussed.

[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.*

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Migraine is common, chronic neurologic disorder that affects over 1 billion people worldwide.[5] In the United States (US), more than 30 million people have 1 or more migraine headaches per year.[6,c] The one year prevalence of migraine was 18% in women, 6% in men, and 12% overall.[6,7] The prevalence peaks between ages 25-55.[7]

Migraines are a primary headache disorder and are characterized by recurrent attacks of headache that are moderate to severe in intensity with a duration of 4 to 72 hours. Typical characteristics for migraine headaches are unilateral location, pulsating quality, moderate or severe intensity, and aggravation by routine physical activity. Associated symptoms include nausea, vomiting, photophobia, and phonophobia. Migraine can be classified into two types: migraine without aura or migraine with aura.[8] Migraine with aura is characterized by unilateral reversible focal neurologic symptoms such as vision impairment or sensory symptoms that precede or sometimes accompany a headache. The headache attack may be preceded by a prodromal phase which may occur hours or days before the headache and some patients experience a postdromal phase after headache resolution.[8]

Migraines can be serious and debilitating, resulting in physical impairment and inability to perform daily activities such as attending school or work. The Global Burden of Disease Study 2016 ranked migraine as a leading cause of disability worldwide in both males and females under the age of 50 years.[9,d]

3.2. Description of Current Treatment Options

There are several treatments approved for the acute treatment of migraine in adults. Goals of treatment are to reduce pain and associated symptoms and disability associated with attacks with minimal side effects.

Pharmacologic treatment options include simple analgesics such as nonsteroidal anti-inflammatory drugs or acetaminophen; ergot derivatives (dihydroergotamine mesylate and ergotamine tartrate), 5-$HT_{1b/1d}$ receptor agonists[e] (more commonly referred to as triptans); lasmiditan; and CGRP antagonists (ubrogepant and rimegepant).

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[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

Treatment selection often depends on severity of migraine, treatment setting, patient factors, and drug factors.[10] Simple analgesics (NSAIDs and acetaminophen) may be used for mild-to-moderate migraines. For patients with moderate to severe migraines, additional drug classes are available for consideration. Triptans are commonly used for acute migraine treatment as they are available in 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 artery disease, as they may increase risk of myocardial ischemia, infarction, or other cardiac or cerebrovascular events.[11] 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.[10] Lasmiditan, a 5-HT_{1f} agonist, was approved in October 2019 for the acute treatment of migraine with or without aura in adults. Its risks include dizziness, sedation, and serotonin syndrome. The CGRP antagonists ubrogepant and rimegepant were the most recently approved options for acute migraine treatment and may be useful in patients with contraindications or insufficient response to triptans. Based on the available safety data, risks may include hypersensitivity, including delayed reactions with rimegepant. None of the agents approved for acute migraine have required a REMS. See Section 10.2, Appendix A for detailed risk information for FDA-approved agents. In addition, several agents are used off-label for acute treatment of migraine or associated symptoms including antiemetics, NSAIDs, steroids, and antiepileptic agents.

Non-pharmacologic therapies used as adjunct to treat migraine include biofeedback, cognitive-behavioral therapy, relaxation therapy, and nerve stimulation/neuromodulation. There are several neuromodulation devices available for treatment. Neuromodulation devices target different pathways to relieve migraine and include transcranial magnetic stimulation (e.g., Cerena TMS), external trigeminal nerve stimulation (e.g., Cefaly Dual, Relivion), non-invasive vagus nerve stimulation (e.g., GammaCore Sapphire), remote electrical neuromodulation (e.g., Nerivio Migra).

There remains an unmet need for acute treatment options, especially in patients who are unresponsive to current therapies or have contraindications. If approved, zavegepant would be the first non-oral option available in the CGRP class for acute treatment of migraines. A non-oral option is beneficial as many migraine patients experience nausea/vomiting.

