▼ 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 70 mg/mL contains 70 mg of erenumab in 1.0 mL.

AIMOVIG 140 mg/mL contains 140 mg of erenumab in 1.0 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 a sterile, preservative-free solution, clear to opalescent; colourless to yellowish solution, practically free from particles.

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 as a single injection of the 70 mg or 140 mg dose.

AIMOVIG is intended for patient self-administration.

Administration should be performed by an individual who has been trained to administer the product.

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 (see section 4.4 Special Warnings and Precautions for use, and 4.8 Adverse Effects (Undesirable effects)).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity Reactions

Hypersensitivity reactions (some of which were serious), including rash, angioedema, and anaphylactoid reactions, have been reported with AIMOVIG in post-marketing experience. These reactions may occur within minutes, although some may occur more than one week after treatment. If a serious or severe hypersensitivity reaction occurs, discontinue administration of AIMOVIG and initiate appropriate therapy (see section 4.3 Contraindications).

Constipation with Serious Complications

Constipation with serious complications has been reported following the use of AIMOVIG in the post-marketing setting. There were cases that required hospitalization, including cases where surgery was necessary. In a majority of these cases, the onset of constipation was reported after

the first dose of AIMOVIG; however, patients have also presented with constipation later on in treatment. AIMOVIG was discontinued in most reported cases of constipation with serious complications. Many of the cases of constipation with serious complications were reported for patients who have a history of constipation or concurrently use medications associated with decreased gastrointestinal motility. Constipation was one of the most common (up to 3%) adverse reactions reported in clinical studies (see section 4.8 Adverse Effects, Undesirable effects).

Monitor patients treated with AIMOVIG for severe constipation and manage as clinically appropriate. The concurrent use of medications associated with decreased gastrointestinal motility may increase the risk for more severe constipation and the potential for constipation-related complications.

Hypertension

Development of hypertension and worsening of pre-existing hypertension have been reported following the use of AIMOVIG in the post-marketing setting. Many of the patients had pre-existing hypertension or risk factors for hypertension. There were cases requiring pharmacological treatment and, in some cases, hospitalisation. Hypertension may occur at any time during treatment but was most frequently reported within seven days of dose administration. In the majority of the cases, the onset or worsening of hypertension was reported after the first dose. AIMOVIG was discontinued in many of the reported cases.

Monitor patients treated with AIMOVIG for new-onset hypertension, or worsening of pre-existing hypertension, and consider whether discontinuation of AIMOVIG is warranted if evaluation fails to establish an alternative etiology.

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 performed in patients with hepatic impairment. Erenumab, as a human monoclonal antibody, is not metabolised by cytochrome P450 enzymes and hepatic clearance is not a major clearance pathway for erenumab.

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

Clinical studies of AIMOVIG did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. No dose adjustment is required as the pharmacokinetics of erenumab are not affected by age.

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 283 or 123-fold higher than the clinical dose of 70 mg or 140 mg once monthly, respectively, 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 40 or 17-fold higher than those achieved in patients receiving erenumab at the 70 or 140 mg once monthly dosing regimen, respectively 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, 893 subjects received 70 mg dose of AIMOVIG and 507 subjects received 140 mg dose of AIMOVIG.

The overall safety population for including ongoing open label extension phase with AIMOVIG includes 2537 patients (3040.2 patient years) who received at least one dose of AIMOVIG: 2280 patients were exposed for at least 6 months and 1320 patients were exposed for at least 12 months, and 217 patients were exposed through 5 years. The overall safety profile of AIMOVIG remained consistent through 5 years of long-term open-label treatment.

TABULATED SUMMARY OF ADVERSE REACTIONS

Table 1 summarises all treatment-emergent adverse events which were reported by $\geq$ 1 % and Table 2 summarises all adverse reactions that occurred in AIMOVIG-treated patients 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 generalized 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 grade 1 (mild) in severity. In the healthy volunteer study, injection site pain was transient and typically subsided within 1 hour after administration. One subject treated with AIMOVIG 70 mg SC discontinued due to injection site rash and no subject treated with AIMOVIG 140 mg SC discontinued due to injection site reactions in the 12-week placebo-controlled period of studies.

Constipation

In the integrated 12-week placebo-controlled period of studies, 28 cases of constipation were reported out of 1400 AIMOVIG-treated patients. All were mild or moderate severity. A majority of the cases (23) had onset within one month after the first dose; however, some patients also presented with constipation later on in treatment. In most cases (18), constipation resolved within 3 months. All but one case continued treatment.

