▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

Australian Product Information – AIMOVIG® Solution for injection, for subcutaneous use

1 NAME OF THE MEDICINE

The active ingredient of Aimovig is erenumab.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

AIMOVIG contains 70 mg of erenumab in 1.0 mL (70 mg/mL).

AIMOVIG is a human immunoglobulin G2 (IgG2) monoclonal antibody that has high affinity binding to the CGRP receptor. AIMOVIG is composed of 2 heavy chains, each containing 456 amino acids and 2 light chains of the lambda subclass, each containing 216 amino acids

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Solution for injection, for subcutaneous use

AIMOVIG is provided as:

- Carton of two* 70 mg/mL (140 mg dose) (injection) prefilled syringe with Type 1 glass syringe and stainless steel needle.
- Carton of one* (70 mg dose), two* or six* (multipack of 3x2) 70 mg/mL (140 mg dose) (injection) prefilled pen with Type 1 glass syringe and stainless steel needle.

** Not all pack sizes or presentations may be marketed*.

Aimovig is a sterile, preservative-free solution, clear to opalescent; colourless to yellowish solution, practically free from particles.

The needle cover of the glass pre-filled syringe and the pre-filled pen is made from dry natural rubber (a derivative of latex).

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

AIMOVIG is indicated for prophylaxis of migraine in adults.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

AIMOVIG should be initiated under the guidance of a neurologist or specialist in the management of migraine.

The recommended dose of AIMOVIG is 70 mg injected subcutaneously once every 4 weeks. Some patients may benefit from a dosage of 140 mg injected subcutaneously once every 4 weeks.

Treatment response should be evaluated by the prescriber after 8-12 weeks as recommended by the current Australian treatment guideline

If AIMOVIG dose is missed, administer as soon as possible. Thereafter, AIMOVIG can be scheduled monthly from the date of the last dose.

The need for treatment continuation should be re-evaluated within regular intervals of 3-6 months as recommended by the current treatment guideline.

Efficacy and safety of erenumab in patients has not been assessed in patients with fewer than 4 migraine days per month.

Efficacy and safety of concomitant administration of Aimovig with other prophylactic treatments for migraine was not formally evaluated, although concomitant use of prophylactic medication was allowed in a subset of patients in the pivotal study for episodic migraine.

Method of Administration

AIMOVIG is administered subcutaneously.
AIMOVIG is intended for patient self-administration.
Administration should be performed by an individual who has been trained to administer the product. To administer the 140 mg dose, give two consecutive subcutaneous injections of 70 mg each of AIMOVIG.

For detailed instructions on storage, handling and administration, follow the directions provided in the “Instructions for Use” available in the package leaflet.

Important Administration Instructions

- Visually inspect AIMOVIG for particles and discoloration. AIMOVIG is a clear to opalescent, colourless to light yellow solution. Do not use if the solution is cloudy or discoloured or contains flakes or particles.
- Administer AIMOVIG in the abdomen, thigh, or upper arm subcutaneously. If you want to use the same injection site, make sure it is not the same spot you used for a previous injection. Do not inject into areas where the skin is tender, bruised, red, or hard.
- Both prefilled syringe and prefilled pen are for single use in one patient only and designed to deliver the entire contents with no residual content remaining. Discard any residue.
- The needle cover of the AIMOVIG prefilled syringe and pen contain dry natural rubber, which may cause allergic reactions in individuals sensitive to latex.
- Prior to subcutaneous administration, allow AIMOVIG to sit at room temperature for at least 30 minutes and protect from direct sunlight. Do not warm by using a heat source such as hot water or microwave.

4.3 CONTRAINDICATIONS

AIMOVIG is contraindicated in patients with hypersensitivity to erenumab or to any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Traceability

In order to improve the traceability of biological medicinal products, the name and batch number of the administered medicinal product should be clearly recorded.

Use in hepatic impairment

No clinical studies have been conducted to evaluate the effect of hepatic impairment.

Use in renal impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment. 57 patients with moderate renal impairment have been studied. Population pharmacokinetic analysis of integrated data from the AIMOVIG clinical trials did not reveal a difference in the pharmacokinetics of erenumab in patients with mild or moderate renal impairment relative to those with normal renal function. Patients with severe renal impairment (eGFR < 30 mLs/min/1.73 m2) have not been studied.

Use in the elderly

Dose adjustments for patients aged 65 years and older are not recommended due to insufficient data to determine whether they respond differently from younger subjects.

Paediatric use

The safety and effectiveness of AIMOVIG has not been studied in paediatric patients.