4. Benefit Assessment

The efficacy and safety of zavegepant nasal spray for the acute treatment of migraine was demonstrated in two pivotal studies, phase 3 study BHV3500-301 [National Clinical Trial (NCT) 04571060] and Phase 2/3 study BHV3500-201 (NCT 03872453). The two pivotal studies were similar in design: multicenter, randomized, double-blind, placebo controlled, and single-dose trials. The populations studied in the pivotal trials were similar and included adults with history of migraines for at least 1 year and no more than 8 attacks of moderate to severe pain intensity per month within the last 3 months preceding screening. In study BHV3500-301 (hereafter referred to as Study 301), subjects were randomized 1:1 to a single dose of zavegepant nasal spray 10 mg or placebo. Study BHV3500-201 (hereafter referred to as

Study 201) was a dose ranging study with patients randomized in a 1:1:1:1 ratio to either a single dose of zavegepant 5 mg, 10 mg, 20 mg or placebo. Randomization in both studies was stratified by use of prophylactic migraine medications. Both studies were 11 weeks in duration and included a screening phase, treatment phase that could last up to 45 days or until the subject had a moderate to severe migraine, and an end of treatment visit after study drug administration. Subjects received study medication at randomization (baseline visit) and were instructed to self-administer the study drug at the onset of the moderate or severe pain intensity migraine headache.

The co-primary efficacy endpoints for both pivotal trials included the following:

- Pain freedom at 2 hours post dose[f]
- Most bothersome symptom (MBS) freedom at 2 hours post dose[g]

The key secondary endpoints for both pivotal trials included:

- Pain relief at 2 hours post dose
- Return to normal function at 2 hours post dose
- Sustained pain freedom from 2-48 hours post dose
- Phonophobia freedom at 2 hours post-dose
- Photophobia freedom at 2 hours post-dose

Results:[12-14]

This review focuses on the key efficacy and safety data for the proposed dose for marketing, zavegepant 10 mg.[h] The modified intention to treat (mITT) population in both trials included randomized subjects who had a migraine of moderate or severe pain intensity at the time of dosing, took study drug, and had post dose efficacy data. Across the pivotal studies, the mITT population across both pivotal studies included 1014 subjects treated with zavegepant 10 mg and 1047 subjects treated with placebo.

A statistically significant difference was observed for both of the co-primary efficacy endpoints for the zavegepant 10 mg treatment arms compared to placebo in both pivotal trials. The primary efficacy results for the pivotal studies, Study 301 and Study 201, are summarized in Tables 1 and 2, respectively. Key secondary endpoints were significant in Study 301; however, none were statistically significant in any treatment arm in Study 201 compared to placebo.

[f] Pain freedom was assessed using the percentage of subjects with a pain intensity of none at 2 hours post dose. Pain intensity was measured on a 4-point numeric rating scale (0=none; 1=mild; 2=moderate; 3=severe)

[g] MBS freedom was assessed using the percentage of subjects with an MBS (e.g., nausea, phonophobia, and photophobia) that was self-reported before dosing and was absent 2 hours post dose.

[h] In Study 201, statistical significance compared to placebo was observed in the zavegepant 10 mg and 20 mg groups only. The phase 3 trial evaluated only the lowest effective dose, zavegepant 10 mg.

Table 1. Overview of Co-Primary Efficacy Endpoints in Study 301 (mITT population)[13,14]

	Placebo N = 646	Zavegepant 10 mg N = 623
Pain Freedom at 2 hours post dose		
n (%)	96 (14.9)	147 (23.6)
Percentage Difference (zavegepant –placebo)[a]	N/A	8.8
(95% CI)	N/A	(4.5, 13.1)
p-value	N/A	<0.001*
MBS freedom at 2 hours post dose		
n (%)	201 (31.1)	247 (39.6)
Percentage Difference (zavegepant – placebo)[a]	N/A	8.7
(95% CI)	N/A	(3.4, 13.9)
p-value	N/A	0.0012*

Source: Adapted from DN2 Clinical Review and Study 301 CSR, Table 11-1

[a] Stratified by prophylactic migraine medication use at randomization with CMH weighting

*Statistically significant

Table 2. Overview of Co-Primary Efficacy Endpoints in Study 201 (mITT population)[13,14]