POST-MARKETING EXPERIENCE

Immune system disorders

- Hypersensitivity reactions including rash, angioedema and anaphylactoid reactions (see section 4.4 Special Warnings and Precautions for Use).

Gastrointestinal disorders

- Constipation with serious complications (see section 4.4 Special Warnings and Precautions for Use)
- Oral sores, e.g. stomatitis, mouth ulceration, oral mucosal blistering.

Skin and subcutaneous tissue disorders

- Alopecia
- Rash, e.g. rash popular, exfoliative rash, rash erythematous, urticaria, blister.

Vascular disorders

- Hypertension (see section 4.4 Special Warnings and Precautions for Use).

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.

During the double-blind treatment phase of the four migraine prophylaxis efficacy studies, [20120178, 20120295, 20120296 and 20120297], the incidence of anti-erenumab antibody development during the double-blind treatment phase was 6.3% (56/884) among subjects receiving the 70 mg dose of AIMOVIG (3 of whom had in-vitro neutralising activity) and 2.6% (13/504) among subjects receiving the 140 mg dose of AIMOVIG (none of whom 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. Including overall data from the 4 studies through the open-label extension, the incidence of anti-erenumab antibody development was 8.0% (185/2303) among patients who only received 70 mg or 140 mg of AIMOVIG throughout the entire study (8 of whom had *in vitro* neutralizing activity). 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

PHARMACOKINETIC GROUP: NERVOUS SYSTEM, ANTIMIGRAINE PREPARATIONS: CALCITONIN GENE-RELATED (CGRP) ANTAGONISTS, ATC CODE NO2CD01.

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 two 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 20120295

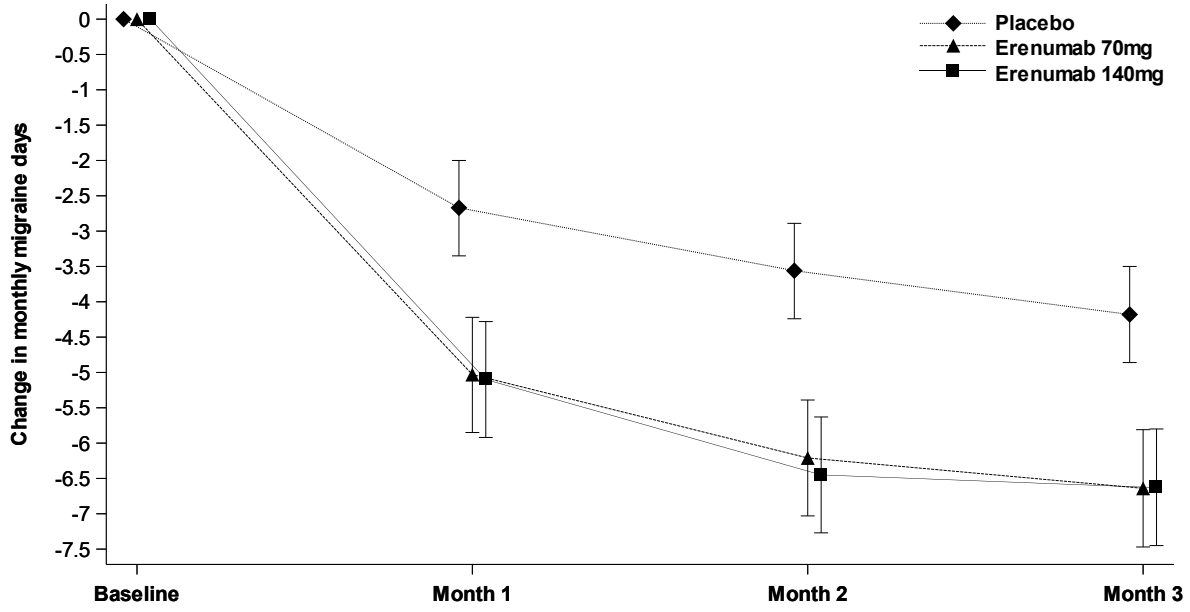
AIMOVIG was evaluated for prophylaxis of chronic migraine in a randomised, multi-centre, 12-week, placebo-controlled, double-blind study. A total of 667 patients with a history of migraine with or without aura (≥ 15 headache days per month with ≥ 8 migraine days per month) were randomised to receive 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 three 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 one or more previous prophylactic treatments due to lack of efficacy or poor tolerability, and 49% had failed two 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 23 (3.4%) 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 from month 1 and in a follow-up weekly analysis an onset of AIMOVIG effect was seen from 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 ratio (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.

