▼This medicinal product is subject to additional monitoring in Australia due to approval of an extension of indications. 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 PI – AJOVY® (FREMANEZUMAB) SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

Fremanezumab

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One pre-filled syringe contains 225 mg fremanezumab in 1.5 mL (150 mg/mL). One autoinjector contains 225 mg fremanezumab in 1.5 mL (150 mg/mL).

Fremanezumab is a fully humanised monoclonal antibody produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

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

3 PHARMACEUTICAL FORM

AJOVY is a sterile, preservative-free solution for injection available as follows:

225 mg/1.5 mL in a single-dose autoinjector

225 mg/1.5 mL in a single-dose pre-filled syringe.

AJOVY is a clear to opalescent, colourless to slightly yellow solution with a pH of 5.5 and an osmolality of 320-420 mOsm/kg.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

AJOVY is indicated for the preventive treatment of migraine in adults and for the preventive treatment of episodic migraine (between 4 and 14 migraine days per month) in paediatric patients aged 6 years and older, weighing at least 45 kg.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

AJOVY should be initiated by a physician experienced in the diagnosis and treatment of migraine. AJOVY should only be administered by subcutaneous injection.

Adults

Two dosing options are available:

- 225 mg once monthly (monthly dosing); or
- 675 mg every three months (quarterly dosing)

When switching dosing regimens, the first dose of the new regimen should be administered on the next scheduled dosing date of the prior regimen.

Paediatric Patients

The recommended dosage for the preventive treatment of episodic migraine in Paediatric Patients aged 6 years and older, weighing at least 45 kg:

- 225 mg once monthly (monthly dosing)

AJOVY is not approved in paediatric patients weighing less than 45 kg because of the lack of an appropriate strength presentation.

Adults and Paediatric Patients

The treatment benefit should be assessed 8-12 weeks after initiation of treatment. Any further decision to continue treatment should be taken on an individual patient basis. Evaluation of the need to continue treatment is recommended regularly thereafter.

Missed dose

If an AJOVY injection is missed on the planned date, dosing should resume as soon as possible on the indicated dose and regimen. A double dose must not be administered to make up for a missed dose.

Method of administration

Subcutaneous use.

Instructions for use

AJOVY may be administered by healthcare professionals, patients, and/or caregivers. For paediatric patients aged 13 to 17 years who self-inject, adult supervision and appropriate training are recommended. Provide proper training to patients and/or caregivers on the preparation and administration of AJOVY pre-filled syringe or autoinjector prior to use according to the Instructions for Use. Instruct patients and/or caregivers to read and follow the Instructions For Use each time they use AJOVY pre-filled syringe or autoinjector.

In paediatric patients aged 6 to 12 years, AJOVY must be administered by a healthcare professional or adult caregiver.

AJOVY is for single use in one patient only. Discard any residue. Follow clean injection technique every time AJOVY is administered.

Remove AJOVY from the refrigerator. Prior to use, allow AJOVY to reach room temperature for 30 minutes. Do NOT use AJOVY if it has been stored unrefrigerated for longer than 7 days, or at temperatures higher than 30°C.

The pre-filled syringe and autoinjector should not be shaken.

Visually inspect AJOVY for particles or discolouration prior to administration. AJOVY is a clear to opalescent, colourless to slightly yellow solution. Do not use if the solution is cloudy, discoloured, or contains particles. Do not use if AJOVY is frozen.

Administer AJOVY by subcutaneous injection into areas of the abdomen, thigh, or upper arm that are not tender, bruised, red, or indurated. For multiple injections, do not use the same injection site.

Do not co-administer AJOVY with other injectable drugs at the same injection site.

Dosage Adjustments

Renal or hepatic impairment

No dose adjustment is required in patients with renal or hepatic impairment.

Elderly

There is limited data available on the use of AJOVY in patients ≥65 years of age. Based on the results of population pharmacokinetic analysis, no dose adjustment is required.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

Identified precautions

Hypersensitivity

Hypersensitivity reactions, including rash, pruritus, drug hypersensitivity and urticaria, were reported with fremanezumab in clinical trials and in the post-marketing setting. Hypersensitivity reactions were reported with AJOVY in less than 1% of patients in clinical trials. If a hypersensitivity reaction occurs, discontinuation of AJOVY administration should be considered and appropriate therapy should be initiated.

Anaphylactic reactions have been reported rarely with fremanezumab. These reactions mostly occurred within 24 hours of administration although some reactions have been delayed.

In the post-marketing period, one patient who was taking multiple concomitant medications including lamotrigine, and treated with fremanezumab, was reported to have Stevens-Johnson Syndrome. This reaction has also been rarely reported to occur in patients taking other anti-CGRP monoclonal antibodies, along with concomitant medications including lamotrigine.

Major cardiovascular diseases

Patients with certain major cardiovascular diseases were excluded from clinical studies (see section 5.1). No safety data are available in these patients.

Hypertension

Development of hypertension and worsening of pre-existing hypertension have been reported following the use of CGRP antagonists, including AJOVY, in the post-marketing setting. Some of the patients who developed new-onset hypertension had risk factors for hypertension. There were cases requiring initiation of pharmacological treatment for hypertension and, in some cases, hospitalisation. Hypertension may occur at any time during treatment but was most frequently reported within 7 days of therapy initiation. Use of CGRP antagonists, including AJOVY, were discontinued in many of the reported cases.

Monitor patients treated with AJOVY for new-onset hypertension or worsening of pre-existing hypertension, and consider whether discontinuation of AJOVY is warranted if evaluation fails to establish an alternative aetiology or blood pressure is inadequately controlled.

Use in the elderly

No data available

Paediatric use

Episodic Migraine

The safety and effectiveness of AJOVY for the preventive treatment of episodic migraine in paediatric patients younger than 6 years of age have not been established.