Effects on laboratory tests

Interference of AIMOVIG with laboratory and/or diagnostic tests has not been studied.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

In an open-label, pharmacokinetic drug interaction study of AIMOVIG and a combined oral contraceptive in healthy female subjects, erenumab (140 mg subcutaneous [SC], single-dose) did not affect the pharmacokinetics of a combined oral contraceptive containing ethinylestradiol and norgestimate.

In a randomised, double-blind, placebo-controlled study in healthy volunteers, concomitant administration of erenumab (140 mg intravenous [IV], single-dose) with sumatriptan had no effect on resting blood pressure compared with sumatritpan alone. AIMOVIG had no effect on the pharmacokinetics of sumatriptan.

Erenumab is not metabolised by cytochrome P450 enzymes and is unlikely to cause marked changes in pro-inflammatory cytokines that may impact cytochrome P450 enzyme expression or activity. As a result, interactions with concomitant medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data are available on the effect of AIMOVIG on human fertility. However, there were no adverse effects on surrogate markers of fertility (anatomic pathology or histopathology changes in reproductive organs) in the chronic toxicology study in sexually mature monkeys subcutaneously administered AIMOVIG at dose levels up to 150 mg/kg twice weekly for 6 months, at systemic exposures up to 123-fold higher than the clinical dose of 140 mg once monthly, based on serum AUC.

Use in pregnancy – Pregnancy Category B1

There are no adequate and well-controlled studies on the use of AIMOVIG in pregnant women. In a cynomolgus monkey reproduction study, there were no effects on pregnancy, embryo-fetal or post-natal development (up to 6 months age) when erenumab was dosed throughout pregnancy at exposure levels 17-fold higher than those achieved in patients receiving erenumab at the 140 mg once monthly dosing regimen based on area under the concentration curve (AUC). Measurable erenumab serum concentrations were observed in the infant monkeys at birth, confirming that erenumab, like other IgG antibodies, crosses the placental barrier.

Animal studies are not always predictive of human response and therefore, it is not known whether AIMOVIG can cause fetal harm when administered to a pregnant woman. AIMOVIG should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in lactation.

It is not known whether AIMOVIG is present in human milk. There are no data on the effects of AIMOVIG on the breastfed child or the effects of AIMOVIG on milk production. Because drugs are excreted in human milk and because of the potential for adverse effects in nursing infants from AIMOVIG, a decision should be made whether to discontinue nursing or discontinue AIMOVIG, taking into account the potential benefit of AIMOVIG to the mother and the potential benefit of breast feeding to the infant.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

AIMOVIG is expected to have no influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

SUMMARY OF THE SAFETY PROFILE

Data from two phase 3 and two phase 2 clinical studies in migraine were pooled to evaluate the safety of AIMOVIG in comparison to placebo up to 12 weeks after treatment initiation.

There were a total of 2656 patients (1613 AIMOVIG and 1043 placebo) in these studies. Of these, 507 subjects received 140 mg dose of AIMOVIG.

The overall safety population for including ongoing open label extension phase with AIMOVIG includes 2537 patients (2310.3 patient years) who received at least one dose of AIMOVIG: 2066 patients were exposed for at least 6 months and 1213 were exposed for at least 12 months.

TABULATED SUMMARY OF ADVERSE REACTIONS

Table 1 summarises all treatment-emergent adverse events which were reported by ≥ 1 % and Table 2 summarises all adverse reactions that occurred in AIMOVIG-treated patients at the recommended 140 mg dose during the 12-week placebo-controlled period of the pooled trials. Most Adverse Drug Reactions were mild or moderate in severity.

Table 1 Frequency of treatment-emergent adverse events regardless of causality (reported by >=1% in AIMOVIG 140 mg and 70 mg)

