CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761077Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Reviewer Name(s)	Laura Zendel, PharmD, Division of Risk Management (DRISK)
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Review Completion Date	May 17, 2018
Subject	Evaluation of Need for a REMS
Established Name	Erenumab
Trade Name	Aimovig
Name of Applicant	Amgen, Inc
Therapeutic Class	Calcitonin Gene-Related Peptide (CGRP) Receptor Blocker
Formulation(s)	Subcutaneous Injection
Dosing Regimen	70 mg or 140 mg once monthly

Reference ID: 4264817

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Aimovig (erenumab) is necessary to ensure the benefits outweigh its risks. Amgen submitted a Biologic Licensing Application (BLA 761077) for erenumab with the proposed indication for prevention of migraine in adults. The risks associated with erenumab include a theoretical risk of calcitonin gene related peptide (CGRP) antagonism that could lead to major adverse cardiovascular events (MACE) and theoretical risk of liver toxicity. The applicant did not submit a REMS with this application (b) (4) [redacted].

DRISK and the Division of Neurology Products agree that a REMS is not needed to ensure the benefits of erenumab outweigh its risks. The theoretical risk of CGRP antagonism that could lead to MACE was not apparent in the clinical studies as cases of MACE were limited and confounded with other plausible alternative etiologies. Most adverse events were mild or moderate in severity; there was no discernable pattern of adverse events that led to discontinuation, and no safety concerns were identified. The impact of use of erenumab during pregnancy remains unknown; (b) (4) [redacted] Based on the safety profile and efficacy demonstrated in the clinical trials, the benefit-risk profile is acceptable and risk mitigation beyond labeling is not required.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Aimovig (erenumab) is necessary to ensure the benefits outweigh its risks. Amgen, Inc submitted a Biologic Licensing Application (BLA) 761077 for erenumab with the proposed indication for prevention of migraine in adults. This application is under review in the Division of Neurology Products (DNP). The applicant did not submit a REMS with this application (b) (4) [redacted].

2 Background

2.1 PRODUCT INFORMATION

Erenumab, a new molecular entity[a] and first in its class, is an anti-calcitonin gene-related peptide (CGRP) receptor antibody proposed for the indication of prophylaxis of migraine in adults. Erenumab injection is a human immunoglobulin G2 (IgG2) monoclonal antibody that has high affinity binding to the CGRP receptor. CGRP is a potent vasodilator in the cerebral, coronary, and renal vascular beds.[1] CGRP has

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

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been shown to have a role in migraine pathophysiology. Plasma CGRP levels increase during migraine attacks and infusion of CGRP has been shown to induce migraine-like attacks in susceptible people.[2] Erenumab competes with the binding of CGRP and inhibits the function of CGRP at its receptor. The proposed dosing of erenumab is 70 mg or 140 mg once monthly administered using a single dose prefilled syringe or auto-injector by subcutaneous route. The product is intended to be prescribed for prophylaxis of both episodic and chronic forms of migraine for patient self-administration. Erenumab is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761077 relevant to this review:

- 5/17/2017: BLA 761077 submission received
- 11/1/2017: A Mid-cycle meeting was held between the Agency and the Applicant. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for erenumab
- 2/14/2018: A Late-cycle meeting was held between the Agency and the Applicant. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for erenumab

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Migraine is a common disorder that affects up to 12% of the general population in the United States and tends to run in families.[3] Migraine is more common in women of prime working and childbearing age[b], with the highest prevalence among women aged 30-39 years.[4] Migraine is characterized by recurrent headaches that last 4-72 hours and is often accompanied by symptoms such as nausea, vomiting, sensitivity to light and sound, and can be aggravated by routine physical activity. Migraine is typically categorized based on the frequency of migraine days per month. Episodic migraine (EM) is defined as less than 15 migraine days per month, while chronic migraine (CM) is defined as 15 or more headache days per months, at least eight of which are typical migraine days.[5] The headache attack may be preceded by nonspecific prodromes such as irritability, drowsiness, or photo/phonophobia, or warning systems, known as aura, immediately prior to the headache and is followed by a nonspecific postdrome phase with symptoms such as fatigue, poor concentration, and depressed mood that can last several days. Migraine can result in physical impairment and the inability for patients to perform everyday

