CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211765Orig1s000

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	211765
PDUFA Goal Date	December 26, 2019
OSE RCM #	2018-2817
Reviewer Name(s)	Ingrid N. Chapman, PharmD, BCPS
Team Leader	Donella Fitzgerald, PharmD
Deputy Division Director	Jamie Wilkins, PharmD
Review Completion Date	December 17, 2019
Subject	Evaluation of Need for a REMS
Established Name	Ubrogepant
Trade Name	Ubrelvy
Name of Applicant	Allergan Sales, LLC
Therapeutic Class	Calcitonin gene-related peptide antagonist
Formulation(s)	50 mg tablet, 100 mg tablet
Dosing Regimen	Recommended dose; 50 mg or 100 mg taken orally

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Ubrelvy (ubrogepant) is necessary to ensure the benefits outweigh its risks. Allergan Sales LLC submitted a New Drug Application (NDA 211765) for ubrogepant 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. No serious risks related to the use of ubrogepant 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 ubrogepant outweigh its risk for the proposed indication, acute treatment of migraine with or without aura in adults.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Ubrelvy (ubrogepant) is necessary to ensure the benefits outweigh its risks. Allergan Sales LLC submitted a New Drug Application (NDA 211765) for ubrogepant 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 I (DN I). The Applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION[1]

Ubrogepant, 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. Ubrogepant is proposed as 50 mg or 100 mg tablets for oral administration. The recommended dose is 50 mg or 100 mg by mouth once. If needed, a second dose may be administered at least 2 hours after the first dose (maximum daily dose = 200 mg). Treatment is administered as needed.[b] Ubrogepant is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 211765 relevant to this review:

- 12/26/2018: NDA 211765 submission for acute treatment of migraines with or without aura in adults received.
- 06/17/2019: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for ubrogepant.

3 Therapeutic Context and Treatment Options

[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.*

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

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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

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 ubrogepant for the treatment of acute migraine with and without aura was demonstrated in two pivotal phase 3 studies UBR-MD-01 (NCT# 02828020) and UBR-MD-02 (NCT# 02867709). The two studies were similar in design: multicenter, randomized, double-blind, placebo-controlled, single attack efficacy/safety studies. The studies had the same coprimary efficacy endpoints of pain freedom at 2 hours and absence of the most bothersome migraine-associated symptom (MBS) at 2 hours following the initial dose of study drug.[f] Both studies also had the same secondary endpoints: pain relief at 2 hours, sustained pain relief from 2 to 24 hours, and sustained pain freedom from 2 to 24 hours as well as absence of photophobia, phonophobia, and nausea at 2 hours. Patients enrolled in the studies had up to 60 days to treat a single qualifying migraine attack. If the patient had a non-responding migraine or migraine recurrence, an optional blinded second dose of study drug or rescue medication (patient's own) was administered. Also, an additional pharmacokinetic dose of study drug was administered at Visit #3 (Day 4 post-treatment visit).

Both studies enrolled patients 18 to 75 years who had a history of migraine with or without aura for at least 1 year consistent with a diagnosis according to the International Classification of Headache Disorders criteria, 3rd edition, beta version (ICHD-3 beta, 2013), and had a history of having between 2 to 8 migraine attacks with moderate to severe headache pain in each of the 3 months before screening (Visit 1).

The objective of Study UBR-MD-01 was to evaluate the efficacy, safety, and tolerability of two doses of ubrogepant, 50 mg and 100 mg, compared to placebo. Overall, 1327 treated patients recorded a baseline migraine headache severity measurement and at least 1 post-dose migraine headache severity or migraine-associated symptom measurement within 2 hours after dosing (placebo = 456; ubrogepant 50 mg = 423; ubrogepant 100 mg = 448). See Table 1 for study results.

The objective of Study UBR-MD-02 was to evaluate the efficacy, safety, and tolerability of two doses of ubrogepant, 25 mg and 50 mg, compared to placebo. Overall, 1355 treated patients recorded a baseline migraine headache severity measurement and at least 1 post-dose migraine headache severity or migraine-associated symptom measurement within 2 hours after dosing (placebo = 456; ubrogepant 25 mg = 435; ubrogepant 50 mg = 464). See Table 1 for study results.

Table 1:[8] Pivotal Studies Efficacy Results

	Study UBR-MD-01			Study UBR-MD-02		
Co-Primary Endpoints	50 mg n = 423	100 mg n = 448	Placebo n = 456	25 mg n = 435	50 mg n = 464	Placebo n = 456

[f] 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.*

Pain freedom at 2 hrs	81 (19.2%)	95 (21.2%)	54 (11.8)	90 (20.7%)	101 (21.8%)	65 (14.3%)
P-value	0.0017	0.0001	N/A	0.0143	0.0065	N/A
Adjusted P-value	0.0023	0.0003	N/A	0.0285	0.0129	N/A
Absence of the MBS* at 2 hrs	162 (38.6%)	169 (37.7%)	126 (27.8%)	148 (34.1%)	180 (38.9%)	125 (27.4%)
P-value	0.0003	0.0008	N/A	0.0355	0.0005	N/A
Adjusted P-value	0.0023	0.0023	N/A	0.0711	0.0129	N/A

