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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Clinical Data on a Preventive Migraine Treatment

Announcer
You're listening to ReachMD. This Medical Industry Feature titled "Clinical Data on a Preventive Migraine Treatment", is sponsored by Teva Pharmaceuticals.

Dr. Torphy
Hello - thanks for joining me today to learn more about long-acting protection against migraine with AJOVY.[1] Before we get into it, allow me to introduce myself. I am Dr Brad Torphy–Managing Director of Chicago Headache and Research Institute.

Something important to consider when prescribing a preventive migraine medication is—will it wear off or last to the next dose?

That's why I want to talk to you today about AJOVY - the long-acting anti-CGRP injection with lasting protection against migraine.[1] As a reminder, AJOVY is indicated for the preventive treatment of migraine in adults. Please note AJOVY is contraindicated in patients with serious hypersensitivity to fremanezumab-vfrm or to any of the excipients. Reactions have included anaphylaxis and angioedema.

During this presentation today we'll take an in-depth look at the clinical trials to review how AJOVY demonstrated sustained efficacy, reductions in use of acute medication, and no evidence of wearing off from one dose to the next.

Before reviewing the clinical results, let's first look at the trial designs for both the HALO trial and the Long-Term Extension study. The HALO study consisted of two phase 3, 12-week, randomized, double-blind, placebo-controlled, parallel-group trials.[2,3]

Patients were randomized in either AJOVY monthly dosing, AJOVY quarterly dosing, or the placebo arm, after which they underwent a screening visit, a 28-day preintervention, and a run-in period, followed by a 12-week intervention period, with a final evaluation at Week 12.[2,3] Some of the patients in the 12-week HALO studies rolled over into the Long-Term Extension study—a 12-month, multicenter, randomized, double-blind, parallel-group clinical trial. The long-term extension study was not placebo controlled, but patients were blinded as to the dosing regimen.[4]

Please note, today we will only be looking at the episodic migraine results. If you'd like to see the results for chronic migraine, please visit AJOVYHCP.com.

The primary endpoint in the HALO episodic migraine trial was mean change from baseline in the monthly average number of migraine days for both monthly and quarterly dosing options during the 12-week period.[3]

As you can see AJOVY demonstrated a statistically significant improvement in the mean reduction from baseline of 4.3 migraine days at month 3 versus 3.1 days for placebo. The Long-Term Extension study further demonstrated a mean reduction of 5.1 migraine days with monthly dosing. Similar results were observed for patients taking quarterly dosing.[1,3,4,5]

Be aware that hypersensitivity reactions, including rash, pruritus, drug hypersensitivity, and urticaria were reported with AJOVY in clinical trials. Most reactions were mild to moderate, but some led to discontinuation or required corticosteroid treatment. Most reactions were reported from within hours to one month after administration. Cases of anaphylaxis and angioedema have been reported in the post marketing setting. If a hypersensitivity reaction occurs, consider discontinuing AJOVY and institute appropriate therapy.

I want to also mention a secondary endpoint of the HALO trial–change in use of acute medication. During the 12-week treatment period, patients with episodic migraine receiving the AJOVY monthly dosing regimen had a 3.0 reduction in the average number of days of use

of acute headache medication compared with 1.6 days for placebo. Similar results were also seen in chronic migraine.[1]

This endpoint tells us that patients taking AJOVY significantly decreased their need for acute medication. What might these data mean for your patients?

Now I want to take you through the post-hoc analyses that showed no evidence of AJOVY wearing off from one dose to the next. To assess these dosing periods, data for patients with chronic and episodic migraine from the HALO trials who rolled over into the Long-Term Extension study were included in the post hoc analyses. We will, again, only be discussing the episodic patients.

The analyses looked at the mean number of weekly migraine days in patients on monthly dosing during months 3, 6, 9, and 15. Each of these months—3, 6, 9, and 15—was split into two: weeks 1 through 3, or the beginning of the dosing period, versus week 4, the end of the dosing period. Let's look at the figures for the weekly average number of migraine days during weeks 1 through 3. And now let's compare them with the number of migraine days during week 4. As you can see, the weekly number of migraine days was similar between the beginning and end of the dosing period, across all the months shown.[6] Note, for all post hoc analyses, no determination of statistical significance can be made and no conclusions should be drawn.

Now, let's think back to our consideration for preventive migraine therapy, "will it wear off or last until the next dose?" With these data in mind, wouldn't you consider AJOVY an appropriate option for your patients needing preventive therapy?