In the open label extension of Study 1 patients received 70 mg and/or 140 mg AIMOVIG. 74.1% of patients completed the 52-week extension. Pooled across the two doses, a reduction of 9.3 MMD was observed after 52 weeks relative to core study baseline. 59% of patients completing the study achieved a 50% response in the last month of the study.

Episodic Migraine

Study 20120296

Study 20120296 was a randomised, multi-centre, 24-week, placebo-controlled, double-blind study evaluating AIMOVIG for prophylaxis of episodic migraine. A total of 955 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 use of prophylactic medications (concomitant, prior use or no prior use) 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 two previous prophylactic treatments. The study excluded patients with medication overuse. Overall, 865 (90.6%) patients completed the double-blind phase, including 294 (92.2%) patients in the AIMOVIG 140 mg group, 287 (90.5%) patients in the AIMOVIG 70 mg group and 284 (89.0%) patients in the placebo arm completed the double-blind phase. Of the 87 (9. 1%) patients who discontinued treatment, 7 patients in the 70 mg AIMOVIG group, 6 patients in the 140 mg AIMOVIG group and 7 patients in the placebo group discontinued due to adverse events.

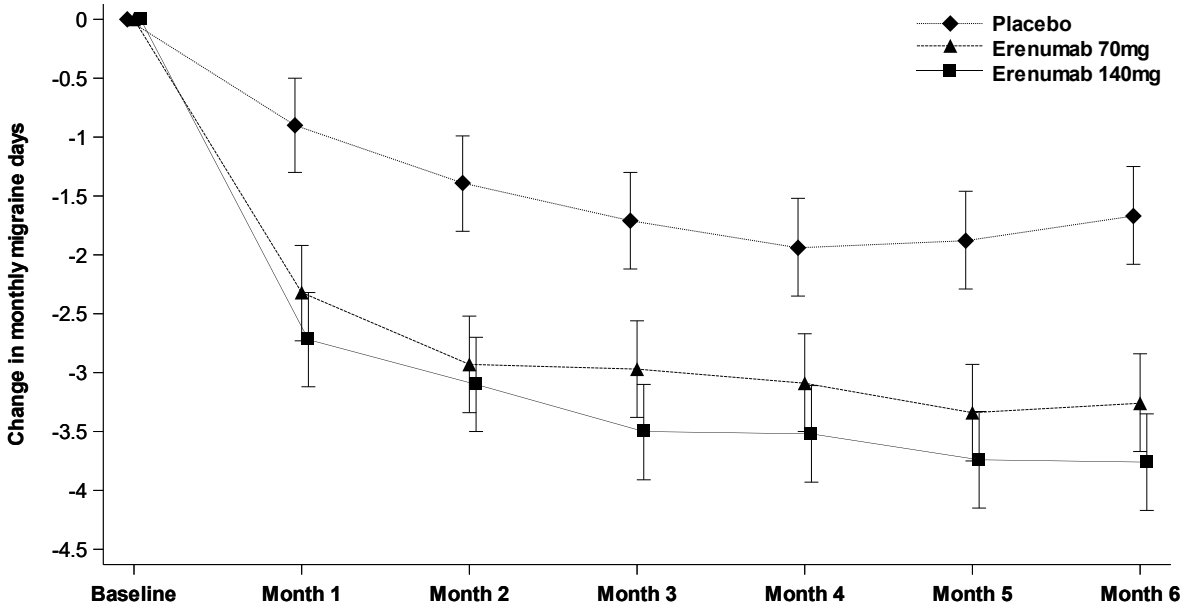
The primary outcome measure was the change from baseline during months 4-6 in monthly migraine days. Secondary outcome measures included the achievement of a at least 50% reduction in mean monthly migraine days from baseline (≥ 50% responders), change from baseline in mean monthly acute migraine-specific 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.

Study 20120178

Study 20120178 was a phase 2, randomised, multi-centre, 12-week, double-blind, placebo-controlled, study followed by a 256-week, open-label treatment phase evaluating AIMOVIG for prophylaxis of episodic migraine. In the double-blind treatment phase, a total of 483 patients were randomized to receive placebo, AIMOVIG 7 mg, 21 mg or 70 mg monthly, and 383 patients continued into the open-label treatment phase initially receiving AIMOVIG 70 mg (median exposure: 2.0 years), of which 250 patients increased their dose to 140 mg (median exposure: 2.7 years). Among those 250 patients, 214 (85.6%) patients completed the open-label treatment phase. Out of the 383 patients who entered the 256-week, open-label treatment phase, the most common reasons for discontinuing AIMOVIG were patient request (84 patients, 21.9%), adverse events (19 patients, 5.0%), and lost to follow-up (14 patients, 3.7%).

