Erenumab-aooe

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Abstract

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Keywords

formulary management/P&T, drug information, neurology

Generic Name: ERENUMAB-AOOE

Proprietary Name: *Aimovig* (Amgen/Novartis)

Approval Rating: 1S

Therapeutic Class: Calcitonin Gene-Related Peptide Receptor Monoclonal Antibodies

Similar Drugs: None

Sound- or Look-Alike Names: Almotriptan, *Arava*, *Eraxis*, *Erelzi*, Erlotinib, *Vimizim*, *Vimpat*, *Vimovo*

Indications

Erenumab-aooe, previously known as AMG 334, is Food and Drug Administration (FDA)-approved for the preventive treatment of migraine in adults.¹

Clinical Pharmacology

Calcitonin gene-related peptide (CGRP) is a peptide expressed in the peripheral and central nervous systems.^{2,3} At nerve endings located on cerebral vascular smooth muscle, CGRP is a potent proinflammatory peptide that is released from the trigeminal ganglia neurons, resulting in vasodilation of the cranial vasculature.²⁻⁵ CGRP receptors are found in the vasculature, trigeminal sensory afferents, trigeminal ganglion, and trigeminal nucleus caudalis.^{2,4,5} CGRP modulates vascular nociception and acts as a neurotransmitter in the trigeminal ganglion and second-order neurons in the trigeminal nucleus caudalis to facilitate nociceptive transmission.^{2,3} CGRP has high affinity for the CGRP receptor and calcitonin receptor–like receptor/receptor activity–modifying protein 1 (RAMP1) complex, which is composed of the calcitonin receptor–like receptor and the RAMP1. It also has high affinity

for the amylin receptor AMY1 and the calcitonin receptor/RAMP1 complex.²

Elevated blood and salivary CGRP levels occur in patients with migraines, cluster headaches, facial pain disorders, trigeminal neuralgia, chronic paroxysmal hemicrania, trigeminal neuralgia, and rhinosinusitis. Levels are elevated during a migraine attack and between migraine attacks in patients with chronic migraines. In studies to determine the role of elevated CGRP levels in patients with migraine headaches (ie, causative or secondary to migraine), exogenous CGRP infusions were shown to trigger migraine attacks. In addition, elevated CGRP levels predict patient response to treatment with triptans and dihydroergotamine mesylate in those with acute migraine attacks, and to onabotulinumtoxinA in those with chronic migraines. Monoclonal antibody therapies targeting the CGRP receptor have shown efficacy in episodic and chronic migraine prevention.²

Erenumab-aooe is a human immunoglobulin G2 (IgG2) monoclonal antibody produced from Chinese hamster ovary cells.^{1,2} Erenumab-aooe is specific and selective to CGRP receptors exerting action by full competitive inhibition of the receptor.^{2,3,6} Erenumab-aooe at maximal doses did not have any antagonist or agonist activity on human adrenomedullin, calcitonin, and amylin receptors.^{2,3}

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Table 1. Pharmacokinetic Parameters of Erenumab-aooe (Standard Deviation).¹

	Erenumab-aooe 70 mg Subcutaneously once monthly	Erenumab-aooe 140 mg Subcutaneously once monthly
C_{max} (mean) ^a	6.1 µg/mL	15.8 µg/mL
AUC_{last} (mean) ^a	159 µg day/mL	505 µg day/mL
C_{min}		
Episodic migraine	5.7 µg/mL	12.8 µg/mL
Chronic migraine	6.2 µg/mL	14.9 µg/mL

Note. C_{max} = peak serum concentrations; C_{min} = trough serum concentration; AUC = area under the curve.

^aFrom a single-dose study.

