Therapeutic Class Overview
Calcitonin gene related peptide (CGRP) inhibitors

INTRODUCTION

- Migraine is a common, recurrent, incapacitating disorder characterized by moderate to severe headaches and disabling features, including nausea, vomiting, neurologic symptoms, photophobia, and phonophobia (*International Headache Society [IHS] 2013, Starling et al 2015).*
- There are 4 phases of a migraine attack, although not all migraine attacks unfold into all 4 phases. These phases include prodrome, development of aura, the headache phase, and postdrome. Combined, all 4 phases can last anywhere between 3 and 5 days (*Burgos−Vega et al 2015).*
- The pathophysiology of migraines is assumed to involve the activation of trigeminal sensory nerves, which triggers the release of vasoactive neuropeptides including CGRP, neurokinin A, and substance P. CGRP is involved in migraine pathophysiology through nociceptive mechanisms in the trigeminovascular system. CGRP is a vasodilator and is found at higher concentrations during a migraine attack. Vasodilation of dural blood vessels may occur with extravasation of dural plasma, resulting in inflammation *(Goadsby et al 2017, Starling et al 2015, Silberstein et al 2012)*.
- The International Classification of Headache Disorders (ICHD) defines chronic migraine as ≥ 15 headache days per month for > 3 months with the features of migraine headache for at least 8 migraine days per month (MMD). The most common cause of symptoms suggestive of chronic migraine is medication overuse. According to the ICHD, around 50% of patients apparently with chronic migraine revert to an episodic migraine type after drug withdrawal; such patients are in a sense wrongly diagnosed with chronic migraine. In most clinical trials, migraine that is not chronic (ie, with < 15 headache days per month) is considered to be episodic migraine, although the condition is not clearly defined in the ICHD (*IHS 2013, Silberstein et al 2008, Starling et al 2015*).
- Migraines have a global prevalence of 15 to 18% and are a leading cause of disability worldwide. Chronic migraine is estimated to occur in 2 to 8% of patients with migraine, whereas episodic migraine occurs in more than 90% of patients (*Global Burden of Disease Study [GBD] 2016, IHS 2013, Lipton et al 2016, Manack et al 2011*).
- Treatments for migraines are divided into acute and preventive therapies. Evidence and reputable guidelines clearly delineate appropriate therapies for episodic migraine treatment and prophylaxis; options stretch across a wide variety of therapeutic classes and are usually oral therapies. For the prevention of migraines, treatment options include oral prophylactic therapies, injectable prophylactic therapies, and neuromodulator devices. Guidelines discourage the overuse of acute headache therapies, including analgesics, triptans, and ergots, which can precipitate medication overuse headache. Additionally, opioids and barbiturates should not be prescribed as they may contribute to the development of chronic daily headache (*American Migraine Foundation [AMF] 2017, Edvinsson et al 2017, IHS 2013, Silberstein et al 2008, Silberstein et al 2012, Simpson et al 2016, Starling et al 2015)*.
  - Oral prophylactic therapies have modest efficacy (with reduction estimates of 1.5 headaches/month to standard mean differences of −0.57 from baseline [*Jackson et al 2015*]); however, certain oral therapies may not be appropriate for individual patients due to intolerability or eventual lack of efficacy.
  - Onabotulinumtoxin A (Botox), the first injectable drug approved for the prophylaxis of chronic migraine, has been found to be ineffective for the prophylactic treatment of episodic migraines.
  - Other options include devices which leverage electrical, temperature−altering, or magnetic approaches to treatment (ie, Cefaly, SpringTMS, and gammaCore); these devices are considered to have no significant adverse events known or expected.
- Aimovig (erenumab−aooe) is a first−in−class CGRP inhibitor. Other CGRP inhibitors under clinical development include:
  - Fremanezumab (administered subcutaneously [SC] monthly or quarterly) and galcanezumab (administered SC monthly), which are anticipated to be FDA−approved in September 2018 (*BioPharmCatalyst 2018, Eli Lilly press release 2018, House 2018, Teva press release 2018*).
  - Eptinezumab (administered intravenously) and atogepant (the first oral CGRP inhibitor), which are anticipated to pursue the indication for prevention of migraines with potential 2019 FDA−approval dates (*Alder press release 2018, Allergan press release 2018*).
- Medispan class: Migraine products – monoclonal antibodies; Calcitonin gene−related peptide (CGRP) receptor antagonists