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

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activities such as attending school or work, and functioning socially with disability increasing with higher attack frequency.[c,6,7]

3.2 Description of Current Treatment Options

There are several FDA approved therapies for migraine prophylaxis, as well as many other drugs that are used off-label. FDA approved therapies include the anticonvulsants divalproex sodium and topiramate, the beta-blockers, propranolol and timolol, and the neuromuscular blocking agent, onabotulinumtoxin A (CM only). The American Academy of Family Physicians considers divalproex, valproic acid, propranolol, timolol, topiramate, and the antidepressant, amitriptyline, as first-line agents for pharmacologic migraine prophylaxis.[8] Frovatriptan, naratriptan, and zolmitriptan have shown some evidence of effectiveness in prevention of menstrually related migraine and are also approved as acute treatment for migraine. Other medications have shown some efficacy in the prevention of EM or CM, but are not FDA approved for this indication (see Appendix 10.1).[9]

The currently FDA-approved treatments all have some limitations. They all have a modest effect at reducing the frequency of migraine headaches, however, most patients will continue to have migraines even on therapeutic doses of effective medication. Except for onabotulinumtoxin A, all must be taken at least daily and up to three times daily for propranolol. Onabotulinumtoxin A requires 31 injections in the head and neck, and needs to be administered every three months. Several of the available prophylactic medications have some intolerable side effects such as fatigue, nausea, difficulty thinking, and trouble functioning making it difficult for some patients to justify continuing to take a daily medication that does not completely prevent migraines, however, none require a REMS. Existing treatments are associated with variable efficacy and tolerability and were not originally developed for migraine prevention. As such, the treatment armamentarium would benefit from therapeutic options that are more efficacious and better tolerated.

4 Benefit Assessment

Erenumab was evaluated for prevention of migraine in two pivotal phase 2/3 studies, study 20120295[d] in chronic migraine and study 20120296 (NCT02456740) in episodic migraine as well as a supportive study, 20120297[e], in episodic migraine. All studies enrolled patients with a history of migraine, with and without aura, according to the International Classification of Headache Disorders (ICHD-III) diagnostic

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[c] 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.*

[d] Study 20120295, a Phase 2 study, was initially designed as a dose-ranging study with 70 mg and 140 mg doses, but was amended to meet the standards for it to serve as a pivotal study. NCT02066415

[e] Study 2012097 was designed as a pivotal study evaluating the efficacy of erenumab at the 70 mg dose, but the Applicant considered it supportive in this marketing application. The review team has reviewed the study in support of the 70 mg dose. NCT02483585

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criteria and allowed subjects to use acute headache treatments including triptans, ergotamine derivatives and non-steroidal anti-inflammatory drugs (NSAIDs) during the studies. Patients with a history of medication overuse[f] or on other chronic migraine therapy were excluded.

Safety data was integrated from two phase 2 studies (20120178 in EM, NCT01952574, and 20120295 in CM including its open label extension, 20130255, NCT02174861) and two phase 3 studies (20120296 and 20120297).

Study 20120295 was a randomized, multi-center, 12-week, placebo-controlled, double blind study. Patients with a history of chronic migraine with or without aura (≥15 headache days/month with ≥8 migraine days/month) were randomized 2:1 to receive placebo or erenumab 140 mg subcutaneous injections monthly for 12 weeks. The primary outcome measure was the change from baseline at month 3 in monthly migraine days. Secondary outcomes included the achievement of 50-100% reduction in monthly migraine days from baseline (≥ 50% responders) and change from baseline in monthly acute migraine-specific medication days.

Studies 20120296 and 20120297 were multicenter, randomized, double-blind, placebo-controlled, parallel group studies evaluating erenumab for prevention of episodic migraine. Patients with a history of migraine, with or without aura, for a duration of ≥ 12 months and 4-14 migraine days/month were included. In study 20120297, subjects were randomized 1:1 to receive either erenumab 70 mg, or placebo by subcutaneous injection monthly for 3 months. The double blind treatment period was followed by a 28 week open-label period which included a single arm of 70 mg which was followed by an 8 week safety follow-up period. In Study 20120296, subjects were randomized 1:1:1 to erenumab 70 mg, erenumab 140 mg, or placebo by subcutaneous injection monthly for 6 months. The double blind treatment period was followed by an additional 28-week active treatment period where subjects were re-randomized 1:1 to 70 mg or 140 mg and were blinded to the actual dose received. The active treatment period was followed by a 12 week safety follow up.