Animal studies have determined the trigeminal ganglion is not protected by the blood-brain barrier, so it may not be necessary for a drug like erenumab-aooe to cross the blood-brain barrier to be effective.⁷

Approximate molecular weight of erenumab-aooe is 150 kDa.¹

Pharmacokinetics

Erenumab-aooe exposure is increased more than dose proportionally at doses ranging from 1 mg to 70 mg, while exposure increases are approximately dose proportional at doses ranging from 70 mg to 210 mg; this nonlinear profile is a result of binding to the CGRP receptor.^{1,6} Peak serum concentrations (C_{max}) and area under the curve (AUC) are affected by patient dose requirements (see Table 1).¹ Doses from 1 to 70 mg achieved a more than 2000-fold increase in mean AUC_{last} (from 0.0851 to 171 µg day/mL), whereas a 3-fold increase in erenumab-aooe dose from 70 mg to 210 mg caused a 3.8-fold increase in mean AUC_{last} (from 171 to 652 µg day/mL). Maximal drug concentrations increased from 0.0077 µg/mL to 6.25 µg/mL for doses of 1 mg to 70 mg, and from 6.25 µg/mL to 15.2 µg/mL following an increase in erenumab-aooe dose from 70 mg to 210 mg.⁶ Median time to peak serum concentration following a single subcutaneous erenumab-aooe dose of 70 mg or 140 mg is achieved in approximately 6 days.¹ Mean volume of distribution during the terminal phase was 3.86 L after a single intravenous dose of 140 mg.¹

Multiple dosing of erenumab-aooe resulted in mean accumulation ratios ranging from 1.42 to 1.69 across all doses in healthy patients, and from 1.5 to 1.78 across all doses in patients with migraine.⁶

Serum trough concentrations approach steady state by 3 months following routine dosing. The effective half-life of erenumab-aooe is 28 days.¹

Two elimination phases were observed for erenumab-aooe. At low concentrations, elimination is predominantly through saturable binding to target CGRP receptors. At higher concentrations, the elimination is mainly though a nonspecific, nonsaturable proteolytic pathway.¹

Pharmacokinetic parameters are not affected by age, gender, race, or subtypes of migraine spectrum (episodic or chronic

migraine). Population pharmacokinetic analysis based on clinical trial data shows patients with mild or moderate renal impairment did not demonstrate any pharmacokinetic differences. Effects of severe renal impairment (less than 30 mL/min/1.73 m²) have not been studied. Effects of hepatic impairment on pharmacokinetics of erenumab-aooe have not been evaluated. Renal or hepatic impairment is not expected to affect erenumab-aooe pharmacokinetics.¹

Comparative Efficacy

Indication: Prevention of Episodic Migraine and Chronic Migraine

Guidelines

Guideline: The 2012 American Headache Society/American Academy of Neurology (AHS/AAN) guidelines for prevention of episodic migraine: a summary and comparison with other recent clinical practice guidelines

Reference: AHS/AAN, 2012⁸

Comments: Updated AHS/AAN guidelines for the preventive treatment of episodic migraine summarize and compare key recommendations of 2 other recent migraine prevention guidelines from the Canadian Headache Society and the European Federation of Neurological Societies. The 3 guidelines provide similar recommendations and support use of topiramate, divalproex/sodium valproate, propranolol, and metoprolol as first-line therapies based on the highest level of evidence. Recommendations regarding the use of gabapentin and feverfew differed substantially among the guidelines. Erenumab-aooe was not evaluated in any of the guidelines.

Studies

Drug: Erenumab-aooe vs Placebo

Reference: Goadsby PJ et al, 2017 (STRIVE trial)^{1,9,10}

Study Design: Randomized, double-blind, multicenter, multinational, placebo-controlled study

Study Funding: Amgen

Patients: A total of 955 patients with a history of episodic migraines (with or without aura) for at least 12 months

according to International Headache Society criteria (ie, 4 to less than 15 migraine days per month on average across the 3 months prior to screening and during baseline, less than 15 migraine days per month on average over the 3 months prior to screening and during baseline, and at least 80% compliance with an eDiary). Exclusion criteria included age older than 50 years at migraine onset, history of cluster headache or hemiplegic migraine headache, inability to differentiate migraines from other headaches, no therapeutic response with more than 2 medication categories for prophylactic treatment of migraine after an adequate therapeutic trial, or concomitant use of 2 or more medications with possible migraine prophylactic effects within 2 months prior to the start of the baseline phase or during the baseline phase. Baseline mean number of monthly migraine days (MMDs) was 8.3.