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Aimovig (erenumab−aooe)	–

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Aimovig (erenumab−aooe)
Prevention treatment of migraine in adults	✔

(*Aimovig prescribing information 2018)*

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The approval of erenumab−aooe was based on 4 pivotal trials in approximately 2500 patients with episodic or chronic migraine subtypes and 2 incomplete, open−label extension (OLE) trials with data from interim analyses in published and unpublished formats.
  - The episodic migraine program included 3 trials in 1778 episodic migraine patients. All patients had a history of 4 to 14 MMD:
    - The STRIVE trial was a 6−month, double−blind (DB), placebo−controlled (PC), multi−center (MC), Phase 3 trial in which 955 patients with episodic migraine were randomized to placebo (n = 319), erenumab−aooe 70 mg (n = 317), or erenumab−aooe 140 mg (n = 319) once monthly. A total of 2.5 to 3.1% of patients had current use of add−on preventive therapy during the trial. Patients with medication overuse were not permitted. The primary endpoint was the change in mean MMD from baseline to months 4 to 6, which favored treatment with erenumab−aooe 70 mg (mean change vs placebo, −1.4; 95% confidence interval [CI], −1.9 to −0.9; $p < 0.001$) and erenumab−aooe 140 mg (mean change vs placebo, −1.9; 95% CI, −2.3 to −1.4; $p < 0.001$). Erenumab−aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 70 mg vs placebo, 16.7%; odds ratio [OR], 2.13; difference for 140 mg vs placebo, 23.4%; OR, 2.81). Erenumab−aooe was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 70 mg vs placebo, −0.9; difference for 140 mg vs placebo, −1.4) (*Goadsby et al 2017*).
    - The ARISE trial was a 12−week, DB, PC, MC, Phase 3 trial in which 577 patients with episodic migraine were randomized to placebo (n = 291) or erenumab−aooe 70 mg (n = 286) once monthly. A total of 5.5 to 6.6% of patients had current use of add−on preventive therapy during the trial. Patients with medication overuse were not permitted. The primary endpoint was the change in MMD from baseline to weeks 9 to 12, which favored treatment with erenumab−aooe 70 mg (mean change vs placebo, −1.0; 95% CI, −1.6 to −0.5; $p < 0.001$). Compared to placebo, erenumab−aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference, 10.2%; OR, 1.59). Erenumab−aooe was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference, −0.6) (*Dodick et al 2018*).
    - The LIBERTY trial was a currently unpublished, 12−week, DB, PC, MC, Phase 3b trial in which 246 patients with episodic migraine who failed 2 to 4 prior preventive migraine treatments were randomized to placebo (n = 125) or erenumab−aooe 70 mg (n = 121) once monthly. Erenumab−aooe significantly increased the primary endpoint, the proportion of patients with ≥ 50% reduction in MMD from baseline to the last 4 weeks of DB treatment (weeks 9 to 12) over placebo (difference, 16.6%; OR, 2.73; 95% CI, 1.43 to 5.19; $p = 0.002$). Compared to placebo, a total of 5.9% more patients treated with erenumab−aooe 140 mg reported a 100% reduction in MMD, or migraine cessation. Erenumab 70 mg/month compared with placebo significantly reduced the MMD (difference, −1.61; 95% CI, −2.70 to −0.52; $p = 0.004$). Erenumab−aooe was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference, −1.73) (*Reuter et al 2018*).