AJOVY is not approved in paediatric patients weighing less than 45 kg because of the lack of an appropriate strength presentation.

Bone growth and development (paediatrics)

Longterm effects of CGRP pathway inhibition on skeletal growth and maturation in children are unknown. In the paediatric program, growth and puberty were monitored (e.g., height/weight; Tanner staging); however, clinical exposure is limited in duration, which may be insufficient to detect delayed changes. Health care professionals should periodically monitor growth velocity and pubertal development during treatment (e.g., height z-scores and Tanner staging), and reassess therapy if concerns arise

Chronic Migraine

The safety and effectiveness of AJOVY for the preventive treatment of chronic migraine in paediatric patients has not been established.

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

No formal clinical drug interaction studies have been performed with AJOVY.

The safety and efficacy of AJOVY has been evaluated in patients concurrently taking acute migraine treatments (specifically analgesics, ergots, and triptans) and preventive migraine medications. In population pharmacokinetic analysis, concomitant use of these medications was not found to influence fremanezumab exposure.

CYP450 Substrates

Monoclonal antibodies are not metabolised by cytochrome P450 (CYP) enzymes. Fremanezumab is expected to be metabolised in the same manner as other endogenous proteins; degraded into small peptides and amino acids via catabolic pathways. Therefore, direct pharmacokinetic interactions via the CYP pathway are not expected between AJOVY and co-administered small molecular weight medicinal products.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

There are no fertility data in humans. Available non-clinical data do not suggest an effect on fertility. In a combined fertility/embryofetal development study in rats, fremanezumab had no effect on fertility at exposures corresponding to 22 (females) to 45 (males) times those achieved clinically at a 225 mg/month dose (based on AUC).

No changes in reproductive organ weights, histology, sexual maturation or reproductive function to suggest potential impairment of male or female fertility were observed in young adult rats treated with fremanezumab at subcutaneous doses up to 450 mg/kg/week (yielding 58 [males] and 83 [females] times the systemic exposure [serum AUC] in patients at the maximum recommended human dose of 225 mg/month).

Use in Pregnancy - Pregnancy Category B1

There are limited data from the use of AJOVY in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. In embryo-fetal development (EFD) studies in NZW rabbits and SD rats fremanezumab was administered subcutaneously (achieving exposures approximately 20 times those achieved clinically at a 225 mg/month dose) during the organogenesis period of the pregnancy and was well tolerated and did not induce any maternal or embryo-fetal toxicity at any dose level in either animal species.

Data from an embryo-fetal development study in rabbits demonstrated that fremanezumab crossed the placenta. Concentrations of fremanezumab in newborns were about 9% to 23% exposure relative to the maternal exposure.

In a pre- and postnatal development study in rats (achieving fremanezumab exposures 20 times that achieved clinically at a 225 mg/month dose), no maternal effects were noted as well no effects on F1 offspring following subcutaneous weekly dosing.

Fremanezumab has a long half-life (see Section 5.2 PHARMACOKINETIC PROPERTIES). This should be taken into consideration for women who are pregnant or intend to become pregnant while using AJOVY. Monoclonal antibodies, such as AJOVY, are transported across the placenta in a linear fashion as pregnancy progresses. Therefore, exposure of the fetus is likely to be greater during the second and third trimester of pregnancy.

Use in Lactation

It is unknown whether fremanezumab is excreted in human milk. A risk to the breastfed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from

AJOVY therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

AJOVY has no or negligible influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation 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.

Adults

Summary of the safety profile

The most frequently reported adverse events were local reactions at the injection site [pain (24%), induration (17%), erythema (16%) and pruritus (2%)].

The safety of AJOVY was evaluated in all completed and ongoing clinical studies for all indications. In the four placebo-controlled trials and the single long-term study for migraine, a total of 2,512 patients received at least 1 dose of AJOVY with the mean (standard deviation [SD]) duration of exposure of 244.8 (121.24) days. A total of 2,289 patients (91%) received treatment with AJOVY for ≥3 months, 1,731 patients (69%) received treatment with AJOVY for ≥6 months, and 775 patients (31%) received treatment with AJOVY for ≥12 months.

Table 1 presents the occurrence rates of treatment-emergent adverse events (TEAEs) observed in the double-blind, placebo-controlled trials (phase II and phase III) of the AJOVY clinical development programme. All the adverse events occurring in ≥2% of patients who received AJOVY, at any proposed dose, is presented in the table.

Table 1: Treatment-emergent Adverse Events reported in ≥ 2% of patients who received AJOVY, at any proposed dose, by preferred term and treatment group for all patients in the Placebo-Controlled Studies [a].

MedDRA PT	Number of patients (%)				
	Placebo	Fremanezumab			
	Monthly (N=861)	225 mg monthly (N=386)	675 mg quarterly (N=667)	675/225 mg monthly [b] (N=467)	Total [c] (N=1702)
	n (%)	n (%)	n (%)	n (%)	n (%)
Injection site pain	189 (22)	96 (25)	200 (30)	105 (22)	413 (24)
Injection site induration	113 (13)	71 (18)	131 (20)	90 (19)	292 (17)
Injection site erythema	104 (12)	55 (14)	135 (20)	76 (16)	273 (16)
Upper respiratory tract infection	35 (4)	20 (5)	29 (4)	17 (4)	68 (4)
Nasopharyngitis	35 (4)	13 (3)	30 (4)	16 (3)	62 (4)

Urinary tract infection	15 (2)	7 (2)	14 (2)	9 (2)	35 (2)
Dizziness	9 (1)	4 (1)	9 (1)	12 (3)	31 (2)
Injection site pruritus	2 (<1)	4 (1)	10 (1)	12 (3)	30 (2)
Sinusitis	22 (3)	4 (1)	12 (2)	8 (2)	29 (2)
Back pain	12 (1)	4 (1)	11 (2)	8 (2)	29 (2)
Injection site hemorrhage	16 (2)	4 (1)	16 (2)	8 (2)	28 (2)
Bronchitis	6 (<1)	10 (3)	9 (1)	6 (1)	26 (2)

[a] Double-blind, placebo-controlled studies (phase II and phase III) in patients with episodic and chronic migraine exposed to AJOVY

[b] Patients received fremanezumab at 225 mg monthly with a starting dose of 675 mg.