Intervention: Patients were randomized 1:1:1 to receive subcutaneous injections of erenumab-aooe 70 mg, erenumab-aooe 140 mg, or placebo once a month for 6 months. If the patient was using only 1 prophylactic medication at baseline and the dose was stable for at least 2 months prior to the start of the baseline phase, it could be continued throughout the study.

Results

Primary End Point(s)

- Mean reduction in MMD from baseline was −3.2 days with erenumab-aooe 70 mg ($P < .001$ vs placebo), −3.7 days with erenumab-aooe 140 mg ($P < .001$ vs placebo), and −1.8 days with placebo during weeks 13 to 24.

Secondary End Point(s)

- Reduction in MMD of 50% or more was achieved by 43%, 50%, and 27% of patients in the erenumab-aooe 70 mg, erenumab-aooe 140 mg, and placebo groups, respectively ($P < .001$ for both erenumab-aooe groups vs placebo). The number needed to treat (NNT) was 6.3 for erenumab-aooe 70 mg versus placebo and was 4.4 for erenumab-aooe 140 mg versus placebo.
- Monthly acute migraine-specific medication days were reduced by −1.1, −1.6, and −0.2 days per month in the erenumab-aooe 70 mg, erenumab-aooe 140 mg, and placebo groups, respectively ($P < .001$ for both erenumab-aooe groups vs placebo).
- Change in scores for physical impairment and impact on everyday activities, as measured using the Migraine Physical Function Impact Diary (MPFID): Physical impairment scores were improved compared with placebo (−4.2, −4.8, and −2.4 points in erenumab-aooe 70 mg, erenumab-aooe 140 mg, and placebo groups, respectively [$P < .001$ for both erenumab-aooe groups

vs placebo]). Everyday activities scores were also improved (−5.5, −5.9, and −3.3 points in erenumab-aooe 70 mg, erenumab-aooe 140 mg, and placebo groups, respectively [$P < .001$ vs placebo]).

Other End Point(s)

- Exploratory patient-reported outcome values showed improvements from baseline in quality of life, disability, and migraine-related impact on life. In addition, there was a trend toward better numerical changes in these parameters with erenumab-aooe 140 mg compared with erenumab-aooe 70 mg.¹¹

Comments: The study was conducted in Austria, Belgium, Canada, Czechia, Finland, Germany, the Netherlands, Poland, Slovakia, Sweden, Turkey, the United Kingdom, and the United States. Erenumab-aooe adverse reactions and tolerability were similar to placebo. The efficacy results from this study confirmed the results in phase 2 studies with once-monthly administration of erenumab-aooe 70 mg or 140 mg in patients with episodic and chronic migraines.¹²⁻¹⁴

Limitations: Study results are only available in the form of a meeting abstract, the prescribing information, and on ClinicalTrials.gov.

Reference: Dodick D, et al, 2017 (ARISE trial)^{1,15,16}

Study Design: Randomized, double-blind, phase 3 study

Study Funding: Amgen

Patients: A total of 577 adults with a history of episodic migraines, high migraine frequency, and compliance with the eDiary. Exclusion criteria included age older than 50 years at migraine onset, history of cluster headaches or hemiplegic migraine headaches, inability to differentiate migraines from other headaches, no therapeutic response with more than 2 categories for prophylactic treatment of migraine after an adequate therapeutic trial, concomitant use of 2 or more medications with possible migraine prophylactic effects within 2 months prior to the start of the baseline phase or during the baseline phase, use of botulinum toxin, active chronic pain syndromes (eg, fibromyalgia, chronic pelvic pain), history of major psychiatric disorder or seizure disorder or other significant neurological conditions other than migraine, history of HIV infection or myocardial infarction, stroke, transient ischemic attack, unstable angina, or coronary artery bypass surgery or other revascularization procedure within 12 months prior to screening. Baseline mean number of MMDs was 8.3.