The primary objective was to evaluate the effect of erenumab compared to placebo on the change from baseline in monthly migraine days in patients with episodic migraine and to evaluate the safety and tolerability of erenumab. Secondary outcome measures included the achievement of a 50-100% reduction in mean monthly migraine days from baseline (≥ 50% responders), change from baseline in mean monthly acute migraine-specific medication days and change from baseline in the two Migraine Physical Function Impact Diary (MPFID)[g] domains scores: physical impairment (PI) and impact on everyday activities (EA).

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[f] Medication overuse was defined during the baseline period as the following: ≥ 15 days of simple analgesics, ≥ 10 days of triptans, ≥ 10 days of ergots, ≥ 10 days of combination therapy intake of any combination of ergots, triptans, opiates, combination-analgesic medications or simple analgesics

[g] Migraine Physical Function Impact Diary (MPFID) is a patient reported outcomes instrument that measures the impact of migraine of physical functioning. It contains 13 items evaluating the impact of migraine during the previous 24 hours on two physical function concepts of interest: impact on everyday activities (EA) and physical impairment (PI), and one global item assessing the overall impact on everyday activities. Patients rate the duration

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Results of Study 20120295

A total of 667 patients were randomized to receive erenumab 70 mg (n=191), erenumab 140 mg (n=190) or placebo (n=286). The mean migraine frequency at baseline was approximately 18 migraine days per month and was similar across treatment groups. Erenumab treatment demonstrated statistically significant and clinically meaningful improvements from baseline at month 3 compared to placebo. Efficacy results are summarized in Table 1.

Table 1: Efficacy Results in Study 20120295 at Month 3

	Erenumab 70 mg n = 191	Erenumab 140 mg n = 190	Placebo n = 286
Monthly Migraine Days (MMD)			
Change from baseline	-6.6	-6.6	-4.2
Difference from placebo	-2.5	-2.5	
p-value	<0.001	<0.001	
≥ 50% MMD Responders			
% Responders	39.9%	41.2%	23.5%
p-value	<0.001	<0.001	
Monthly acute migraine-specific medication days[h]			
Change from baseline	-3.4	-4.1	-1.6
Difference from placebo	-1.9	-2.6	
p-value	<0.001	<0.001	

n = number of patients who received at least 1 dose of investigational product and completed at least 1 post-baseline monthly eDiary measurement

Results of Study 20120296

A total of 955 patients were randomized to erenumab 70 mg (n = 317), erenumab 140 mg (n = 319) or placebo (n = 319). The mean migraine frequency at baseline was approximately 8 migraine days per month and was similar across treatment groups. Erenumab treatment demonstrated improvements from baseline during months 4-6 compared to placebo. Efficacy results are summarized in Table 2.

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of impact or level of difficulty associated with migraine on a daily basis. Monthly MPFID scores are averaged over days with and without migraine; higher scores indicate worse impact on the EA and PI domains.

[h] Migraine-specific medications include triptans and ergotamine derivatives

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Table 2: Efficacy Outcomes at Months 4-6 in Study 20120296

	Erenumab 70 mg n = 317	Erenumab 140 mg n = 319	Placebo n = 319
Monthly Migraine Days (MMD)			
Change from baseline	-3.2	-3.7	-1.8
Difference from placebo	-1.4	-1.9	
p-value	<0.001	<0.001	
≥ 50% MMD Responders			
% Responders	43.3%	50%	26.6%
p-value	<0.001	<0.001	
Monthly Acute Migraine-Specific Medication Days			
Change from baseline	-1.1	-1.6	-0.2
Difference from placebo	-0.9	-1.4	
p-value	<0.001	<0.001	
MPFID Physical Impairment Domain			
Change from baseline	-4.2	-4.8	-2.4
Difference from placebo	-1.9	-2.4	
p-value	<0.001	<0.001	
MPFID Impact on Everyday Activities Domain			
Change from baseline	-5.5	-5.9	-3.3
Difference from placebo	-2.2	-2.6	
p-value	<0.001	< 0.001	

n = number of patients who received at least 1 dose of investigational product and completed at least 1 postbaseline monthly eDiary measurement

Results of Study 20120297

A total of 577 patients were randomized to receive either placebo (n = 291) or erenumab 70 mg (n = 286). The mean migraine frequency at baseline was approximately 8 migraine days per month and was similar across treatment groups. There was a small, but statistically significant mean reduction in the change from baseline in the erenumab 70 mg arm as compared to placebo. Efficacy results are summarized in Table 3. Two secondary endpoints related to the MPFID did not reach statistical significance.