Primary system organ class Preferred term	**AMG 334 140 mg (N=507) n (%)**	**AMG 334 70 mg (N=893) n (%)**	**Placebo (N=1043) n (%)**
Gastrointestinal disorders			
Constipation	16 (3.2)	12 (1.3)	11 (1.1)
Diarrhoea	5 (1.0)	4 (0.4)	13 (1.2)
Nausea	10 (2.0)	21 (2.4)	27 (2.6)
Vomiting	5 (1.0)	7 (0.8)	12 (1.2)
General disorders and administration site conditions			
Fatigue	10 (2.0)	20 (2.2)	18 (1.7)
Injection site erythema	10 (2.0)	9 (1.0)	2 (0.2)
Injection site pain	8 (1.6)	33 (3.7)	18 (1.7)
Infections and infestations			
Bronchitis	7 (1.4)	9 (1.0)	6 (0.6)
Influenza	6 (1.2)	19 (2.0)	18 (1.7)
Nasopharyngitis	28 (5.5)	53 (5.9)	76 (7.3)
Sinusitis	10 (2.0)	14 (1.6)	17 (1.6)
Upper respiratory tract infection	14 (2.8)	40 (4.5)	31 (3.0)
Urinary tract infection	6 (1.2)	10 (1.1)	15 (1.4)
Musculoskeletal and connective tissue disorders			
Back pain	5 (1.0)	12 (1.3)	18 (1.7)
Muscle spasms	10 (2.0)	1 (0.1)	4 (0.4)
Nervous system disorders			
Dizziness	7 (1.4)	9 (1.0)	11 (1.1)
Migraine	5 (1.0)	14 (1.6)	21 (2.0)
Psychiatric disorders			
Insomnia	6 (1.2)	6 (0.7)	8 (0.8)
Respiratory, thoracic and mediastinal disorders			
Cough	7 (1.4)	6 (0.7)	10 (1.0)

Skin and subcutaneous tissue disorders			
Pruritus generalised	6 (1.2)	0 (0.0)	1 (<0.1)

Table 2 Adverse Reactions with AIMOVIG

System Organ Class	Adverse Reaction Preferred Term	Frequency Category	Overall subject incidence at 70 mg (N = 893) n (%)	Overall subject incidence at 140 mg (N = 507) n (%)
General disorders and administration site conditions	Injection site reactions[a]	Common	50 (5.6)[a]	23 (4.5)[a]
Gastrointestinal disorders	Constipation	Common	12 (1.3)	16 (3.2)
Musculoskeletal and connective tissue disorders	Muscle spasm	Common	1 (0.1)	10 (2.0)
Skin and subcutaneous tissue disorders	Pruritus[b]	Common	6 (0.7)[b]	9 (1.8)[b]

Note: Frequency is provided by CIOMS category (e.g., Very Common (≥ 10%), Common (≥ 1% and < 10%), uncommon (≥ 0.1% and < 1%), rare (≥ 0.01% and < 0.1%), very rare (< 0.01%)).

[a] Injection Site Reactions includes multiple preferred terms, such as injection site pain and injection site erythema.

[b] Pruritus includes preferred terms of generalised pruritus, pruritus, and pruritic rash.

The incidence of severe adverse events was 1.0 % for AIMOVIG 140 mg and 1.5 % for placebo. The incidence of discontinuation due to adverse events was 2.0 % for AIMOVIG 140 mg and 1.0 % for placebo.

In the integrated 12-week placebo controlled period of studies, majority of all AEs, 93.1% in the AIMOVIG 140 mg group and 93.5% in the placebo group, respectively were grade 1 (mild) or 2 (moderate) in severity and were balanced across the groups. A limited number of grade ≥ 3 (severe) adverse events were reported. None of common adverse events were grade 4 (life-threatening) or grade 5 (fatal). Subject incidence rates of adverse events in the Cardiac disorders SOC was 1.2% in the placebo group and 1.4% in the AIMOVIG 140 mg group. There was no evidence of AIMOVIG related adverse effects on cardiovascular system.

While the data are limited for a comprehensive assessment of withdrawal and rebound effects, there is no evidence of such an effect based on review of migraine adverse events.

Review of adverse events open-label extension/active treatment period combined over a minimum period of 1 year did not reveal any signals or trends that would suggest a potential safety concern with long-term exposure to AIMOVIG.

DESCRIPTION OF SELECTED ADVERSE REACTIONS

Injection site reactions

In the integrated 12-week placebo controlled period of studies, in subjects treated with AIMOVIG the most frequent injection site reactions were injection site pain, injection site erythema, and injection site pruritus. A majority of injection site reactions were mild in severity. No subjects treated with AIMOVIG 140 mg SC discontinued due to injection site reactions in the 12-week placebo-controlled period of studies.

IMMUNOGENICITY

As with all therapeutic proteins, there is potential for immunogenicity. The immunogenicity of AIMOVIG has been evaluated using an immunoassay for the detection of binding anti-erenumab antibodies. For patients whose sera tested positive in the screening immunoassay, an in vitro biological assay was performed to detect neutralising antibodies.