Patients who entered the open-label treatment phase had a median age of 43 years (range: 18-60 years) at study baseline, 79% were female, and 92% were white. Baseline disease characteristics were consistent across the prior placebo and AIMOVIG treatment groups.

The long-term efficacy results are summarized for patients who increased their dose to 140 mg (Table 5).

Table 5 Summary of Efficacy Endpoints During the Open-label Treatment Phase in Patients who increased AIMOVIG Dose From 70 mg to 140 mg

	Monthly Migraine Days (MMD)	**Monthly Migraine-specific Medication Days (MSMD)**	**MMD Responders, n (%)**		
Study baseline[a], Mean (SE) (N1 = 250)	8.69 (0.17)	4.53 (0.23)			
	Change from study baseline, Mean (SE)		**≥ 50%**	**≥ 75%**	**100%**
Week 64[b] (Month 16) (N1 = 230)	-5.00 (0.27)	-2.56 (0.21)	151 (65.7)	97 (42.2)	58 (25.2)
Week 268[c] (Month 67) (N1 = 138)	-5.30 (0.33)	-3.16 (0.30)	98 (71.0)	65 (47.1)	49 (35.5)

All subjects received AIMOVIG 70 mg at week 64 and AIMOVIG 140 mg at week 268.

SE = standard error; N1 = number of patients with observed data; responder rate % = n/N1 * 100

[a] The baseline phase occurred prior to entry into the 12-week double-blind treatment phase.

[b] Clinical outcome assessments were collected daily using an eDiary during the first 52 weeks of the open-label treatment phase (up to the week 64 study visit).

[c] The daily eDiary collection was resumed for 4-week periods during weeks 189 to 192 and every 24 weeks thereafter until the end of the open-label treatment phase (up to week 268). At this point, some patients had completed the study or were past the time points for efficacy data collection.

5.2 PHARMACOKINETIC PROPERTIES

Erenumab exhibits non-linear kinetics as a result of binding to CGRP receptor. Subcutaneous administration of a 70 mg and 140 mg (2 x 70 mg) dose in healthy volunteers resulted in a C_{max} mean (standard deviation [SD]) of 6.1 (2.1) µg/mL and 15.8 (4.8) µg/mL respectively and AUC_{last} mean (SD) of 159 (58) day*µg/mL and 505 (139) day*µg/mL.

Less than 2-fold accumulation was observed in trough serum concentrations (C_{min} [SD] 5.7 [3.1] and 6.2 [2.9] µg/mL for episodic and chronic migraine subjects, respectively following 70 mg doses; 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).

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 70 mg and 140 mg AIMOVIG administered to healthy adults, median peak serum concentrations were attained in approximately 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

70 mg per mL prefilled syringe, prefilled autoinjector/pen

- Sucrose: 73 mg/7.3% (w/v); NF, PhEur, JP
- Glacial acetic acid: 1.5 mg/25 mM; USP, PhEur, JP
- Polysorbate 80: 0.10 mg/0.010% (w/v); NF, PhEur, JP
- Water for injection
- Sodium hydroxide to pH of 5.2; NF, PhEur, JP

140 mg per mL prefilled syringe, prefilled autoinjector

- Sucrose: 65 mg/6.5% (w/v); NF, PhEur, JP
- Glacial acetic acid: 2.0 mg/34 mM; USP, PhEur, JP
- Polysorbate 80: 0.10 mg/0.010% (w/v); NF, PhEur, JP
- Water for injection
- Sodium hydroxide to pH of 5.2; NF, PhEur, JP

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

36 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 7 days. Throw away AIMOVIG that has been left at room temperature for more than 7 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 SureClick® autoinjector with Type 1 glass syringe and stainless-steel needle.
- Carton of one 140 mg/mL (injection) prefilled syringe with Type 1 glass syringe and stainless steel needle.
- Carton of one 140 mg/mL (injection) prefilled SureClick® autoinjector with Type 1 glass syringe and stainless-steel needle.

Not all pack sizes or presentations may be marketed.

The needle shield within the white or orange cap of the prefilled autoinjector and the gray needle cap of the prefilled syringe contain 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

2 July 2018

10 DATE OF REVISION

04 October 2022

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.8	Updated overall safety data. Updated safety data in post-marketing immunogenicity section.
5.1.	Addition of a clinical study, Study 20120178.

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