[c] Adverse events that occurred in patients in all fremanezumab treatment groups, including the 675 mg monthly and 900 mg monthly treatment groups, are included in this total group

MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients; PT=preferred term

Tabulated list of adverse reactions

Adverse drug reactions from clinical studies are presented according to the MedDRA system organ classification. Within each system organ class, events are ranked by frequency, most frequent events first. Within each frequency grouping, adverse drug reactions are presented in the order of decreasing seriousness. Frequency categories are based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

The following Adverse drug reactions have been identified in the AJOVY clinical development programme. Table 2 depicts the relative frequencies of Adverse drug reactions in AJOVY and placebo treated patients.

Table 2: Adverse drug reactions occurring in clinical studies [a]

System Organ Class		**AJOVY N=1702 n (%)**	**Placebo N=861 n (%)**
General Disorders and Administration Site Conditions			
Very Common	Injection Site Pain	413 (24)	189 (22)
	Injection Site Induration	292 (17)	113 (13)
	Injection Site Erythema	273 (16)	104 (12)
Common	Injection Site Pruritus	30 (2)	2 (<1)
Uncommon	Injection Site Rash	13 (<1)	0

[a] Double-blind, placebo-controlled studies (phase II and phase III) in patients with episodic and chronic migraine exposed to AJOVY or placebo for up to 52 weeks of treatment duration.

Description of selected adverse events

Injection site reactions

The most frequently observed local reactions at the injection site were pain, induration and erythema. These reactions were predominantly mild to moderate in severity. Pain, induration and erythema were typically observed immediately after injection while pruritus and rash appeared within a median of 24 and 48 hours, respectively. All injection site reactions resolved, mostly within a few hours or days. Injection site reactions generally did not necessitate discontinuation of the medicinal product.

Immunogenicity

Clinical immunogenicity of AJOVY was monitored by analysing anti-drug antibodies (ADA) and neutralising antibodies in drug-treated patients. In placebo-controlled studies in adult patients, 0.4 % of patients (6 out of 1,701) treated with AJOVY developed anti-drug antibodies (ADA). The antibody responses were of low titer. One of these 6 patients developed neutralising antibodies. With 12 months of treatment, in the long-term study [Study 3], ADA were detected in 2.3% of patients (43 out of 1,888) with 0.95% of the patients developing neutralising antibodies. There were no significant adverse events related to ADA development in patients with treatment-emergent ADA. The safety and efficacy of fremanezumab were not affected by ADA development.

Paediatric Patients

The safety of AJOVY was evaluated in 225 paediatric patients aged 6 years and older with episodic migraine who received at least one dose of AJOVY. Of these patients, 209 received AJOVY monthly for at least 6 months and 100 received AJOVY for at least 12 months. In the placebo-controlled trial, 123 paediatric patients with episodic migraine were treated with AJOVY. The most common adverse reactions of AJOVY observed were injection site reactions. Hypersensitivity reactions were also observed. Overall, the safety profile in paediatric patients is similar to the known safety profile in adults.

In a placebo-controlled study in paediatric patients with episodic migraine, treatment-emergent anti-drug antibody responses were observed in 2 out of 123 (1.6%) AJOVY-treated patients. One of the 2 patients developed anti-fremanezumab neutralizing antibodies at Day 85. The available data are too limited to make definitive conclusions about the impact of the development of anti-fremanezumab antibodies on the pharmacokinetics, efficacy, or safety of AJOVY in paediatric patients.

Adverse Reactions from Post-marketing reports

The following are additional adverse drug reactions that have been reported since the introduction of fremanezumab to the market. Frequency categories are based on the following convention: Very common (≥10%); common (≥1% to <10%); uncommon (≥0.1% to <1%); rare (≥0.01% to <0.1%); very rare (<0.01% including isolated reports).

<u>Immune system disorders</u>

Uncommon: Hypersensitivity reactions such as rash, pruritus, urticaria and swelling

Rare: Anaphylactic reaction

<u>Gastrointestinal disorders</u>

Unknown: Constipation*

<u>General disorders and administration site conditions</u>

Unknown: Fatigue*

*Causal relationship not established

Vascular Disorders

Unknown: Hypertension (see Section 4.4 Special Warnings and Precautions for use)

4.9 OVERDOSE

Doses up to 2000 mg have been administered intravenously in clinical trials without dose-limiting toxicity. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse effects and given appropriate symptomatic treatment if necessary.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Analgesics, antimigraine preparations, ATC code: N02CD03.

Mechanism of action

Fremanezumab is a fully humanised IgG2Δa/kappa monoclonal antibody produced by recombinant DNA technology that is derived from a murine precursor. Fremanezumab potently and selectively binds the calcitonin gene-related peptide (CGRP) ligand and blocks both CGRP isoforms (α-and β-CGRP) from binding to the CGRP receptor preventing the activation of the trigeminal system. While the precise mechanism of action by which fremanezumab prevents migraine attacks is unknown, it is believed that prevention of migraine is obtained by its effect modulating the trigeminal system.

Fremanezumab is highly specific for CGRP and does not bind to closely related family members (e.g., amylin, calcitonin, intermedin and adrenomedullin).