In the pivotal studies, the incidence of anti-erenumab antibody development among subjects receiving 140 mg dose of AIMOVIG was 2.6%. None of these had in vitro neutralising activity. The mean trough levels of erenumab at week 12 were 40% lower among anti-erenumab antibody-positive subjects than among antibody-negative subjects. There was no impact of anti-erenumab antibody development on efficacy or safety of erenumab.

The incidence of anti-drug antibodies (ADAs) is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralising antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to erenumab with the incidence of antibodies to other products may be misleading.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no experience with overdose in clinical trials with AIMOVIG. Doses up to 280 mg SC have been administered in clinical trials with no evidence of dose limiting toxicity.

In the event of an overdose, the patient should be treated symptomatically and supportive measures instituted as required.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Erenumab is a human monoclonal antagonist antibody against the CGRP receptor with no significant pharmacological activity at adrenomedullin, calcitonin, and amylin receptors and lacks agonist activity at the CGRP receptor.

CGRP is a neuropeptide that modulates nociceptive signalling and a vasodilator that has been associated with migraine pathophysiology. In contrast with other neuropeptides, CGRP levels have been shown to increase significantly during migraine and return to normal with headache relief. Intravenous infusion of CGRP induces migraine-like headache in patients suggesting that CGRP may play a causal role in migraine.

CGRP receptor is located at sites that are relevant to migraine pathophysiology. Erenumab potently and specifically competes with the binding of CGRP and inhibits its function at the CGRP receptor.

Pharmacodynamics

In a randomised, double-blind, placebo-controlled study (20140254) to evaluate the effect of AIMOVIG (140 mg IV, single dose) in patients with stable angina, AIMOVIG did not decrease exercise duration during a treadmill test compared to placebo.

A benefit of treatment with erenumab was seen within 4 weeks of commencing treatment.

Clinical trials

AIMOVIG was evaluated for prophylaxis of migraine in 2 pivotal studies across the spectrum of episodic and chronic migraine. Both studies enrolled patients with a history of migraine, with or without aura according to the International Classification of Headache Disorders (ICHD-III) diagnostic criteria.

Excluded from the study were migraine patients with myocardial infarction, stroke, transient ischaemic attacks, unstable angina, coronary artery bypass surgery or other revascularisation procedures within 12 months prior to screening.

AIMOVIG treatment demonstrated statistically significant and clinically meaningful improvements from baseline compared to placebo for key efficacy outcomes.

Chronic Migraine

Study 1 (Study 20120295)

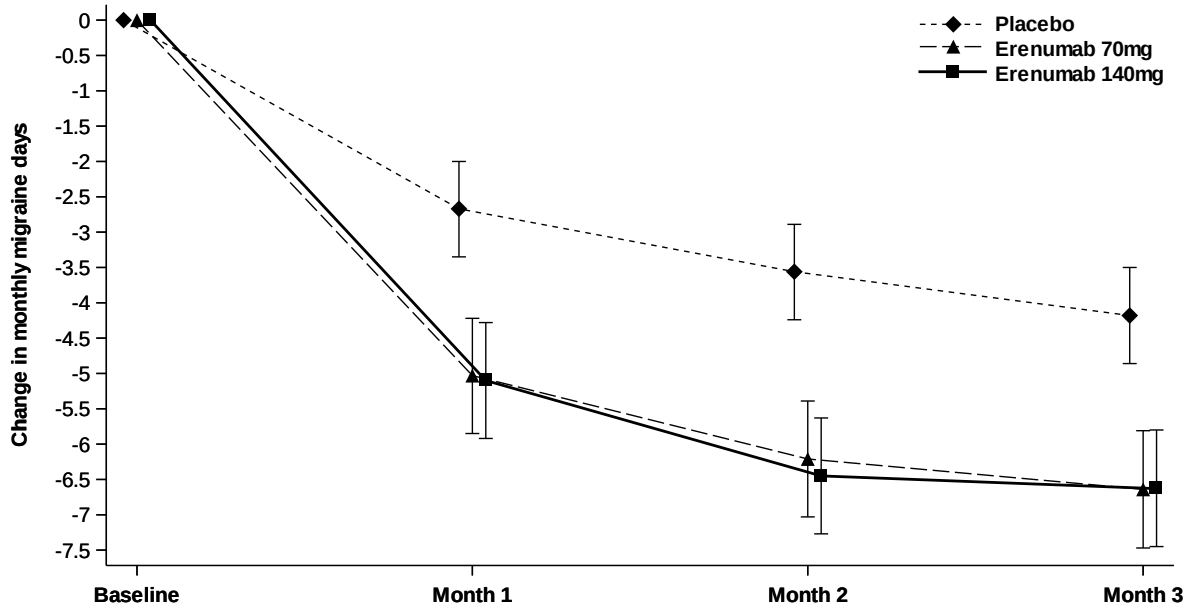
AIMOVIG was evaluated for prophylaxis of chronic migraine in a randomised, multi-centre, 12-week, placebo-controlled, double-blind study. Patients with a history of migraine with or without aura (≥ 15 headache days per month with ≥ 8 migraine days per month) were randomised to receive placebo (n = 286), AIMOVIG 70 mg (n = 191) or AIMOVIG 140 mg (n = 190) subcutaneous injections every 4 weeks for 12 weeks. Randomisation was stratified by region (North America vs. other) and the presence of acute medication overuse (present in 41% of overall patients) excluding patients with opioid overuse. The mean migraine frequency at baseline was approximately 18 migraine days per month and was similar across treatment groups. Patients were allowed to use acute headache treatments including triptans, ergotamine derivatives and NSAIDs during the study.