Intervention: Patients were randomized 1:1 to receive subcutaneous injections of placebo or erenumab-aooe 70 mg once a month for 3 months. If the patient was using only 1 prophylactic medication at baseline and the dose was stable for at least 2 months prior to the start of the baseline phase, it could be continued throughout the study.

Results

Primary End Point(s)

- Mean reduction in MMD from baseline was -2.9 days with erenumab-aooe compared with -1.8 days in the placebo arm ($P < .001$) during weeks 9 to 12.

Secondary End Point(s)

- Reduction in MMD of 50% or more was achieved by 40% and 30% of patients in the erenumab-aooe and placebo groups, respectively (odds ratio = 1.6; $P = .01$); NNT was 10.
- Monthly acute migraine rescue medication use was reduced by a mean of -1.2 days in the erenumab-aooe group and -0.6 days in the placebo group ($P = .002$).
- Proportion of patients achieving improvement (reduction of 5 points or more) in physical impairment and impact on everyday activities scores, measured using the MPFID was not statistically higher with erenumab-aooe compared with placebo (33% vs 27% [$P = .13$] and 40% vs 36% [$P = .26$]).

Other End Point(s)

- Exploratory patient-reported outcome values showed improvements in quality of life, disability, and migraine-related impact on life.¹⁷

Comments: The study was conducted in the United States, Denmark, France, Greece, Portugal, the Russian Federation, Spain, and Switzerland. The safety profile of erenumab-aooe was similar to placebo. Patients completing this trial were offered enrollment in a 28-week open-label extension trial.

Limitations: Study results are available in the form of a meeting abstract, the prescribing information, and on ClinicalTrials.gov.

Contraindications, Warnings, and Precautions

Contraindications

The prescribing information states there are no contraindications to use of erenumab-aooe.¹ Although not stated in the product labeling, hypersensitivity reactions to erenumab-aooe or any components of the formulation (acetate, polysorbate 80, and sucrose) should be considered.

The needle shield of the prefilled autoinjector and the needle cap of the prefilled syringe both contain dry natural rubber (derived from latex), which may be problematic for some patients with a history of such allergies.¹

Warnings and Precautions

Anti-erenumab-binding antibodies have been detected; however, the clinical importance of this has not been determined.^{1,6,13,14} No correlation was found between the development of neutralizing antibodies and the development of adverse effects.^{1,13}

Erenumab-aooe use in pregnant women has not been adequately assessed. No adverse effects on offspring of pregnant monkeys administered supratherapeutic doses of erenumab-aooe were observed, with serum exposures approximately 20 times that in humans at a dose of 140 mg once monthly. Women with migraine may have an increased risk of developing preeclampsia during pregnancy.¹

There are no data to assess the presence of erenumab-aooe in human breast milk or its effects on breastfeeding infants or milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for erenumab-aooe and any potential adverse effects on the breastfed infant from erenumab-aooe or from the underlying maternal condition.¹

Safety and effectiveness in pediatric patients have not been established.¹ Postmarketing studies are required in patients 6 to 17 years of age to determine efficacy and safety.¹⁸

There are insufficient data regarding use of erenumab-aooe in elderly patients to determine whether response is different than in younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.¹

The carcinogenic potential of erenumab-aooe has not been assessed.¹

Genetic toxicology studies assessing mutagenesis of erenumab-aooe have not been conducted.¹