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Table 3: Efficacy Outcomes at Weeks 9-12 in Study 20120297

	Erenumab 70 mg n = 286	Placebo n = 291
Monthly Migraine Days (MMD)		
Change from baseline	-2.9	-1.8
Difference from placebo	-1.1	
p-value	<0.001	
≥ 50% MMD Responders		
% Responders	39.7%	29.5%
p-value	0.010	
Monthly Acute Migraine-Specific Medication Days		
Change from baseline	-1.2	-0.6
Difference from placebo	-0.6	
p-value	0.002	

n = number of patients who received at least 1 dose of investigational product and completed at least 1 postbaseline monthly eDiary measurement

For all three studies, the primary endpoint was reduction from baseline in the number of monthly migraine days compared to placebo and for all three studies, there was a statistically significant difference seen for both the 70 mg and 140 mg doses. The Applicant concluded that erenumab showed consistent efficacy across the studies in EM and CM as well as consistent efficacy over time across a range of endpoints. In the EM and CM pivotal studies that evaluated both 70 mg and 140 mg doses, the Applicant states that greater efficacy was seen with the 140 mg dose. Onset of efficacy with erenumab was observed within the first week of treatment and efficacy was durable over time. The clinical reviewer concluded that erenumab 70 mg and 140 mg were both found to be effective in reducing monthly migraine days in patients with episodic and chronic migraine. On average, patients experienced a 1 to 2.5 day reduction in the number of headache days per month when subtracting out the effect of placebo. The treatment effect seen in these trials is similar to the treatment effect seen in clinical trials for other approved products for migraine prophylaxis.[i]

5 Risk Assessment & Safe-Use Conditions

Erenumab was evaluated for safety in 2537 subjects with migraine who received at least one dose of erenumab, representing 2310.3 patient years of exposure. Safety data was integrated from two phase 2 studies (20120178 in EM and 20120295 in CM including its open label extension, 20130255) and two

[i] The treatment effect seen in divalproex and topiramate ranged from 1 to 2.2 day reduction in monthly migraine days which is similar to onabotulinum toxin A with a 1.4 to 2.3 day reduction from baseline in monthly headache days.

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phase 3 studies (20120296 and 20120297). The safety data was grouped into four pools which include 787 subjects who received 70 mg and 507 subjects who received 140 mg once monthly for 12 weeks. Pool A included 12-week placebo-controlled data collected in the first 3 months of the double-blind, placebo-controlled phases from studies 20120178, 20120295, 20120296, and 20120297. This pool provides an assessment of short-term safety due to availability of controlled data. Pool B included 24-week placebo-controlled data from the double-blind phase of study 20120296. Pool C included the first dose of 70 mg or 140 mg of erenumab through the data cut-off, inclusive of the double blind and open-label extension/active treatment phases. Pool D included subjects with continuous exposure to erenumab 70 mg or 140 mg for a minimum of 1 year through the data cutoff.

Most AEs were mild or moderate in severity. The most common AE was injection site reactions which occurred in 23 (4.5%) subjects who received erenumab 140 mg compared to 33 (3.2%) of subjects who received placebo. The majority of injection site reactions were grade 1 in severity and no subjects treated with erenumab discontinued due to injection site reactions in the 12-week placebo-controlled period of studies. Other common AEs included constipation, muscle spasm, and pruritus. The rates of adverse events leading to discontinuation of investigational product were low and similar across treatment groups. There was no discernable pattern of adverse events that led to discontinuation and no safety concerns were identified.