- The chronic migraine program included 1 trial in 667 chronic migraine patients. All patients had a history of ≥ 15 MMD (baseline average, 17.8 to 18.2):
  - *Tepper et al* was a 12−week, DB, PC, MC, Phase 2 trial in which 667 patients with chronic migraine were randomized to placebo (n = 286), erenumab−aooe 70 mg (n = 191), or erenumab−aooe 140 mg (n = 190) once monthly. No patients were allowed current use of add−on preventive therapy during the trial. Patients with medication overuse were permitted to participate. The primary endpoint was the change in MMD from baseline to weeks 9 to 12, which favored treatment with erenumab−aooe 70 mg and erenumab−aooe 140 mg (mean change for both doses vs placebo, −2.5; 95% CI, −3.5 to −1.4; p < 0.0001). Erenumab−aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 70 mg vs placebo, 17%; OR, 2.2; difference for 140 mg vs placebo, 18%; OR, 2.3). Of note, these outcomes were not dose−dependent. Both erenumab−aooe 70 mg (difference, −1.9) and erenumab−aooe 140 mg (difference, −2.6) significantly reduced the mean acute migraine−specific medication days; however, the higher 140 mg dose had a greater reduction numerically over placebo and reductions may be dose−dependent (*Tepper et al 2017*).
- Two 5−year OLE trials are currently underway in patients with episodic and chronic migraine:
  - Episodic migraine patients from a 12−week, DB, PC parent study continued within an OLE study and received erenumab−aooe 70 mg monthly up to 5 years, of which an interim analysis of data was published with data at 1 year. Of 472 patients in the parent study, 383 (81.1%) remained in the OLE and 307 (80.2%) completed 1 year of treatment. Patients had 8.8 MMDs at parent study baseline. After 3 months of treatment in the parent study, the number of MMDs was reduced to 6.3 days (mean change, 2.5). After a total of 16 months of treatment, the number of MMDs was reduced to 3.7 days (mean change, 5.1). After 64 weeks, a total of 65% (n = 184) of episodic migraine patients achieved a ≥ 50% reduction in MMD and 26% (n = 73) had achieved a 100% reduction in MMDs or migraine−free status (*Ashina et al 2017*).
  - Caution should be exercised in interpreting results from extension trials. The open−label design may contribute to biased reports. Extension trials may have biased outcomes because those experiencing benefit are included in extension trials; however, results are useful for reporting trends in treatment.

CLINICAL GUIDELINES

- According to the American Academy of Neurology and American Headache Society (AAN/AHS) − Evidence−based guideline update on the pharmacologic treatment for episodic migraine prevention in adults (*Silberstein et al 2012*), the following medications are effective preventive treatment options (see Appendix A for a definition of classifications):
  - Level A (established efficacy and > 2 Class I trials):
    - Antiepileptic drugs: divalproex sodium, sodium valproate, and topiramate
    - Beta blockers: metoprolol, propranolol, and timolol
    - Triptans (for menstrual related migraine [MRM]): for short−term prophylaxis, frovatriptan
  - Level B (probably effective and 1 Class I or 2 Class II trials):
    - Antidepressants: amitriptyline and venlafaxine
    - Beta blockers: atenolol and nadolol
    - Triptans (for MRM): for short−term prophylaxis, naratriptan and zolmitriptan
  - Level C (possibly effective and 1 Class II trial):
    - Angiotensin−converting enzyme (ACE) inhibitors: lisinopril
    - Angiotensin II receptor blockers (ARBs): candesartan
    - Alpha agonists: clonidine and guanfacine
    - Antiepileptic drugs: carbamazepine
    - Beta blockers: nebivolol and pindolol
    - Antihistamines: cyproheptadine
- The AAN recommends onabotulinumtoxin A as an effective treatment option that should be offered for chronic migraine. However, onabotulinumtoxin A is considered ineffective for the treatment of episodic migraines and should not be offered. There is insufficient evidence to compare the effectiveness of botulinum neurotoxin A with that of oral prophylactic topiramate (*Simpson et al 2016*).

SAFETY SUMMARY

- There are no contraindications or warnings and precautions associated with erenumab−aooe.

- The most common adverse reactions (% difference from placebo) observed in erenumab−aooe studies included injection site reactions (erenumab−aooe 70 mg, 3%; erenumab−aooe 140 mg, 2%) and constipation (erenumab−aooe 70 mg, 0%; erenumab−aooe 140 mg, 2%).
  - Across studies, adverse effects were generally mild and/or similar to placebo with 1.3% of patients treated with erenumab−aooe discontinuing treatment due to adverse events during trials.
- CGRP is a vasodilator and is found at higher concentrations during a migraine attack. The long−term implications of prolonged CGRP inhibition are not fully established and safety has not been fully characterized for erenumab−aooe.
  - In the 1−year interim analysis of the OLE study, 2 patients had severe adverse events (an arteriosclerosis event and a myocardial ischemia event), of which 1 was fatal and 1 was confounded by sumatriptan administration (*Ashina et al 2017*).
- There are no adequate data on the risks associated in patients who are pregnant, nursing, or in adolescent or pediatric populations. Caution should be exercised in these populations.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Aimovig (erenumab−aooe)	Injection	SC	Once monthly	May be self−administered by patients in the abdomen, thigh, or upper arm. Latex−sensitive patients may have an allergic reaction to the needle shield within the white cap and the gray needle cap of the syringe. There are no data in pregnant women or breastfed infants. A benefit/risk assessment should be taken into consideration prior to administering.