Pharmacodynamic effects

Fremanezumab binds to the C-terminus of CGRP preventing interaction with the CGRP receptor and thereby inhibits physiological signalling of the CGRP receptor. The relationship between the pharmacodynamic activity and the mechanism(s) by which fremanezumab exerts its clinical effects is unknown.

Clinical trials

Patients with certain major cardiovascular diseases were excluded from clinical studies. No safety data are available in these patients.

Adults

The efficacy of AJOVY was assessed in two randomised, 12-week, double-blind, placebo-controlled phase III studies in adult patients with episodic (Study 1) and chronic migraine (Study 2).

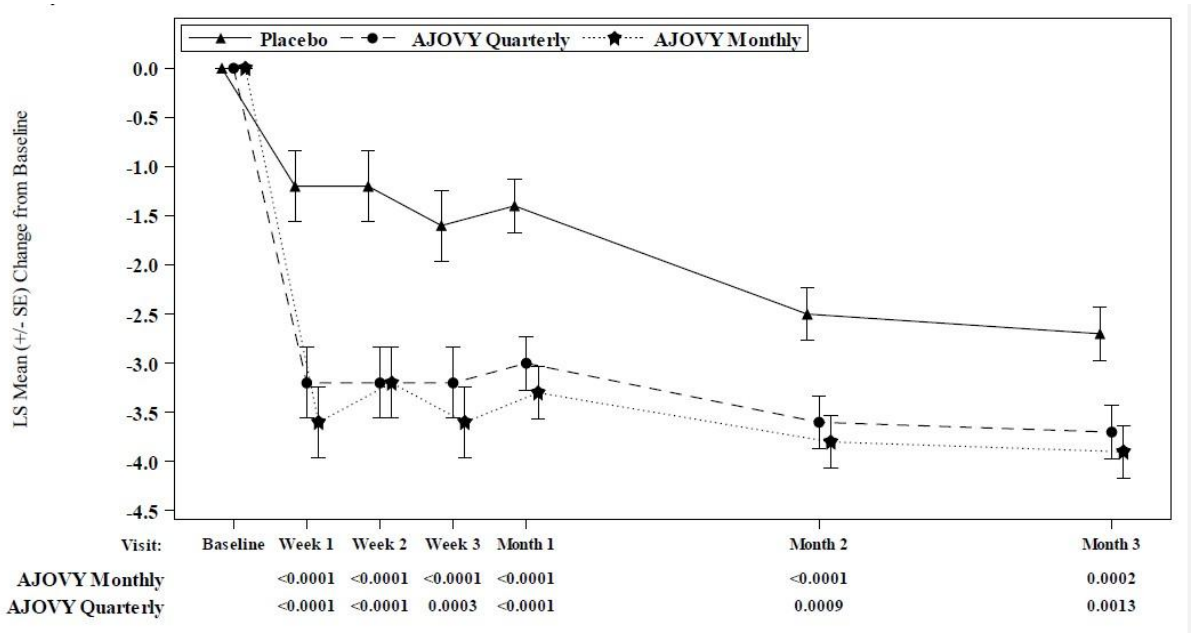
Episodic Migraine

Study 1 included adults with a history of episodic migraine (patients with less than 15 headache days per month). All patients were randomised to one of three arms: 675 mg fremanezumab every three months (quarterly), 225 mg fremanezumab once a month (monthly), or monthly administration of placebo administered via subcutaneous injection. Patients were allowed to use acute headache treatments during the study. A sub-set of patients (21%) were also allowed to use one concomitant, preventive medication, consistent with patient treatment outside of controlled clinical settings.

In Study 1, a total of 875 patients (742 females, 133 males), ranging in age from 18 to 70 years, were randomised. A total of 791 patients completed the 12-week double-blind treatment period.

The primary efficacy endpoint was the mean change from baseline in the monthly average number of migraine days during the 12-week treatment period. Both monthly and quarterly dosing regimens of AJOVY demonstrated statistically significant and clinically meaningful improvement from baseline compared to placebo at all time points over the 12-week treatment period (see Figure 1).

Figure 1: Mean Change from Baseline in the Monthly Average Number of Migraine Days for Study 1



Mean at baseline (monthly average number of migraine days): Placebo: 9.1, AJOVY Quarterly: 9.2, AJOVY Monthly: 8.9.

AJOVY treatment demonstrated statistically significant and clinically meaningful improvements from baseline compared to placebo for all key efficacy variables (see Table 3).

Table 3: Key Efficacy Variables for Study 1

Study 1 Efficacy Endpoint	**AJOVY Monthly (N=287)**	**AJOVY Quarterly (N=288)**	**Placebo (N=290)**
Change from baseline in monthly average number of migraine days***	-3.7**	-3.4**	-2.2
Reduction of at least 50% in monthly average number of migraine days	47.7%**	44.4%**	27.9%

Change from baseline in monthly average number of days of acute headache medication	-3.0**	-2.9**	-1.6
Change from baseline in monthly average number of migraine days at 4 weeks after 1st dose	-3.5**	-3.3**	-1.7
Change from baseline in the monthly average number of migraine days in patients without concomitant migraine preventive medication	-3.7**	-3.5**	-2.4
Change from baseline in disability scores (Migraine Disability Assessment)	-24.6*	-23.0*	-17.5

* Significantly different from placebo (p<0.0025)

** Significantly different from placebo (p<0.0001)

*** Primary efficacy endpoint

On average in a given month, more than 67% of episodic migraine patients treated with AJOVY achieved at least a 25% reduction in monthly migraine days (compared to 53% of placebo), while more than 25% of patients achieved at least a 75% reduction in monthly migraine days (compared to 15% of placebo), and more than 8% of patients achieved a 100% reduction in monthly migraine days (compared to 4% of placebo).