Of course safety must be considered before making any decisions, so let's take a look at those results from the HALO and Long-Term Extension studies. Shown here are the adverse reactions reported by at least 2% of patients on AJOVY and greater than placebo from the HALO trial.[1]

In the Long-Term Extension study, you can see the adverse reactions that occurred in more than 6% of patients.[7] It's important to mention that no new safety signals were identified in the Long-Term Extension study.[5]

Before we wrap things up, I want to remind you that patients have an option to take AJOVY either monthly or quarterly. Having such options may help your patients stay protected–whatever their lifestyle and schedules demand from them. You and your patients should decide together which option would be best.

Thank you for watching my presentation today. I hope the information I've shared helps you and your practice. Remember, AJOVY is the long-acting anti-CGRP injection with lasting protection against migraine. If you need additional details, or the full Prescribing Information, please visit AJOVYHCP.com.

Announcer

INDICATION

AJOVY® (fremanezumab-vfrm) injection is indicated for the preventive treatment of migraine in adults.

IMPORTANT SAFETY INFORMATION

Contraindications: AJOVY is contraindicated in patients with serious hypersensitivity to fremanezumab-vfrm or to any of the excipients. Reactions have included anaphylaxis and angioedema.

Hypersensitivity Reactions: Hypersensitivity reactions, including rash, pruritus, drug hypersensitivity, and urticaria were reported with AJOVY in clinical trials. Most reactions were mild to moderate, but some led to discontinuation or required corticosteroid treatment. Most reactions were reported from within hours to one month after administration. Cases of anaphylaxis and angioedema have been reported in the postmarketing setting. If a hypersensitivity reaction occurs, consider discontinuing AJOVY and institute appropriate therapy.

Adverse Reactions: The most common adverse reactions in clinical trials (≥5% and greater than placebo) were injection site reactions.

Please see the full Prescribing Information for AJOVY.

Announcer

This program was sponsored by Teva Pharmaceuticals. If you missed any part of this discussion, visit ReachMD.com/IndustryFeature. This is ReachMD. Be part of the knowledge.

Please see the full Prescribing Information for AJOVY at https://www.ajovy.com/globalassets/ajovy/ajovy-pi.pdf

References:

1. AJOVY® (fremanezumab-vfrm) injection Current Prescribing Information. North Wales, PA: Teva Pharmaceuticals USA, Inc.
2. Silberstein SD, Dodick DW, Bigal ME, et al. Fremanezumab for the preventive treatment of chronic migraine. *N Engl J Med*. 2017;377(22):2113-2122.
3. Dodick DW, Silberstein SD, Bigal ME, et al. Effect of fremanezumab compared with placebo for prevention of episodic migraine: a randomized clinical trial. *JAMA*. 2018;319(19):1999-2008.
4. Goadsby PJ, Silberstein SD, Yeung PP, et al. Long-term safety, tolerability, and efficacy of fremanezumab in migraine: a randomized study. *Neurology*. 2020;95:e2487–e2499.
5. Data on file. Parsippany, NJ: Teva Pharmaceuticals USA, Inc.
6. Blumenfeld AM, Stevanovic DM, Ortega M, et al. No “Wearing-Off Effect” Seen in Quarterly or Monthly Dosing of Fremanezumab: Subanalysis of a Randomized Long-Term Study. *Headache*. 2020;60(10):2431-2443.
7. Ning X, Cohen JM, Bennett N, Yeung PP, Yang R. Long-termsafety of fremanezumab: results of a 1-year study. Paper presented at: The American Academy of Neurology 71st Annual Meeting; May 4-10, 2019; Philadelphia, PA.

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AJOVY safely and effectively. See full prescribing information for AJOVY.

AJOVY® (fremanezumab-vfrm) injection, for subcutaneous use
Initial U.S. Approval: 2018

INDICATIONS AND USAGE

AJOVY is a calcitonin gene-related peptide antagonist indicated for the preventive treatment of migraine in adults. (1)

DOSAGE AND ADMINISTRATION

- For subcutaneous use only. (2.1, 2.2)
- Two subcutaneous dosing options of AJOVY are available to administer the recommended dosage:
  - 225 mg monthly, or
  - 675 mg every 3 months (quarterly) (2.1)
- The 675 mg quarterly dosage is administered as three consecutive injections of 225 mg each. (2.1)
- Administer in the abdomen, thigh, or upper arm subcutaneously. (2.2)
- See Dosage and Administration for important administration instructions. (2.2)

AJOVY® (fremanezumab-vfrm) injection

DOSAGE FORMS AND STRENGTHS

Injection: 225 mg/1.5 mL solution in a single-dose prefilled autoinjector. (3)
Injection: 225 mg/1.5 mL solution in a single-dose prefilled syringe. (3)

CONTRAINDICATIONS

AJOVY is contraindicated in patients with serious hypersensitivity to fremanezumab-vfrm or to any of the excipients. (4)

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions: If hypersensitivity occurs, consider discontinuing AJOVY and institute appropriate therapy. (5.1)

ADVERSE REACTIONS

The most common adverse reactions (≥5% and greater than placebo) were injection site reactions. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals at 1-888-483-8279 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

AJOVY is indicated for the preventive treatment of migraine in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Two subcutaneous dosing options of AJOVY are available to administer the recommended dosage:

- 225 mg monthly, or
- 675 mg every 3 months (quarterly), which is administered as three consecutive subcutaneous injections of 225 mg each.