See the current prescribing information for full details

CONCLUSION

- Migraine is a common, recurrent, incapacitating disorder characterized by moderate to severe headaches and disabling features, including nausea, vomiting, neurologic symptoms, photophobia, and phonophobia. Migraines have a spectrum of frequency and severity that can significantly affect the quality of life of patients (*IHS 2013, Silberstein et al 2008, Starling et al 2015*).
- Guidelines have not been updated to include the CGRP inhibitors. Current evidence−based prophylactic treatment options and guidance are limited for chronic migraine, and oral prophylactic medications prescribed for episodic migraine are often used also for the preventive treatment of chronic migraine. Prophylactic migraine treatment options include oral agents (mainly anti−seizure agents, antidepressants, and beta blockers), injectable agents (onabotulinumtoxin A for chronic subtypes only), or neuromodulation devices for migraine or headache attacks (ie, Cefaly, Spring TMS, gammaCore). There is no optimal prophylactic migraine therapy and head−to−head trials are lacking (*AMF 2017, Silberstein et al 2012, Simpson et al 2016*).
- Erenumab−aooe is a first−in−class CGRP inhibitor with limited long−term data. Compared to placebo, erenumab−aooe has consistently demonstrated modest, but statistically significant, reductions in MMDs ranging from 1 to 2.5 days after 3 to 6 months of treatment. Overall, the odds for a 50% reduction in MMDs were approximately 2 times higher with erenumab−aooe than placebo. There are no head−to−head studies with erenumab−aooe and no prophylactic migraine agent is clearly superior to others (*Ashina et al 2017, Dodick et al 2018, Goadsby et al 2017, Reuter et al 2018, Tepper et al 20117*).

- CGRP is a vasodilator and is found at higher concentrations during a migraine attack. The long−term implications of prolonged CGRP inhibition are not fully established and safety has not been fully characterized for erenumab−aooe *(Ashina et al 2017, Goadsby et al 2017, Starling et al 2015).*
- Lack of information during pregnancy and breastfeeding is a consideration as many migraine patients are women of childbearing potential. The unknown risks of monoclonal antibodies and the effects on certain vascular conditions are not fully characterized. Important co−morbid populations which suffer migraines were excluded from trials (eg, patients with anxiety, depression, hypertension, or fibromyalgia), which also limits the generalizability to broader groups. Based on current data, the safety profile of erenumab−aooe is generally mild with the most common adverse effects observed being constipation and injection site reactions.
- Overall, erenumab−aooe represents another therapy option in the prevention of episodic or chronic migraines. Based on currently available evidence and the mild safety profile of erenumab−aooe, this product may have a role in a subset of patients unable to tolerate established oral prophylactic therapies.

APPENDIX

- **Appendix A. AAN levels of evidence classification** *(Gronseth et al 2011)*

Rating of recommendation	
A	Established as effective, ineffective, or harmful for the given condition in the specified population
B	Probably effective, ineffective, or harmful for the given condition in the specified population
C	Possibly effective, ineffective, or harmful for the given condition in the specified population
U	Data inadequate or conflicting; given current knowledge, treatment is unproven.
Rating of therapeutic article	
Class I	RCT in representative population with masked outcome assessment. The following are required: a) concealed allocation; b) primary outcome(s) is/are clearly defined; c) exclusion/inclusion criteria are clearly defined; d) adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias; e) certain requirements are needed for noninferiority or equivalence trials claiming to prove efficacy for 1 or both drugs.
Class II	Cohort study that meets a–e (Class I) or RCT that lacks 1 criterion from above (b−e).
Class III	Controlled trials (including well−defined natural history controls or patients serving as own controls), a description of major confounding differences between groups, and where outcome assessment is independent of patient treatment.
Class IV	Does not include patients with the disease, different interventions, undefined/unaccepted interventions or outcomes measures, and/or no measures of effectiveness or statistical precision presented or calculable.

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