Patients had a median age of 43 years (range: 18 – 66 years), 83% were female and 94% were White. Patients could have failed (i.e. no therapeutic response) up to 3 previous prophylactic treatment categories due to lack of efficacy, while there was no limit to the number of previous failures for poor tolerability. Overall in this study population, 68% had failed 1 or more previous prophylactic treatments due to lack of efficacy or poor tolerability, and 49% had failed 2 or more previous prophylactic treatments due to lack of efficacy or poor tolerability. In addition to excluding patients with opioid overuse, the study excluded patients with concurrent use of migraine prophylactic treatments. A total of 182 (96%) patients in the AIMOVIG 140 mg group, 184 (96%) patients in the AIMOVIG 70 mg group and 265 (93%) patients in the placebo arm completed the study (completed week 12 assessment). Of the 17 (3.6%) patients who discontinued treatment, 2 patients in the AIMOVIG 140 mg group, none of the patients in the AIMOVIG 70 mg group and 2 patients in the placebo group discontinued due to adverse events.

The primary outcome measure was the change from baseline at month 3 in monthly migraine days. Secondary outcome measures included the achievement of at least 50% reduction in monthly migraine days from baseline (≥50% responders), change from baseline in monthly acute migraine-specific medication days, and change from baseline in cumulative monthly headache hours. Other than for cumulative monthly headache hours, AIMOVIG treatment demonstrated statistically significant and clinically meaningful improvements from baseline at month 3 compared to placebo for efficacy outcomes as summarised in Figure 1 and Table 3. Reduction in mean monthly migraine days from placebo was observed in a monthly analysis as early as month 1 and in a follow-up weekly analysis an onset of AIMOVIG effect was seen as early as the first week of administration.

The mean difference from placebo in the number of migraine days per month for AIMOVIG 140 mg after 12 weeks of treatment was 2.45 days on a background of 18 migraine days per month. No comparisons between the 70 mg and 140 mg AIMOVIG dose regimens were performed.

Figure 1 Change From Baseline in Monthly Migraine Days in Study 1[a]



[a] Least-square means and 95% confidence intervals are presented. The p-value for the difference in least-square means between erenumab and placebo assessed at Month 3 (primary outcome measure) was < 0.001.

Table 3 Change from baseline in efficacy and patient-reported outcomes at Week 12 in Study 1

	Aimovig 140 mg (n = 187)	Aimovig 70 mg (n = 188)	Placebo (n = 281)	Treatment difference Odds ratioc (95% CI)	p-value[a]
Efficacy outcomes					
Monthly migraine days (MMD) Mean change[b] (95% CI)	-6.63 (-7.45; -5.80)	-6.64 (-7.47, -5.81)	-4.18 (-4.86; -3.50)	TD 140 mg: -2.45 (-3.51; -1.38) 70 mg: -2.46 (-3.52, -1.39)	<0.001
≥50% MMD responders[c] Percentage [%]	41.2%	39.9	23.5%	OR[d] 140 mg: 2.34 (1.56; 3.51) 70 mg: 2.18 (1.46, 3.27)	<0.001
Monthly acute migraine-specific medication days[e] Mean change[b] (95% CI)	-4.13 (-4.70; -3.56)	-3.45 (-4.02, -2.87)	-1.58 (-2.05; -1.11)	TD 140 mg: -2.55 (-3.28; -1.82) 70 mg: -1.86 (-2.60, -1.13	<0.001

CI = confidence interval; MMD = monthly migraine days; TD = treatment difference; OR = odds ratio

[a] All p-values are reported as unadjusted p-values and are statistically significant after adjustment for multiple comparisons.