During the placebo-controlled, randomized period (up to week 12; Pool A), the percentages of subjects reporting serious adverse events (SAEs)[j] were similar across treatment groups with no evidence of a dose-dependent pattern or trend for certain types of events (1% to 1.7% of subjects in the placebo or erenumab treatment groups in the integrated safety data set), with most events reported in single subjects only. SAEs reported by more than one subject in the erenumab treatment groups were cholelithiasis, intervertebral disc protrusion, and migraine (reported for 2 subjects each, 0.1%). Review of SAEs in pools B, C, and D did not reveal any safety concerns. The most frequent adverse events leading to discontinuation in > 1 subject receiving erenumab in Pool A included arthralgia, fatigue, metrorrhagia, palpitations, positional vertigo, and upper abdominal pain (2 subjects each, 0.1%). No patterns in adverse events leading to discontinuation were observed in Pools B, C, and D. A single case of acute liver injury was reviewed from Phase 2 study 20160349 (section 5.2)

The clinical reviewer stated that no serious safety issues related to the use of erenumab were identified and erenumab has an acceptable safety profile for the migraine population. Safety issues have not been adequately evaluated in the population 65 and older, or in patients with major cardiovascular disease.

[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.

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5.1 THEORETICAL RISK OF CGRP ANTAGONISM: MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)

As CGRP is a vasodilator in addition to its role as a modulator of pain transmission, inhibition of the CGRP receptor may pose a theoretical cardiovascular safety risk by interfering with compensatory vasodilation, particularly in the context of the coronary circulation during ischemia-related diseases/conditions. Additionally, migraine is associated with an increased risk of cardiovascular disease, with a stronger association in young women with migraine with aura.[10] Results from the American Migraine Prevalence and Prevention study suggest that migraine was also associated with increased risk of total stroke.[11]

The Applicant concluded that cardiovascular and cerebrovascular events were uncommonly reported; 19 (0.9%) in the 70 mg group and 9 (0.8%) in the 140 mg group in pool C, integrated safety analysis set. The review of the individual cardiovascular cases found that all had confounding factors and there was no notable pattern in type of events or time to onset. Two deaths were reported, one in study 20120178 and the other in 20120296. The causes of death were reported as arteriosclerosis for one subject and heart failure due to arrhythmogenic cardiomyopathy for the other subject. The investigators determined that neither death was related to the study drug and the deaths do not represent a safety signal. DNP consulted the Division of Cardiovascular and Renal Products (DCRP) for further evaluation of the cardiac deaths[12]. The cardiology reviewer stated that both deaths have confirmed non-drug related explanations at post-mortem exam, neither of which appears to be related to drug therapy. The clinical reviewer stated that a relationship between erenumab and these events cannot be entirely ruled out, but is not considered likely. The clinical reviewer also notes that the clinical trials included generally younger, healthier patients and excluded patients over age 65. Patients with major pre-existing cardiovascular disease were effectively excluded. The clinical reviewer recommends a post-marketing requirement to study safety and efficacy in patients over age 65 enriched with patients with major pre-existing cardiovascular disease.

DNP consulted DCRP a second time to review the literature[13] and render an opinion regarding strength and quality of published evidence concerning possible vascular risk with CGRP antagonism. DCRP concluded that there is consensus from well performed nonclinical models that CGRP is a potent microvascular vasodilator. These studies suggest that CGRP is one of multiple redundant control mechanisms of regional and tissue specific blood flow, and that lack of vasodilation from blocking this pathway does not result in tissue-threatening vasoconstriction. For example, CGRP is a vasodilator in coronary arteries, but its antagonism does not induce vasoconstriction nor affect the extent of ischemia secondary to coronary artery stenosis nor vasodilation secondary to a short period of ischemia (reactive hyperemia). Therefore, if CGRP plays a role in coronary flow regulation, there are redundant systems to override inhibition of this modulator. There were several limitations in the literature review including that almost all the coronary flow data derives from in vivo canine studies and most of the studies were old as these types of experiments are currently uncommon. DCRP was unable to find clinical safety data on the effect of CGRP receptor blockers in subjects diagnosed with known Prinzmetal's Angina or severe multi-vessel coronary artery disease. Given the limitations of the current datasets, DCRP suggests that post-marketing assessment of cardiovascular event rates comparing subjects being treated with triptans

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compared to patients being treated with CGRP receptor antagonists be considered using a Sentinel approach.