	Placebo N = 401	zavegepant 5 mg N = 387	zavegepant 10 mg N = 391	zavegepant 20 mg N = 402
Pain Freedom at 2 hours post dose				
n (%)	62 (15.5)	76 (19.6)	88 (22.5)	93 (23.1)
Percentage Difference (zavegepant – placebo)[a]	N/A	4.2	7.0	7.7
(98.3% CI)	N/A	(-2.3, 10.7)	(0.4, 13.7)	(1.1, 14.3)
p-value	N/A	0.1214	0.0113*	0.0055*
MBS freedom at 2 hours post dose				
n (%)	135 (33.7)	151 (39.0)	164 (41.9)	171 (42.5)
Percentage Difference (zavegepant – placebo)[a]	N/A	5.4	8.3	8.9
(98.3% CI)	N/A	(-2.8, 13.6)	(0.1, 16.5)	(0.7, 17.0)
p-value	N/A	0.1162	0.0155*	0.0094*

Source: Adapted from DN2 Clinical Review and Study 201 CSR, Table 10-1

[a] Stratified by prophylactic migraine medication use at randomization with CMH weighting

* Statistically significant

The Clinical Reviewer concluded that the Applicant provided substantial evidence of effectiveness for zavegepant 10 mg based on data from two adequate and well controlled trials. The clinical reviewer

recommends approval of zavegepant 10 mg nasal spray for the acute treatment of migraine with or without aura in adults.[i,13,14]

5. Risk Assessment & Safe-Use Conditions

The safety database for zavegepant is comprised of the pivotal trials, Study 301 and Study 201, and BHV3500-202 (hereafter referred to as Study 202), an open-label multicenter, long-term safety study. The pivotal studies only included safety data for a single dose of zavegepant nasal spray. The Applicant completed an additional supportive safety study, Study BHV3500-106 (hereafter referred to as Study 106) to evaluate repeat, daily dosing and to evaluate hepatic safety.

Across the pivotal trials, a total of 2079 unique subjects received a single dose of zavegepant 10 mg intranasal (N=1023) or placebo (N=1056). Study 202 included 603 subjects with 2-8 migraines per month and subjects could take 1 dose of zavegepant nasal spray as needed per day up to 8 times per month for up to 52 weeks of treatment.

The most common adverse events (occurring in at least 2% of patients treated with zavegepant nasal spray and greater than placebo) included taste disorder (includes dysgeusia and ageusia), nausea/vomiting, and nasal discomfort.[2]

In the pivotal studies, there were no discontinuations due to treatment emergent adverse events. In the long term safety study, 7.5% of patients had treatment emergent adverse events that led to discontinuation with the most common events being due to dysgeusia (1.5%), nasal discomfort (0.8%), AST increase, (0.8%), ALT increase (0.7%), throat irritation (0.7%), dizziness (0.5%), migraine (0.5%), rhinorrhea (0.5%), and nausea (0.5%).[15]

The serious adverse events (SAEs)[j] and selected adverse events of special interest (AESI) will be discussed in Sections 5.1 and 5.2 below.[k]

[i] 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.*

[j] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

[k] 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.*

5.1. Serious Adverse Events

There were no deaths in the pivotal trials, Study 201 or Study 301 or the long term safety study, Study 202.[15,16]

In the pivotal trials, treatment emergent serious adverse events were reported in 2 patients: one patient with thrombosis on zavegepant 10 mg and report of a vestibular migraine in one patient on placebo. Neither were determined to be related to study drug by the investigator.[15] The clinical reviewer concluded that the thrombosis was unlikely related to zavegepant as the patient had multiple confounding factors.[13]

In the long term safety study (Study 202), 9 patients were reported to have 11 treatment emergent SAEs. Treatment emergent SAEs included appendicitis, herpes zoster meningoencephalitis, pneumonia, bile duct stenosis, concussion, fall, back pain, cerebrovascular accident, multiple sclerosis, pleurisy, and psychogenic pseudosyncope. None were determined related to study drug by the investigator. The clinical reviewer determined most of these SAEs were unlikely to be related to zavegepant. Although there is concern for potential cardiovascular or cerebrovascular safety issues due to inhibition of CGRP, the clinical reviewer concluded that cerebrovascular accident was less likely to be related to zavegepant as the onset of the SAE was 8 days after the last dose, however, it could not be ruled out completely.[13]

5.2. Adverse Events of Special Interest

Since CGRP is a potent vasodilator, there are theoretical safety concerns associated with CGRP antagonism including cardiovascular, cerebrovascular, peripheral vascular, and gastrointestinal effects. In theory, CGRP receptor antagonism during times of ischemia may prevent compensatory vasodilatation from occurring, therefore causing vascular concerns. In addition, based on data from early investigational CGRP inhibitors, hepatotoxicity was also a potential safety concern for zavegepant. Thus, the clinical development program reviewed several pre-specified adverse events of special interest (AESI) related to these theoretical risks.