[b] LS mean change from baseline at Month 3, treatment difference and p-value are based on a linear mixed effects model including treatment group, baseline monthly value, stratification factors (region [North America versus other] and medication overuse [presence versus absence]), scheduled visit and the interaction of treatment group with scheduled visit, without any imputation for missing data.

[c] Responders are defined as patients who achieve ≥50% reduction on MMD from baseline

[d] Odds ratio and p-value for ≥50% responders at Month 3 are based on a stratified Cochran-Mantel-Haenszel test after missing data were imputed as non-response.

[e] Migraine-specific medications include triptans and ergotamine derivatives.

Based on a pre-specified analysis, Aimovig was efficacious in patients who had previously failed migraine prophylactic treatments due to lack of efficacy or intolerance and in patients with a history of medication overuse.

In general, the efficacy of Aimovig across subgroups in this study were robust and comparable to the general population.

Episodic Migraine

Study 2 (Study 20120296, STRIVE)

Study 2 was a randomised, multi-centre, 24-week, placebo-controlled, double-blind study evaluating AIMOVIG for prophylaxis of episodic migraine. Patients with history of migraine with or without aura for a duration of ≥ 12 months and 4-14 migraine days per month were randomised to receive either AIMOVIG 140 mg (n = 319), AIMOVIG 70 mg (n = 317) or placebo (n = 319) by subcutaneous injection every 4 weeks for 6 months. Randomisation was stratified

by prior, concomitant, or no prior use of prophylactic medications and region (North America vs. other). The mean migraine frequency at baseline was approximately 8 migraine days per month and was similar across treatment groups. Patients were allowed to use acute headache treatments including triptans, ergotamine derivatives and NSAIDs during the study. Concomitant use of prophylactic medication was allowed in a subset of patients. 10 patients (3.1%) in the placebo group and 8 patients (2.5 %) in the 140 mg group received concomitant prophylactic medication.

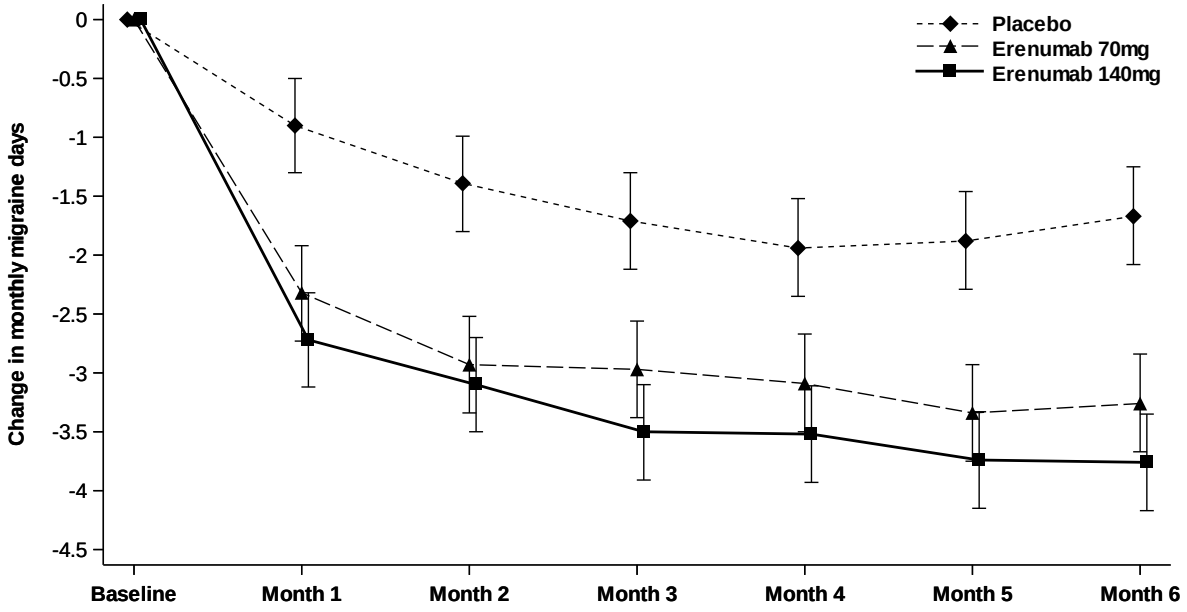
Patients had a median age of 42 years (range: 18 – 65 years), 85% were female and 89% were White. Patients could have failed to respond up to 2 previous prophylactic treatments. The study excluded patients with medication overuse. A total of 292 (92%) patients in the AIMOVIG 140 mg group, 284 (89%) patients in the AIMOVIG 70 mg group and 282 (88%) patients in the placebo arm completed the double-blind phase. Of the 87 (9. 1%) patients who discontinued treatment, 7 patients each in the AIMOVIG treated groups and 8 patients in the placebo group discontinued due to adverse events.