The review team considered additions to the Warnings and Precautions section of labeling to include information about the theoretical risk of CGRP antagonism. DNP sought input and guidance from the Medical Policy Council (MPC) regarding the need for description in labeling of a theoretical risk of ischemia with CGRP blockade in patients with underlying vascular disease on April 20, 2018. The possible theoretical cardiovascular or cerebrovascular risks of prolonged antagonism of CGRP including worsening of ischemia due to impairment of compensatory vasodilation in the setting of ischemic vascular events and interference with the process of ischemic preconditioning, i.e., brief periods of ischemia and reperfusion prior to prolonged ischemia and reperfusion were discussed. The MPC concluded that the literature review and animal data are not suggestive of adverse outcomes and that there is insufficient evidence to include this theoretical risk in labeling at this time. Therefore, the theoretical risk of ischemia with CGRP blockade will not be included in the labeling.

5.2 HEPATIC EFFECTS

The development of the small-molecule-gepant class of CGRP receptor antagonists was stopped due to the risk of potential liver toxicity after continuous exposure.[14] Although hepatotoxicity was considered an off-target effect, the potential hepatotoxic effect of erenumab was assessed. A total of 13/1785 (0.7%) subjects exposed to erenumab 70 mg and 3/644 (0.4%) who received erenumab 140 mg for 3 months experienced ALT > 3 times the upper limit of normal (ULN). A total of 3/1025 (0.3%) subjects exposed to erenumab 70 mg and 3/644 (0.4%) dosed with erenumab 140 mg for 3-6 months experienced ALT > 3x ULN. A total of 7/1042 (0.7%) subjects exposed to erenumab 70 mg and 4/556 (0.7%) dosed with erenumab 140 mg for 6-12 months experienced ALT > 3x ULN. Some patients were found to have alternative etiologies for the transaminase elevations such as alcoholic hepatitis and hemangioma, while a few patients did not have any attributable etiology for liver enzyme elevations. The Applicant concluded that the clinical data do not reveal any evidence of potential hepatotoxicity.

One subject experienced acute hepatitis 10 days after a single dose of erenumab during phase 2 study 20160349 as evidenced by biochemical testing and a clinical picture consistent with hepatocellular injury. This was the only Hy's Law case observed in the clinical program. The pattern of injury was consistent with drug induced liver injury (DILI) but was confounded by the use of other hepatotoxic drugs (i.e. amoxicillin-clavulanate). DNP consulted the Division of Gastroenterology and Inborn Errors Products (DGIEP) for further evaluation of the potential DILI[15]. The hepatology reviewer believes an unidentified cause may be the most likely explanation. The second most likely explanation is a bile duct stone, with erenumab or amoxicillin as unlikely culprits. DGIEP recommends considering a Limitation of Use statement in labeling for patients with pre-existing liver disease, as there are no data to support use of erenumab in patients with hepatic impairment. DGIEP also recommends including in labeling that if a patient experiences liver-related symptoms such as jaundice, right upper quadrant abdominal pain, nausea, or vomiting, this may be indicative of serious liver injury and should lead to discontinuation of erenumab.

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6 Expected Postmarket Use

Erenumab is expected to be prescribed by specialists and used primarily by patients in an outpatient setting. The proposed dose is 70 mg or 140 mg by subcutaneous injection for self-administration monthly. Patients and their caregivers should be trained on how to prepare and administer erenumab prior to use, according to the Instructions for Use.

7 Risk Management Activities Proposed by the Applicant

Amgen proposes [redacted] (b) (4)

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of erenumab on the basis of the efficacy and safety information currently available.

Migraine is a common, chronic neurologic condition with a broad spectrum of frequency and severity. It is characterized by recurrent headache attacks with accompanying symptoms of nausea, vomiting, photophobia, and phonophobia. These attacks are of moderate to severe intensity and can at times be disabling and impact the quality of patients' lives. There are several FDA approved drugs for the prophylaxis of migraine. They have limitations related to tolerability and to their frequency or route of administration.

The efficacy of erenumab was demonstrated in three randomized clinical trials. Two trials were conducted in episodic migraine and one trial conducted in chronic migraine. Both erenumab 70 mg and 140 mg demonstrated reduction in monthly migraine days as compared to placebo. In episodic migraine trials, patients had a baseline of about 8 migraines per month. Erenumab reduced monthly migraine days by about 1-2 days compared to placebo. In the chronic migraine trial, patients had a baseline of about 18 migraines per month. Erenumab reduced monthly migraine days by about 2-3 days compared to placebo.