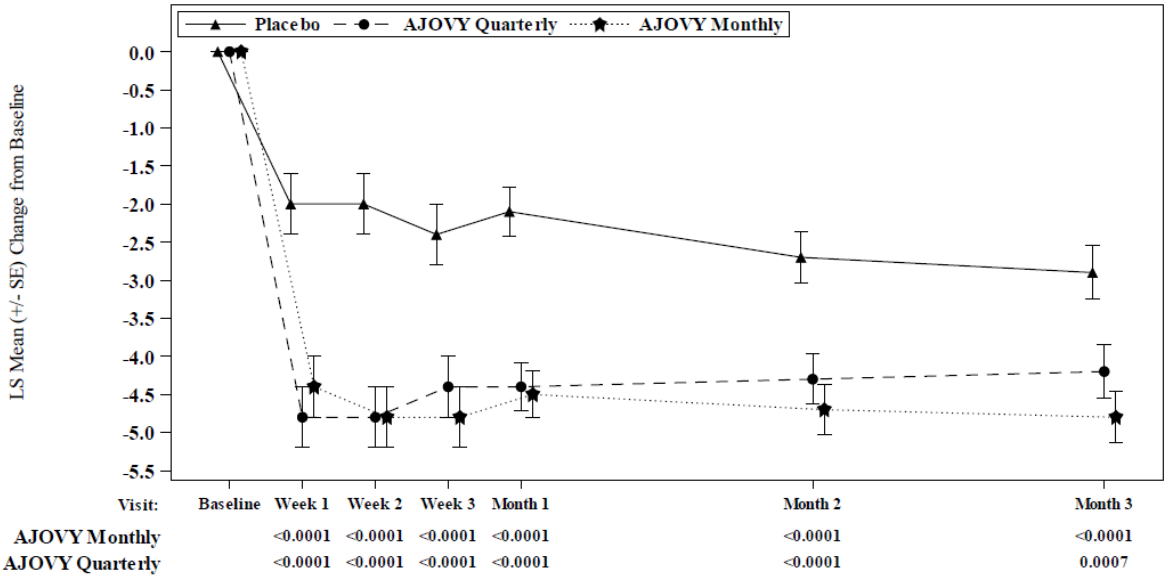
Chronic Migraine

Study 2 included adults with a history of chronic migraine (patients with 15 headache days or higher per month). All patients were randomised to one of three arms: 675 mg fremanezumab for the starting dose followed by 225 mg fremanezumab once a month (monthly), 675 mg fremanezumab every three months (quarterly), or monthly administration of placebo administered via subcutaneous injection. Patients were allowed to use acute headache treatments during the study. A sub-set of patients (21%) were also allowed to use one concomitant, preventive medication, consistent with patient treatment outside of controlled clinical settings.

In Study 2, a total of 1,130 patients (991 females, 139 males), ranging in age from 18 to 70 years, were randomised. A total of 1,034 patients completed the 12-week double-blind treatment period.

The primary efficacy endpoint was the mean change from baseline in the monthly average number of headache days of at least moderate severity during the 12-week treatment period (See Table 4). Both monthly and quarterly dosing regimens of AJOVY demonstrated statistically significant and clinically meaningful improvement from baseline compared to placebo at all time points over the 12-week treatment period (see Figure 2).

Figure 2: Mean Change from Baseline in the Monthly Average Number of Headache Days of At Least Moderate Severity for Study 2



Mean at baseline (monthly average number of headache days of at least moderate severity): Placebo: 13.3, AJOVY Quarterly: 13.2, AJOVY Monthly: 12.8.

AJOVY treatment demonstrated statistically significant and clinically meaningful improvements from baseline compared to placebo for all key efficacy variables.

Table 4: Key Efficacy Variables for Study 2

Study 2 Efficacy Endpoint	**AJOVY Monthly (N=375)**	**AJOVY Quarterly (N=375)**	**Placebo (N=371)**
Change from baseline in the monthly average number of headache days of at least moderate severity***	-4.6**	-4.3**	-2.5
Change from baseline in the monthly average number of migraine days in patients	-5.0**	-4.9**	-3.2
Change from baseline in monthly average number of headache days of at least moderate severity at 4 weeks after 1st dose	-4.6**		-2.3
Reduction of at least 50% in monthly average number of headache days of at least moderate severity	40.8%**	37.6%**	18.1%
Change from baseline in monthly average number of days of acute headache medication	-4.2**	-3.7**	-1.9
Change from baseline in the monthly average number of headache days of at least moderate severity in patients without concomitant migraine preventive medication	-4.8**	-4.6**	-2.6
Change from baseline in disability scores (6- Item Headache Impact Test)	-6.8**	-6.4*	-4.5

* Significantly different from placebo (p=0.0001)
** Significantly different from placebo (p<0.0001)

*** Primary efficacy endpoint

On average in a given month, more than 61% of chronic migraine patients treated with AJOVY achieved at least a 25% reduction in monthly headache days of at least moderate severity (compared to 46% of placebo), while more than 20% of patients achieved at least a 75% reduction in monthly headache days of at least moderate severity (compared to 10% of placebo), and more than 7% of patients achieved a 100% reduction in monthly headache days of at least moderate severity (compared to 4% of placebo).

Long-term open label study (Study 3)

For all episodic and chronic migraine patients, efficacy was sustained for up to 12 additional months in the long-term open label study (Study 3), in which patients received 225 mg fremanezumab monthly or 675 mg quarterly. 79% of patients completed the 12-month treatment period of Study 3. Pooled across the two dosing regimens, a reduction of 6.6 monthly migraine days was observed after 15 months relative to Study 1 and Study 2 baseline. 61% of patients completing Study 3 achieved a 50% response in the last month of the study. No safety signal was observed during the 15-month combined treatment period.