The primary outcome measure was the change from baseline during months 4-6 in monthly migraine days. Secondary outcome measures included the achievement of a at least 50% 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 2 Migraine Physical Function Impact Diary (MPFID) domains scores: physical impairment (PI) and impact on everyday activities (EA). The MPFID measures the impact of migraine on everyday activities (EA) and physical impairment (PI) using an electronic diary administered daily. Monthly MPFID scores are averaged over 28 days, including days with and without migraine; scores are scaled from 0 to 100. Higher scores indicate worse impact on EA and PI. Reductions from baseline in MPFID scores indicate improvement

AIMOVIG treatment demonstrated statistically significant and clinically meaningful improvements from baseline during months 4-6 compared to placebo for efficacy outcomes as summarised in Figure 2 and Table 4. Differences from placebo were observed as early as month 1.

The mean difference from placebo in the number of migraine days per month for AIMOVIG 140 mg after 4 – 6 months of treatment was 1.84 days per month on a background of 8 migraine days per month. No comparisons between the 70 mg and 140 mg AIMOVIG dose regimens were performed.

Figure 2 Change From Baseline in Monthly Migraine Days in Study 2[a]



[a] Least-square means and 95% confidence intervals are presented. The p-value for the difference in least-square means between erenumab and placebo assessed as the average over Months 4, 5, and 6 (primary outcome measure) was < 0.001.

Table 4 Change from baseline in efficacy and patient reported outcomes at Weeks 13-24 in Study 2

	Aimovig 140 mg (n = 318)	**Aimovig 70 mg (n = 312)**	**Placebo (n = 316)**	**Treatment difference / Odds ratio (95% CI)**	**p-value[a]**
Efficacy outcomes					
Monthly migraine days (MMD) Mean change[b] (95% CI)	-3.67 (-4.02; -3.33)	-3.23 (-3.58, -2.88)	-1.83 (-2.18; -1.48)	TD 140 mg: -1.85 (-2.33; -1.37) 70 mg: -1.40 (-1.88, -0.92)	<0.001
≥50% MMD responders[c] Percentage [%]	50.0	43.3%	26.6	OR[d] 140 mg: 2.81 (2.01, 3.94) 70 mg: 2.13 (1.52, 2.98)	<0.001
Monthly acute migraine-specific medication days[e] Mean change[b] (95% CI)	-1.61 (-1.83; -1.40)	-1.13 ((-1.34, -0.92))	-0.20 (-0.41; 0.02)	TD 140 mg: -1.42 (-1.71; -1.12) 70 mg: -0.94 (-1.23, -0.64)	<0.001
Patient-reported outcome measures					
MPFID physical impairment domain Mean change[b] (95% CI)	-4.81 (-5.59; -4.03)	-4.24 (-5.02, -3.45)	-2.38 (-3.16; -1.59)	TD 140 mg: -2.43 (-3.51; -1.35) 70 mg: -1.86 (-2.95, -0.77)	<0.001

MPFID everyday activity domain Mean change[b] (95% CI)	-5.86 (-6.62; -5.10)	-5.52 (-6.28, -4.75)	-3.30 (-4.06; -2.53)	TD 140 mg: -2.57 (-3.62; -1.51) 70 mg: -1.86 (-2.95, -0.77)	<0.001

CI = confidence interval; MMD = monthly migraine days; MPFID = Migraine Physical Function Impact Diary; TR = treatment difference; OR = odds ratio

a All p-values are reported as unadjusted p-values and are statistically significant after adjustment for multiple comparisons

b Least-square mean change from baseline at Months 4-6, treatment difference and p-value are based on a linear mixed effects model including treatment group, baseline value, stratification factors (region [North America vs others] and prior prophylactic medication use [naïve, prior use only, concurrent use]), scheduled visit and the interaction of treatment group with scheduled visit, without any imputation for missing data.

c Responders are defined as patients who achieve ≥50% reduction on MMD from baseline

d Odds ratio and p-value for ≥50% responders at Months 4-6 are based on a stratified Cochran-Mantel-Haenszel test after missing data were imputed as non-response.

e Migraine-specific medications include triptans and ergotamine derivatives

Based on a pre-specified analysis, AIMOVIG 140 mg and 70 mg was efficacious in patients who had previously failed migraine prophylactic treatments due to lack of efficacy or intolerance.