No major, serious toxicities were identified in the clinical trials. Most AEs were mild or moderate in severity. The most common AE was injection site reactions and other common AEs included constipation, muscle spasm, and pruritus. There was no discernable pattern of adverse events that led to discontinuation and no safety concerns were identified. A theoretical risk of ischemia with CGRP blockade and MACE exists with the use of erenumab. A relationship between erenumab and MACE events observed in the clinical trials is considered unlikely, but cannot be ruled out, however at the time of this review, will not be addressed in labeling as the review team currently has not determined this to be beyond a theoretical risk to the studied patient population. As most of the patients in the study were under age 65, the review team is also recommending a PMR to study safety and efficacy in patients over

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the age of 65 enriched with patients with major pre-existing cardiovascular disease and for a pregnancy registry study. In addition, the review team is recommending PMRs to further evaluate the effect of erenumab on pregnancy outcomes. These PMRs combined with routine pharmacovigilance and product labeling will further clarify the risks associated with erenumab in the postmarketing setting.

Based on the data available, the risks associated with erenumab do not require a REMS for the benefits of the drug to outweigh its risks. Therefore, DRISK is not recommending a REMS for the management of the risks of erenumab therapy.

9 Conclusion & Recommendations

Based on the available data, the benefit-risk profile is favorable therefore, a REMS is not necessary for erenumab to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

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

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10 Appendices

10.1 Summary of Treatment Options for Prevention of Migraine[k]

Brand (generic)		Route	Warnings & Precautions	REMS/Boxed Warning/MG
Beta Blockers				
Inderal LA, Inderal (propranolol)		Oral	Heart Failure, bronchospastic disease, pheochromocytoma, major surgery, diabetes/hypoglycemia, hepatic impairment, thyrotoxicosis, anaphylactic reactions, peripheral vascular disease, calcium channel blockers	None
Not FDA Approved for this indication	Toprol XL, Lopressor (metoprolol)	Oral		Boxed Warning (Ischemic heart disease)
	(Timolol)	Oral		None
	Tenormin (Atenolol)	Oral		None
	Corogard (Nadolol)	Oral		None
	Bystolic (Nebivolol)	Oral		None
Antiepileptics				
Depakote ER, Depakote (divalproex sodium)		Oral	Hepatoxicity, teratogenicity, pancreatitis, suicidal behavior or ideation, bleeding/hematopoietic disorders, hyperammonemia, hypothermia, drug reaction with eosinophilia and systemic symptoms (DRESS), somnolence	Boxed Warning (hepatotoxicity, teratogenicity, pancreatitis)
Depakene (valproic acid)		Oral		Medication Guide, Boxed Warning (hepatotoxicity, teratogenicity, pancreatitis)
Qudexy XR, Trokendi XR, Topamax (topiramate)		Oral	Acute myopia and secondary angle closure glaucoma, visual field defects, oligohydrosis and hyperthermia, metabolic acidosis, suicidal behavior and ideation, cognitive/neuropsychiatric, fetal toxicity, withdrawal effects, hyperammonemia and encephalopathy, kidney stones, hypothermia with concomitant valproic acid use	Medication Guide
Not FDA Approved for this indication	Carbatrol, Tegretol, Tegretol XR, Epitol, Equetro, Teril (Carbamazepine)	Oral	Serious dermatologic reactions, Steven's Johnson Syndrome with HLH-B*1502 allele, hypersensitivity reactions with HLA-A*3101 allele, aplastic anemia and agranulocytosis, DRESS, suicidal behavior and ideation	Medication Guide, Boxed Warning (Serious dermatologic reactions, Aplastic Anemia and Agranulocytosis)

[k] Medications included in the table have at least Level C evidence (possibly effective) per the American Headache Society and American Academy of Neurology.