There were no clear safety signals identified for cardiovascular, cerebrovascular, or peripheral vascular adverse events. However, the clinical reviewer notes the population studied may not be generalizable as studies excluded major cardiovascular disease and only included a limited number of patients older than 65 years. Based on these theoretical risks and the SAEs (the death due to hypertensive cardiovascular disease and SAE of cerebrovascular disease), the clinical reviewer recommends enhanced pharmacovigilance for myocardial infarction and stroke.[13]

5.2.1. Hypersensitivity

Hypersensitivity was identified as an adverse event of special interested in the clinical development program. Hypersensitivity, including facial swelling and urticaria occurred in less than 1% of patients treated with zavegepant.[2] The risk of hypersensitivity will be communicated in Section 5 – Warnings and Precautions of labeling.

5.2.2. Hepatotoxicity

Hepatotoxicity was an AESI based on the termination of clinical development programs for two investigational small molecule CGRP receptor inhibitors due to hepatotoxicity. The pivotal trials for zavegepant monitored for hepatic adverse events; however, these were limited to a single dose of zavegepant. Based on the concerns for potential hepatotoxicity with this drug class, Study 106 was completed to evaluate hepatic safety from repeated oral doses of zavegepant. Study 106 was an open-label multicenter, 8-week safety study evaluating daily dosing of oral zavegepant 100 mg[l] in 364 healthy patients.

DN2 consulted the Division of Hepatology and Nutrition, Drug-induced Liver Injury (DILI) Team to review the cases of elevated aminotransferases seen in the clinical development program.[17] The DILI team reviewed the data from Studies 201, 301, 202 and 106. The DILI reviewer assessed 32 cases of potential DILI across the studies. The consult reviewer assessed that 27 (84%) of the liver injury cases were unlikely related to zavegepant. The remaining cases of probable or possible DILI were mild injuries without hyperbilirubinemia and there were no Hy's Law cases. There was no imbalance in liver enzyme elevations between treatment and comparator arms in the controlled studies; however, these studies only evaluated a single dose of zavegepant. There were modest transaminase elevations in the repeat dose studies (Study 202 and Study 106). The clinical reviewer notes that this would be the first CGRP delivered intranasally, thus bypassing portal circulation on initial pass. However, available nonclinical and clinical data do not suggest a significant risk of DILI associated with zavegepant. Considering this product is proposed to be used as needed for acute treatment of migraines and will be labeled to not exceed 8 doses per month, the DILI reviewer determined there was a low concern for DILI. The DILI reviewer recommended standard pharmacovigilance and no substantial labeling for hepatotoxicity.

The DN2 clinical reviewer recommends enhanced pharmacovigilance for hepatotoxicity based on the possible concerns for hepatotoxicity with this drug class, the modest transaminase elevations in the repeat dose studies, and because patients may use zavegepant more frequently than labeled.

[l] According to the Applicant, oral zavegepant 100 mg daily results in similar exposure as 10 mg daily given intranasally.

6. Expected Postmarket Use

Zavegepant will likely be prescribed primarily in the outpatient setting for use by patients for acute treatment of headaches. The likely prescribers include neurologists, headache specialists, and primary care providers. These prescribers are likely familiar with the CGRP antagonist drug class as there are other agents in this class approved for migraine treatment and prevention.

7. Risk Management Activities Proposed by the Applicant

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

8. Discussion of Need for a REMS

The Clinical Reviewer recommends approval of zavegepant 10 mg nasal spray on the basis of the efficacy and safety information currently available.