*MBS = most bothersome migraine-associated symptom

The Clinical Reviewer concluded that the treatment effect measured in each of the two pivotal studies was statistically significant for each of the co-primary endpoints for the 50 mg and 100 mg doses. Additionally, the 25 mg dose reached statistical significance for pain freedom at 2 hours, but only nominal significance for absence of MBS at 2 hours. The Clinical Reviewer recommends approval of all three doses of ubrogepant (25 mg, 50 mg, and 100 mg) for the acute treatment of migraine with and without aura in adults. The Clinical Reviewer also stated that the studies demonstrate that all three doses are efficacious for the acute treatment of migraine and the lowest efficacious dose should be made available for patients.[9]

5 Risk Assessment & Safe-Use Conditions

The safety database for ubrogepant is comprised of five Phase 2b/3 studies (including Studies UBR-MD-01 and UBR-MD-02) and 18 Phase 1 clinical pharmacology studies. In the integrated summary of safety (ISS), these studies were analyzed in seven groups.[10]

- **Group 1**: 4 completed, Phase 2b/3, randomized, double-blind, placebo-controlled single-attack studies that evaluated the efficacy, safety, and tolerability of oral ubrogepant in the acute treatment of migraine with or without aura (P006, P007, UBR-MD-01 and UBR-MD-02)
- **Group 1a**: 2 completed, Phase 3 pivotal studies (UBR-MD-01 and UBR-MD-02)
- **Group 2**: 52-week, long-term extension, open-label, multiple-dose safety study (UBR-MD-04, NCT# 02873221) that included participants who completed one of the Phase 3 lead-in studies (UBR-MD-01 or UBR-MD-02)
- **Groups 1 + 2**: Studies P006, P007, UBR-MD-01, UBR-MD-02, and UBR-MD-04; Only participants exposed to ubrogepant are included in the pooling.
- **Group 3**: Study 3110-105-002 (hepatic safety study), a Phase 1 multicenter, randomized, double-blind, placebo-controlled, parallel-group study, which evaluated the safety and tolerability of high-frequency dosing with ubrogepant 100 mg administered intermittently (2 days on and 2 days off) for 8 weeks in healthy participants.
- **Group 4**: Study P004, a Phase 1 single-center, randomized, double-blind, placebo-controlled, multiple-dose study, which evaluated the safety and tolerability of oral doses of ubrogepant 150 mg administered once daily for 28 consecutive days to healthy male participants.

– **Group 5**: Other Phase 1 studies: 14 completed, single- or multiple-dose studies for which there is systemic exposure to ubrogepant.

This review will focus on the primary safety data from the pivotal studies in Group 1a. No serious risks related to the use of ubrogepant were identified during this review.[g] Common adverse events in the studies that occurred in ≥ 1% of ubrogepant-treated patients included viral infections, nausea, somnolence, confusion, dizziness, dry mouth, and abdominal pain.[9]

5.1 DEATHS

There was a single death during the clinical development program. In a phase 1 study, a 35-year-old male died in a road traffic accident. The patient received ketoconazole 400 mg once daily for 5 days with a single dose of ubrogepant 20 mg on day 2 of the 5-day dosing of ketoconazole. The accident occurred 14 days after administration of the last dose of ketoconazole. The investigator considered the event unrelated to dosing with the ubrogepant.[10] The Clinical Reviewer concluded the death was unlikely to be related to the use of ubrogepant due to its half-life of 5-7 hours (expected clearance in less than 3 days).[9]

5.2 HEPATOTOXIC EFFECTS

Because hepatoxic effects were seen in other small molecule CGRP antagonists (no longer in development), the Applicant was asked to conduct a dedicated hepatic safety study.[9] Study 3110-105-002 included 516 patients who received at least one dose of ubrogepant with 468 patients completing the entire treatment phase. Treatment-emergent hepatic adverse events were low, and similar in both treatment groups. There were no clinically meaningful mean changes from baseline in aspartate transaminase, alanine transaminase, total bilirubin, or alkaline phosphatase. There were no cases of Hy's law.[9] The proposed label does not include information related to hepatotoxic effects.[1]

6 Expected Postmarket Use

Ubrogepant 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 ubrogepant including nausea, dry mouth, and somnolence.

7 Risk Management Activities Proposed by the Applicant

The applicant did not propose any risk management activities beyond labeling and routine pharmacovigilance for ubrogepant.

[g] 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.*

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of ubrogepant based on the efficacy and safety information currently available. The pivotal studies demonstrate that all three doses of ubrogepant are efficacious for the acute treatment of migraine.

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. Ubrogepant offers an additional option to treat acute migraine with a different mechanism of action and no known serious risks. Healthcare providers prescribing ubrogepant are likely to be familiar with managing the common adverse events of ubrogepant including nausea, dry mouth, and somnolence. DRM recommends that, should ubrogepant be approved, a REMS is not necessary to ensure its benefits outweigh its risk for the acute treatment of migraine with or without aura.

9 Conclusion & Recommendations

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

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10.2 TABLE: TREATMENT OPTIONS FOR MIGRAINE[11]

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)	Acute treatment of migraine with or without aura in adults; acute	**Warnings and Precautions (rizatriptan)** Myocardial ischemia, myocardial infarction, and Prinzmetal's angina Arrhythmias Chest/throat/neck/jaw pain, tightness, pressure, or heaviness	**Labeling** – Warning & Precautions, and Contraindications

Frovatriptan (2001) Naratriptan (1998) Rizatriptan (1998) Sumatriptan (1992) Zolmitriptan (1997)	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 migraine with or without aura in pediatric patients 6 to 17 years of age **(rizatriptan only).**	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 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

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