Intrinsic and extrinsic factors

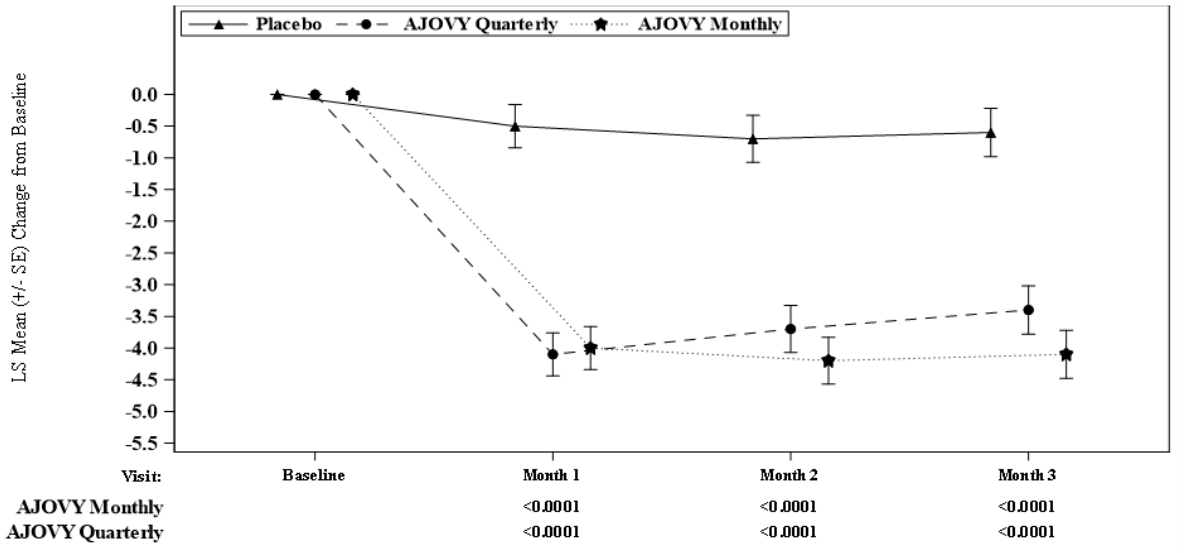
The efficacy and safety of AJOVY was demonstrated regardless of age, gender, race, use of concomitant preventive medications, use of topiramate for migraine in the past, and use of onabotulinumtoxin A for migraine in the past.

Difficult to treat migraine

The efficacy and safety of fremanezumab in a total of 838 episodic and chronic migraine patients with documented inadequate response to two to four classes of prior migraine preventive medicinal products was assessed in a randomised study (Study 4), which was composed of a 12-week double-blind, placebo-controlled treatment period followed by a 12-week open-label period.

The primary efficacy endpoint was the mean change from baseline in the monthly average number of migraine days during the 12-week double-blind treatment period. Key secondary endpoints were the achievement of at least 50% reduction from baseline in monthly migraine days, the mean change from baseline in the monthly average number of headache days of at least moderate severity and change from baseline in monthly average number of days of acute headache medicinal product use. Both monthly and quarterly dosing regimens of fremanezumab demonstrated statistically significant and clinically meaningful improvement from baseline compared to placebo for key endpoints. Therefore, the results of Study 4 are consistent with the main findings of the previous efficacy studies and in addition demonstrate efficacy in difficult to treat migraine, including mean reduction in monthly migraine days (MMD) of -3.7 (95% CI: - 4.38, -3.05) with fremanezumab quarterly and -4.1 (95% CI: -4.73, -3.41) with fremanezumab monthly compared to -0.6 (95% CI: -1.25, 0.07) in placebo-treated patients. 34% of the patients treated with fremanezumab quarterly and 34% of the patients treated with fremanezumab monthly achieved at least 50% reduction in MMD, compared to 9% in placebo-treated patients ($p<0.0001$) during the 12-week treatment period. The effect also occurred from as early as the first month and was sustained over the treatment period (see Figure 3). No safety signal was observed during the 6-month treatment period.

Figure 3: Mean Change from Baseline in Monthly Average Number of Migraine Days for Study 4



Mean at baseline (monthly average number of migraine days): Placebo: 14.4, AJOVY Quarterly: 14.1, AJOVY Monthly: 14.1.

Paediatric Patients

The efficacy of AJOVY for the preventive treatment of episodic migraine in paediatric patients aged 6 years and older was evaluated in a multicenter, randomized, 3-month, double-blind, placebo-controlled study.

Episodic Migraine.

The study included paediatric patients aged 6 years and older with a history of episodic migraine (patients with <15 headache days per month). All patients had at least 4 migraine days per month and were randomized (1:1) to receive monthly subcutaneous injections of either AJOVY or placebo, over a 3-month period. Patients who weighed 45 kg or more received AJOVY 225 mg and patients who weighed under 45 kg received AJOVY 120 mg. Patients were allowed to use acute headache treatments during the study. The chronic use of two concomitant preventive migraine medications for any condition was allowed for the duration of the study for approximately 30% of subjects as per the study protocol. At baseline, 21% (50/235) of subjects were receiving up to two preventative medications and continued to receive this medication during the study.

The primary efficacy endpoint was the mean change from baseline (28-day baseline period) in the monthly average number of migraine days during the 12-week period after the first dose of study drug. Secondary endpoints included the proportion of patients reaching at least a 50% reduction in monthly average number of migraine days during the 3-month treatment period; the mean change from baseline in the monthly average number of days of use of any acute headache medication during the 3-month treatment period; and the mean change from baseline in monthly average number of headache days of at least moderate severity during the 3-month treatment period.