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Antidipressants (SSRI/SSNRI/TCA) *Not FDA Approved for this indication*			
(amitriptyline)	Oral	Clinical worsening and suicide risk, serotonin syndrome, elevations in blood pressure, abnormal bleeding, angle closure glaucoma, activation of mania/hypomania	Medication Guide, Boxed Warning (suicidality)
Effexor XR (venlafaxine)	Oral		Medication Guide, Boxed Warning (suicidality)
ACE Inhibitors *Not FDA approved for this indication*			
Zestril, Prinivil, Qbrelis (Lisinopril)	Oral	Anaphylactoid reaction/angioedema, renal impairment, hypotension, hyperkalemia, hepatic failure, fetal/neonatal morbidity and mortality	Boxed Warning (Fetal Toxicity)
Angiotensin receptor blockers *Not FDA Approved for this indication*			
Atacand (Candesartan)	Oral	Hypotension, renal impairment, hyperkalemia	Boxed Warning (Fetal Toxicity)
Alpha-Agonists *Not FDA Approved for this indication*			
Catapres, Kapvay (Clonidine)	Oral	Bradycardia, hypotension, syncope, somnolence, cardiac conduction abnormalities	None
Intuniv, Tenex (Guanfacine)	Oral		None
Antihistamines *Not FDA Approved for this indication*			
Periactin (Cyproheptadine)	Oral	Somnolence, blood dyscrasias, caution in patients with bronchial asthma, increased intraocular pressure, hyperthyroidism, cardiovascular disease, hypertension	None
Neuromuscular Blocker			
Botox **OnabotulinumtoxinA**	Injection	Potency units of Botox are not interchangeable with other preparations of botulinum toxin products. Spread of toxin effects, swallowing and breathing difficulties, potential serious adverse reactions after botox injections for unapproved uses, concomitant neuromuscular disorder may exacerbate clinical effects, caution in patients with compromised respiratory function, corneal exposure and ulceration due to reduced blinking, retrobulbar hemorrhage and compromised retinal circulation, bronchitis and upper respiratory tract infections, urinary tract infections and urinary retention.	Medication Guide, Boxed Warning (distant spread of toxin effect)

10.2 References

[1] Russel F, King R, Smilie S, Kodji X, and S Brain. Calcitonin Gene-Related Peptide: Physiology and Pathophysiology. Physiol Rev. 2014, Oct; 94(4):1099-1142

Reference ID: 4264817

[2] Hansen J, Hauge A, Olesen J, M Ashina. Calcitonin Gene-Related Peptide Triggers Migraine-Like Attacks in Patients with Migraine with Aura. Cephalalgia. 2010 Oct; 30(10):1179-1186

[3] Litpon RB, Bigal ME, Diamond M, et al. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology. 2007; 68:343-349

[4] Lipton RB, Stewart WF, Diamond S, et al. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. Headache 2001; 41:646

[5] Headache Classification Committee of the International Headache Society (HIS). The Internal classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013;33:629-808

[6] Holland S, Silberstein SD, Freitag F, et al. Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology. 2012;78:1346-1353.

[7] Ramadan NM, Silberstein SD, Freitag FG, et al. Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management for prevention of migraine [online]. Available at: http://tools.aan.com/professionals/practice/pdfs/gl0090.pdf Accessed 5/31/2017

[8] Modi S, Lowder DM. Medications for Migraine Prophylaxis. American Family Physician. 2006;73(1):72-78

[9] Silberstein SD, Holland S, Freitag F, et al. Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology. 2012;78:1337-1345

[10] Burley DS, Hamid SA, Baxter GF. Cardioprotective actions of peptide hormones in myocardial ischemia. Heart Fail Rev. 2007;12:279-291

[11] Bigal ME, Kurth T, Santanello N, et al. Migraine and cardiovascular disease: a population based study. Neurology. 2010;74:625-35

[12] Dunnmon, P. Division of Cardiovascular and Renal Products (DCRP) consult for BLA 761077. Dated November 13, 2017.

[13] Dunnmon P, Koerner J. Division of Cardiovascular and Renal Products (DCRP) consult for BLA 761077. Dated April 7, 2018.

[14] Tepper SJ, Cleves C. Telcagepant, a calcitonin gene-related peptide antagonist for the treatment of migraine. Curr Opin Investig Drugs. 2009;10(7):711-720

[15] Mehta, R. Division of Gastroesterology and Inborn Errors Products (DGIEP) consult for BLA 761077. Dated November 16, 2017

Reference ID: 4264817

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