Adverse Reactions

Adverse effects associated with erenumab-aooe and occurring at an incidence of 3% or greater were injection-site reactions (5% to 6%) and constipation (1% to 3%).¹ Other clinical trials have reported other adverse reactions such as arthralgia, back pain, headache, gastroenteritis, influenza-like illness, diarrhea, nausea, nasopharyngitis, and upper respiratory tract infections.^{6,10,13,14,16}

There is no apparent evidence of increased risk of cardiovascular outcomes or changes in blood pressure associated with erenumab-aooe.^{1,13}

Drug Interactions

Erenumab-aooe is not metabolized by cytochrome P450 enzymes; therefore, interactions with coadministered

medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.¹

Erenumab-aooe does not alter the pharmacokinetics of estrogen/progestin combination oral contraceptives, and no change in contraceptive efficacy is expected.¹⁹

Recommended Monitoring

No special monitoring is required for use of erenumab-aooe.¹ However, the FDA is requesting postmarketing surveillance for liver toxicity, myocardial infarction, and stroke after exposure to erenumab-aooe.¹⁸

Dosing

The recommended erenumab-aooe dosage is 70 mg subcutaneously once monthly. Some patients may benefit from a higher dose (140 mg) once monthly, which is administered as 2 consecutive 70 mg subcutaneous injections.¹

Erenumab-aooe is intended for patient self-administration. Patients or caregivers should be instructed on proper subcutaneous injection administration technique, including aseptic technique, and how to use the supplied autoinjector or prefilled syringes. Erenumab-aooe prefilled autoinjectors and prefilled syringes are single-dose only, and methods for proper disposal of used syringes and autoinjectors should be followed.¹

Prior to self-administration, erenumab-aooe should be removed from the refrigerator and allowed to sit at room temperature, protected from sunlight, for at least 30 minutes. No additional heat source such as hot water or microwave should be used to bring erenumab-aooe to room temperature. Erenumab-aooe should not be shaken; visually inspect for particulate matter or solution discoloration prior to subcutaneous administration.¹

Recommended injection sites are the abdomen, thigh, or the upper arm. Erenumab-aooe should not be injected into areas where the skin is tender, bruised, red, or hard.¹

Missed doses should be administered as soon as possible, with the subsequent dose given 1 month later.¹

Product Availability

The Biologics License Application for erenumab-aooe was submitted to the FDA in May 2017 and was approved in May 2018.^{18,20}

Erenumab-aooe is available as a sterile, clear to opalescent, colorless to light yellow, preservative-free solution in a single-dose prefilled autoinjector and single-dose prefilled glass syringe. Each 1 mL prefilled syringe or autoinjector contains 70 mg of erenumab-aooe, 1.5 mg of acetate, 0.1 mg of polysorbate 80, and 73 mg of sucrose. The solution has a pH of 5.2. The needle shield within the cap of the prefilled autoinjector and gray needle cap of the prefilled syringe contain dry natural rubber.¹

Erenumab-aooe is packaged as packs containing 1 or 2 syringes or autoinjectors. Patients requiring 140 mg dosing should receive the pack containing two 70 mg/mL prefilled syringes or autoinjectors.¹

Erenumab-aooe should be refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until time of use. It should not be frozen or shaken.¹

Once removed from the refrigerator, erenumab-aooe should be kept at room temperature (up to 25°C [77°F]) in the original carton and used within 7 days. If more than 7 days have elapsed since the pack was removed from the refrigerator, erenumab-aooe should be discarded.¹

Drug Safety/Risk Evaluation and Mitigation Strategy (REMS)

No REMS is required for erenumab-aooe.¹⁸

Conclusion

Erenumab-aooe, a human IgG2 monoclonal antibody with specific and selective activity on CGRP receptors, is approved for the preventive treatment of migraine in adults. It has demonstrated the potential to reduce MMDs in patients with episodic or chronic migraines. Overall, data from clinical trials indicate that erenumab-aooe is well tolerated.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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