A total of 237 patients were randomized. Two subjects were excluded from the analysis sets due to Good Clinical Practice non-compliance. A total of 235 subjects (130 females, 105 males) were included in the intent-to-treat analysis set and safety analysis set

AJOVY demonstrated statistically significant improvements for efficacy endpoints compared to placebo over the 12 week period, as summarized in Table 5.

Table 5: Efficacy Endpoints for Paediatric Study

Efficacy Endpoint	**Placebo (N=111) ***	**Fremanezumab combined (N=123)****
Monthly migraine days (MMD) #		
Baseline	7.5	7.8
LS mean change from baseline[a]	-1.4	-2.5
LS mean difference from placebo (95% CI) [a]		-1.0 (-1.90, -0.16)
P-value (vs. placebo) [a]		0.0210
Monthly headache days of at least moderate severity #		
Baseline	7.9	8.2
LS mean change from baseline[a]	-1.5	-2.6
LS mean difference from placebo (95% CI)		-1.1 (-2.06, -0.20)
P-value (vs. placebo) [a]		0.0172
≥ 50% MMD responders		
Percentage [%]	27.0%	47.2%
Estimated difference from placebo		20.1%
P-value (vs. placebo) [a]		0.0016
Monthly acute headache medication days #		
Baseline	5.6	5.8
LS mean change from baseline[a]	-1.0	-2.1
LS mean difference from placebo (95% CI) [a]		-1.1 (-1.77, -0.42)
P-value (vs. placebo) [a]		0.0016

FAS (Full Analysis Set): Includes all randomized patients who received at least 1 dose of study drug and had at least 10 days of post-baseline efficacy assessments on the primary endpoint.
CI = confidence interval.
LS= least squares
A fixed-sequence (hierarchical) testing procedure was implemented to control the type I error rate at 0.05.

* One patient in the placebo group was excluded from the analysis due to not having at least 10 days of post-baseline efficacy data.
**Fremanezumab combined group (N = 123) includes 36 patients treated with 120 mg and 87 patients treated with 225 mg.
Those efficacy endpoints are continuous. No missing data imputation is done for those endpoints as all patients in FAS have their monthly average number of days of efficacy variables during the 12-week period.
[a] Based on the ANCOVA model that included treatment, gender, region, and baseline preventive medication use (yes/no) as fixed effects and corresponding baseline value and years since onset of migraine as covariates.
[b] p-value is from a logistic regression model with the following factors: treatment, sex, region, puberty status, weight category, and preventive migraine medication use at baseline (Yes/No).

Figure 4: Change from Baseline in Monthly Migraine Days for Paediatric Study

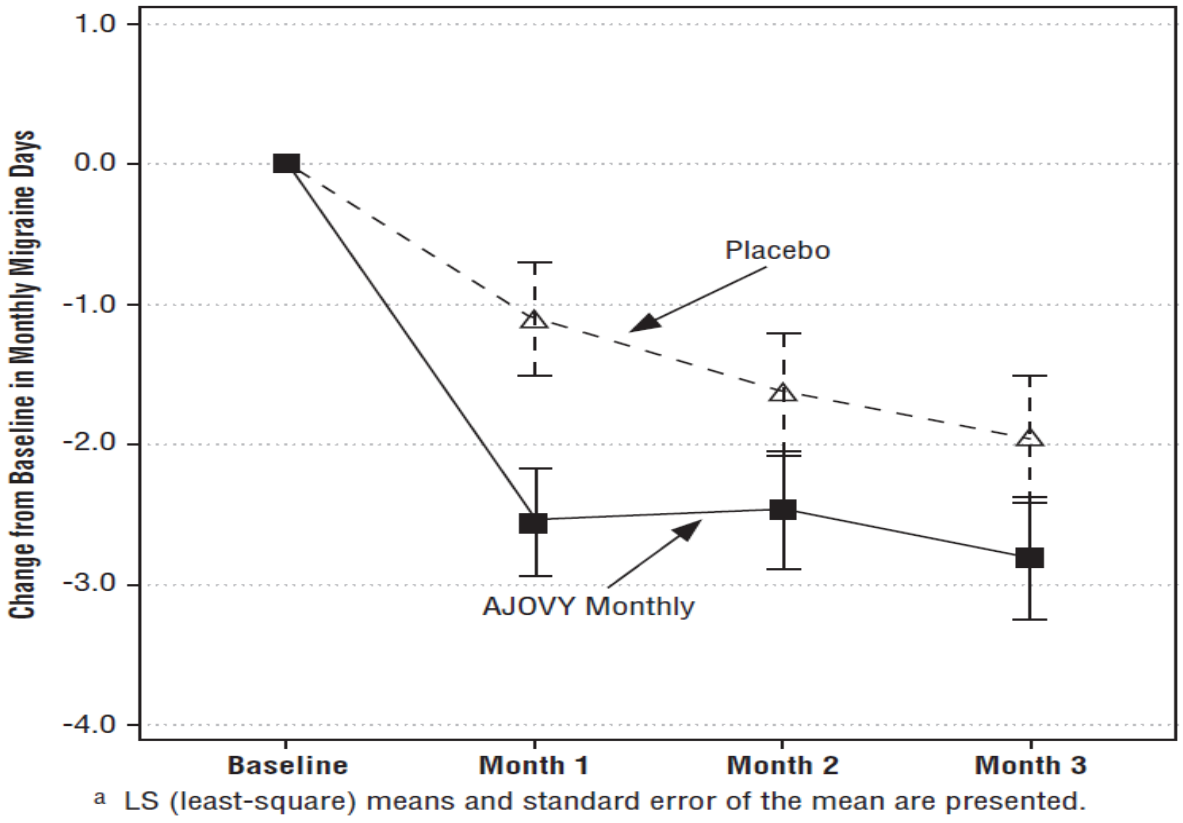


Figure 4 displays the mean change from baseline in the average monthly number of migraine days.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