Migraine is a common, chronic neurologic condition characterized by recurrent headache attacks with accompanying symptoms of nausea, vomiting, and sensitivity to light and sounds. These attacks may be disabling and impact quality of life. There are several agents approved for the acute treatment of migraines. However, several agents are limited by contraindications in patients with coronary artery disease, peripheral vascular disease, cerebrovascular disease, and uncontrolled hypertension due to vasoconstrictive properties. Additionally, non-oral formulations like nasal sprays offer benefits for patients with concurrent nausea/vomiting. Therefore, there is a need for new options for acute migraine treatment.

The pivotal studies show a significant difference between zavegepant nasal spray and placebo for the co-primary endpoints of pain freedom at 2 hours post dose and MBS freedom at 2 hours post dose.

Although there are theoretical cardiovascular, cerebrovascular, peripheral vascular, and gastrointestinal safety concerns due to the CGRP antagonism, no clear safety signals were identified in the trials. However, limitations to the available data include: limited number of older patients in the trials, exclusion of patients with concurrent cardiovascular disease, and the pivotal controlled trials were single dose studies. The clinical reviewer recommends enhanced pharmacovigilance for myocardial infarction and stroke to monitor safety in the post-market setting. This enhanced pharmacovigilance is similar to other agents within the drug class.

Although none of the currently approved CGRP antagonists have labeling for hepatotoxicity, the potential for hepatotoxicity was evaluated for zavegepant as the clinical development programs for two

investigational CGRP inhibitors were terminated due to hepatotoxicity. The DILI team reviewed cases and concluded there was a low concern for DILI when used as labeled. There were no Hy's Law cases and no imbalances of liver enzyme elevations in the placebo-controlled trials. No labeling for this risk was recommended. The clinical reviewer recommends enhanced pharmacovigilance to monitor hepatic safety in the post-marketing setting with real-world use.

The proposed label for zavegepant will only include a Section 5, Warning and Precaution for hypersensitivity. Hypersensitivity in trials included urticaria and facial swelling which occurred in less than 1% of patients treated with zavegepant. This is consistent with other CGRP antagonists currently approved.

Based on the available safety and efficacy data, this reviewer concludes that a REMS is not necessary to ensure the benefits outweigh the risks. The safety profile is comparable to the other CGRP antagonists approved for the same indication. The clinical team recommends enhanced pharmacovigilance for myocardial infarction, stroke, and hepatotoxicity to continue to evaluate long-term safety in the post-market setting.

9. Conclusion & Recommendations

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

Should the Division of Neurology 2 have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10. Appendices

10.1. References

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10.2. Appendix A: Available Options for Acute Treatment of Migraine[18]

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	**Labeling** – Boxed Warning, Warning & Precautions, and Contraindications

		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.	
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 lasting 4 hours or more when untreated **(almotriptan only)**; acute treatment of	**Warnings and Precautions**[m] Myocardial ischemia, myocardial infarction, and Prinzmetal's angina Arrhythmias Chest/throat/neck/jaw pain, tightness, pressure, or heaviness Cerebrovascular Events (e.g., cerebral hemorrhage, subarachnoid hemorrhage, and stroke) Other vasospasm related events (e.g., gastrointestinal vascular ischemia and infarction, splenic infarction, Raynaud's syndrome) Medication overuse headache: Serotonin syndrome Increase in blood pressure Anaphylactic Reactions	**Labeling** – Warning & Precautions, and Contraindications

[m] Summary of the common Warnings and Precaution in labeling across this class; however, agent-specific differences may exist and full prescribing information is available via Drugs@FDA

	migraine with or without aura in pediatric patients 6 to 17 years of age **(rizatriptan only).**	**Contraindications**[n] Ischemic coronary artery disease or coronary artery vasospasm Wolf-Parkinson-White Syndrome or other cardiac accessary conduction pathway disorders Uncontrolled hypertension 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	
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 – oral tablet)	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
Rimegepant (February 2020 - orally disintegrating tablets)	Acute treatment of migraine with or without aura in adults and preventive treatment of episodic migraine	**Warnings and Precautions** Hypersensitivity Reactions	**Labeling** – Warning & Precautions

[n] Summary of the common contraindications in labeling across this class; however, agent-specific differences may exist and full prescribing information is available via Drugs@FDA

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