When switching dosage options, administer the first dose of the new regimen on the next scheduled date of administration. If a dose of AJOVY is missed, administer as soon as possible. Thereafter, AJOVY can be scheduled from the date of the last dose.

2.2 Important Administration Instructions

AJOVY is for subcutaneous use only.

AJOVY may be administered by healthcare professionals, patients, and/or caregivers. Prior to use, provide proper training to patients and/or caregivers on the preparation and administration of AJOVY prefilled syringe, including aseptic technique *[see Instructions for Use]*:

- Remove AJOVY from the refrigerator. Prior to use, allow AJOVY to sit at room temperature for 30 minutes protected from direct sunlight. Do not warm by using a heat source such as hot water or a microwave. Do not use AJOVY if it has been at room temperature for 7 days or longer *[see How Supplied/Storage and Handling (16.2)]*.
- Follow aseptic injection technique every time AJOVY is administered.
- Inspect AJOVY for particles or discoloration prior to administration *[see Dosage Forms and Strengths (3)]*. Do not use if the solution is cloudy, discolored, or contains particles.
- 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, you may use the same body site, but not the exact location of the previous injection.
- Do not co-administer AJOVY with other injectable drugs at the same injection site.

3 DOSAGE FORMS AND STRENGTHS

AJOVY is a sterile, clear to opalescent, colorless to slightly yellow solution, available as follows:

- Injection: 225 mg/1.5 mL single-dose prefilled autoinjector
- Injection: 225 mg/1.5 mL single-dose prefilled syringe

4 CONTRAINDICATIONS

AJOVY is contraindicated in patients with serious hypersensitivity to fremanezumab-vfrm or to any of the excipients. Reactions have included anaphylaxis and angioedema *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions, including rash, pruritus, drug hypersensitivity, and urticaria, were reported with AJOVY in clinical trials. Most reactions were mild to moderate, but some led to discontinuation or required corticosteroid treatment. Most reactions were reported from within hours to one month after administration. Cases of anaphylaxis and angioedema have been reported in the postmarketing setting.

If a hypersensitivity reaction occurs, consider discontinuing AJOVY, and institute appropriate therapy *[see Contraindications (4)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug, and may not reflect the rates observed in clinical practice.

The safety of AJOVY was evaluated in 2512 patients with migraine who received at least 1 dose of AJOVY, representing 1279 patient-years of exposure. Of these, 1730 patients were exposed to AJOVY 225 mg monthly or AJOVY 675 mg quarterly for at least 6 months, 775 patients for at least 12 months, and 138 patients for at least 15 months. In placebo-controlled clinical trials (Studies 1 and 2), 662 patients received AJOVY 225 mg monthly for 12 weeks (with or without a loading dose of 675 mg), and 663 patients received AJOVY 675 mg quarterly for 12 weeks *[see Clinical Studies (14)]*. In the controlled trials, 87% of patients were female, 80% were White, and the mean age was 41 years.

The most common adverse reactions in the clinical trials for the preventive treatment of migraine (incidence at least 5% and greater than placebo) were injection site reactions. The adverse reactions that most commonly led to discontinuations were injection site reactions (1%). Table 1 summarizes adverse reactions reported in the 3-month placebo-controlled studies (Study 1 and Study 2), and the 1-month follow-up period after those studies.

Table 1: Adverse Reactions Occurring with an Incidence of At Least 2% for Either Dosing Regimen of AJOVY and At Least 2% Greater Than Placebo in Studies 1 and 2

Adverse Reaction	AJOVY 225 mg Monthly (n=290) %	AJOVY 675 mg Quarterly (n=667) %	Placebo Monthly (n=668) %
Injection site reactions[a]	43	45	38

[a] Injection site reactions include multiple related adverse event terms, such as injection site pain, induration, and erythema.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing 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 fremanezumab-vfrm in the studies described below with the incidence of antibodies in other studies to other products may be misleading. Clinical immunogenicity of AJOVY was monitored by analyzing anti-drug antibodies (ADA) and neutralizing antibodies in drug-treated patients. The data reflect the percentage of patients whose test results were positive for antibodies to AJOVY in specific assays.