After single subcutaneous administrations of 225 mg, 675 mg, and 900 mg fremanezumab, median time to maximum concentrations (t_{max}) was 5 to 7 days. The absolute bioavailability of fremanezumab after subcutaneous administration was about 55% as determined by subcutaneous vs. intravenous administrations of 225 mg and 900 mg. Dose proportionality, based on population pharmacokinetics, was observed between 225 mg to 900 mg. The geometric mean (%CV) for fremanezumab maximum concentration (C_{max}) was 29.7 (13.7%) µg/mL and total systemic exposure ($AUC_{0\text{-}inf}$) was 42.5 (17.5%) h*mg/mL following administration of 225 mg fremanezumab. The geometric mean (%CV) for fremanezumab maximum concentration (C_{max}) was 104.8 (28.8%) µg/mL and total systemic exposure

($AUC_{0\text{-}inf}$) was 132.8 (31.7%) h*mg/mL following administration of 675 mg fremanezumab. Steady state was achieved by approximately 168 days (approximately 6 months) following 225 mg subcutaneous monthly and 675 mg subcutaneous quarterly dose regimens.

Median accumulation ratio, based on once monthly and once quarterly dosing regimens, is approximately 2.3 and 1.2, respectively.

Distribution

Fremanezumab has an apparent volume of distribution of approximately 6 litres (for a patient at a weight of 71 kg), suggesting minimal distribution to the extravascular tissues.

Metabolism

Similar to other monoclonal antibodies, fremanezumab is expected to be degraded by enzymatic proteolysis into small peptides and amino acids (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Elimination

As fremanezumab binds to a soluble target, it is not expected to be eliminated through a target-mediated clearance. Fremanezumab has an apparent clearance of approximately 0.141 L/day (for a patient at a weight of 71 kg). Fremanezumab has an estimated half-life of 31 days.

Special populations

A population pharmacokinetic analysis looking at age, race, gender, and weight was conducted on data from 2,287 subjects. No dose adjustments are required for AJOVY.

Renal or hepatic impairment

Since monoclonal antibodies are not known to be eliminated via renal pathways or metabolised in the liver, renal and hepatic impairment are not expected to impact the pharmacokinetics of fremanezumab. No clinical studies were conducted to assess the effect of renal or hepatic impairment on the pharmacokinetics of fremanezumab.

Paediatric Patients

Following subcutaneous administration of 225 mg AJOVY monthly in the paediatric population weighing 45 kg or more, the predicted steady state fremanezumab exposures (maximum plasma concentration [C_{max}], area under the plasma concentration-time curve [AUC]) are similar to those of adults.

5.3 PRECLINICAL SAFETY DATA

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity or toxicity to reproduction and development in studies conducted in rats and monkeys.

Intravenous and subcutaneous repeated administrations to rats (up to 3 months) and monkeys (up to 6 months) did not induce toxic effect and no target organs were identified (including injection sites). In the pivotal 6-month chronic toxicity study in monkeys at the NOAEL (No Observed Adverse Effects Level) dose of 300 mg/kg/week (at least 158 times the exposure achieved at MRHD (Maximum Recorded Human Dose) on an AUC (Area Under the Curve) basis) subcutaneous weekly dosing was well tolerated.

Safety pharmacology studies to assess cardiovascular (CV) effects in cynomolgus monkeys demonstrated no CV effects following single and repeated administrations. No effect on CNS and respiratory function was noted following a single administration to SD (Sprague Dawley) rats.

Genotoxicity

As fremanezumab is a monoclonal antibody, no genotoxicity studies have been conducted.

Carcinogenicity

As fremanezumab is a monoclonal antibody no carcinogenicity studies have been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each pre-filled syringe or autoinjector contains the following excipients:

Histidine
Histidine hydrochloride monohydrate Sucrose
Disodium edetate Polysorbate 80
Water for injections

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

- Store in a refrigerator (2°C to 8°C). Do not freeze.
- Store in the original carton in order to protect from light.
- AJOVY may be stored unrefrigerated for up to 7 days at a temperature up to 30°C. AJOVY must be discarded if not used within 7 days of removal from refrigeration.

6.5 NATURE AND CONTENTS OF CONTAINER

AJOVY is supplied as follows:

Autoinjector:

Autoinjector containing an integrated 1.5 mL solution in a 2.25 mL Type I glass pre-filled syringe with plunger stopper (bromobutyl rubber) and needle.

Pack sizes of 1 or 3 autoinjectors. Not all pack sizes may be marketed.

Pre-filled syringe:

1.5 mL solution in a 2.25 mL Type I glass syringe with plunger stopper (bromobutyl rubber) and needle. The pre-filled syringe cap is not made with natural rubber latex.

Pack sizes of one 225mg/1.5mL or three 225mg/1.5mL pre-filled syringes. Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Dispose of carefully in a sharps container. Do not throw away (dispose of) loose needles, syringes, pre-filled syringes or autoinjectors in your household rubbish.

Do not recycle used sharps disposal container.

6.7 PHYSIOCHEMICAL PROPERTIES

Chemical Structure

$C_{6470}H_{9952}N_{1716}O_{2016}S_{46}$

CAS number

1655501-53-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only

8 SPONSOR

Teva Pharma Australia Pty Ltd
Level 1, 37 Epping Rd
Macquarie Park, NSW, 2113
Ph: 1800 288 382
www.tevapharma.com.au

9 DATE OF FIRST APPROVAL

Ajovy pre-filled syringe: 20th September 2019

Ajovy autoinjector: 2nd June 2021

10 DATE OF REVISION

30 0ctober 2026

Summary table of changes

Section Changed	Summary of new information
All	Indication extended to include paediatric patients