In patients failing one or more prophylactic pharmacotherapies the treatment difference for the reduction of MMD observed between erenumab 140 mg and placebo was 2.5 (95% CI: 3.4, 1.7) and between erenumab 70 mg and placebo 2.0 (95% CI: 2.8, 1.2). There was also a higher proportion of subjects treated with erenumab who achieved at least 50% reduction of MMD compared to placebo (39.7% for 140 mg and 38.6% for 70 mg, with an odds ratio of 3.1 [95% CI: 1.7, 5.5] and 2.9 [95% CI: 1.6, 5.3], respectively).

In general, the efficacy of Aimovig across subgroups in this study were robust and comparable to the general population.

Open label extension studies suggest that patients remaining on treatment continue to benefit. Withdrawal effects were not seen.

5.2 PHARMACOKINETIC PROPERTIES

Erenumab exhibits non-linear kinetics as a result of binding to CGRP-R. Subcutaneous administration of a 140 mg dose in healthy volunteers resulted in a C_{max} mean (standard deviation [SD]) of 15.8 (4.8) µg/mL and AUC_{last} mean (SD) of 505 (139) day*µg/mL.

Less than 2-fold accumulation was observed in trough serum concentrations (C_{min} [SD] 12.8 [6.53] and 14.9 [6.45] µg/mL for episodic and chronic migraine subjects, respectively) following 140 mg doses administered subcutaneously every 4 weeks and serum trough concentrations approached steady state by 12 weeks of dosing. The effective half-life of AIMOVIG is 28 days.

Absorption

Following a single subcutaneous dose of 140 mg AIMOVIG administered to healthy adults, median peak serum concentrations were attained in 4 to 6 days, and estimated absolute bioavailability was 82%.

Distribution

Volume distribution at steady-state (7600 mL) suggested limited tissue distribution outside of plasma.

Metabolism and Excretion

Two elimination phases were observed for AIMOVIG. At low concentrations, the elimination is predominantly through saturable binding to target (CGRP-R), while at higher concentrations the elimination of AIMOVIG is largely through a non-specific, non-saturable proteolytic pathway.

Specific Populations

The pharmacokinetics of erenumab were not affected by age, gender, race, migraine subtype (episodic or chronic migraine), or creatinine clearance, across all approved populations based on population pharmacokinetics (PK) analysis.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

The mutagenic potential of AIMOVIG has not been evaluated; however, monoclonal antibodies are not expected to alter DNA or chromosomes.

Carcinogenicity

Carcinogenicity studies have not been conducted with AIMOVIG. A comprehensive carcinogenicity assessment based on non-clinical and clinical data and literature did not identify any carcinogenic risk associated with the mechanism of action of AIMOVIG blocking the receptor for CGRP.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each prefilled syringe or prefilled pen contains sucrose, glacial acetic acid, polysorbate 80, water for injection and sodium hydroxide.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

24 months at 2°C to 8°C.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

- Store refrigerated at 2°C to 8°C in the original carton to protect from light until time of use.
- If removed from the refrigerator, AIMOVIG should be kept at controlled room temperature (up to 30°C) in the original carton and must be used within 14 days. Throw away AIMOVIG that has been left at room temperature for more than 14 days.
- Do not freeze.
- Do not shake.

6.5 NATURE AND CONTENTS OF CONTAINER

AIMOVIG is provided as:

- Carton of two* 70 mg/mL (140 mg dose) (injection) prefilled syringe with Type 1 glass syringe and stainless steel needle.
- Carton of one* (70 mg dose), two* or six* (multipack of 3x2) 70 mg/mL (140 mg dose) (injection) prefilled pen with Type 1 glass syringe and stainless steel needle.

** Not all pack sizes or presentations may be marketed*.

The needle cover of the glass prefilled syringe and the pen is made from dry natural rubber (a derivative of latex).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical name: Immunoglobulin G2-lambda, anti-(human calcitonin gene-related peptide type 1 receptor (CGRP type 1 receptor; calcitonin receptor-like receptor); human monoclonal antibody

CAS number: 1582205-90-0

Molecular formula: $C_{6472}H_{9964}N_{1728}O_{2018}S_{50}$ (peptide)

Molecular weight: AIMOVIG has an approximate molecular weight (MW) of 150 kDa.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

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10 DATE OF REVISION

N/A

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