In 3-month placebo-controlled studies, treatment-emergent ADA responses were observed in 6 out of 1701 (0.4%) AJOVY-treated patients. One of the 6 patients developed anti-AJOVY neutralizing antibodies at Day 84. In the ongoing long-term open-label study, ADA were detected in 1.6% of patients (30 out of 1888). Out of 30 ADA-positive patients, 17 had a neutralizing activity in their post-dose samples. Although these data do not demonstrate an impact of anti-fremanezumab-vfrm antibody development on the efficacy or safety of AJOVY in these patients, the available data are too limited to make definitive conclusions.

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of AJOVY. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. *Immune System Disorders* – Anaphylactic reactions and angioedema *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to AJOVY during pregnancy. Healthcare providers are encouraged to register pregnant patients, or pregnant women may enroll themselves in the registry by calling 1-833-927-2605 or visiting www.tevamigrainepregnancyregistry.com.

Risk Summary

There are no adequate data on the developmental risk associated with the use of AJOVY in pregnant women. AJOVY has a long half-life *[see Clinical Pharmacology (12.3)]*. This should be taken into consideration for women who are pregnant or plan to become pregnant while using AJOVY. Administration of fremanezumab-vfrm to rats and rabbits during the period of organogenesis or to rats throughout pregnancy and lactation at doses resulting in plasma levels greater than those expected clinically did not result in adverse effects on development *[see Animal Data]*. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The estimated rate of major birth defects (2.2-2.9%) and miscarriage (17%) among deliveries to women with migraine are similar to rates reported in women without migraine.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Published data have suggested that women with migraine may be at increased risk of preeclampsia and gestational hypertension during pregnancy.

Data

Animal Data

When fremanezumab-vfrm (0, 50, 100, or 200 mg/kg) was administered to male and female rats by weekly subcutaneous injection prior to and during mating and continuing in females throughout organogenesis, no adverse embryofetal effects were observed. The highest dose tested was associated with plasma exposures (AUC) approximately 2 times that in humans at a dose of 675 mg.

Administration of fremanezumab-vfrm (0, 10, 50, or 100 mg/kg) weekly by subcutaneous injection to pregnant rabbits throughout the period of organogenesis produced no adverse effects on embryofetal development. The highest dose tested was associated with plasma AUC approximately 3 times that in humans (675 mg).

Administration of fremanezumab-vfrm (0, 50, 100, or 200 mg/kg) weekly by subcutaneous injection to female rats throughout pregnancy and lactation resulted in no adverse effects on pre- and postnatal development. The highest dose tested was associated with plasma AUC approximately 2 times that in humans (675 mg).

8.2 Lactation

Risk Summary

There are no data on the presence of fremanezumab-vfrm in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for AJOVY and any potential adverse effects on the breastfed infant from AJOVY or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of AJOVY did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

11 DESCRIPTION

Fremanezumab-vfrm is a fully humanized IgG2Δa/kappa monoclonal antibody specific for calcitonin gene-related peptide (CGRP) ligand. Fremanezumab-vfrm is produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells. The antibody consists of 1324 amino acids and has a molecular weight of approximately 148 kDa.

AJOVY (fremanezumab-vfrm) injection is a sterile, preservative-free, clear to opalescent, colorless to slightly yellow solution for subcutaneous injection, supplied in a single-dose 225 mg/1.5 mL prefilled autoinjector and a single-dose 225 mg/1.5 mL prefilled syringe.

AJOVY® (fremanezumab-vfrm) injection

Each prefilled autoinjector or prefilled syringe delivers 1.5 mL of solution containing 225 mg fremanezumab-vfrm, disodium ethylenediaminetetraacetic acid dihydrate (EDTA) (0.204 mg), L-histidine (0.815 mg), L-histidine hydrochloride monohydrate (3.93 mg), polysorbate-80 (0.3 mg), sucrose (99 mg), and Water for Injection, and has a pH of 5.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fremanezumab-vfrm is a humanized monoclonal antibody that binds to calcitonin gene-related peptide (CGRP) ligand and blocks its binding to the receptor.

12.2 Pharmacodynamics

The relationship between the pharmacodynamic activity and the mechanism(s) by which fremanezumab-vfrm exerts its clinical effects is unknown.

12.3 Pharmacokinetics

Absorption

After single subcutaneous (SC) administrations of 225 mg, 675 mg, and 900 mg fremanezumab-vfrm, median time to maximum concentrations (tmax) was 5 to 7 days. Dose-proportionality, based on population PK, was observed between 225 mg to 900 mg. Steady state was achieved by approximately 168 days (about 6 months) following 225 mg SC monthly and 675 mg SC quarterly dosing regimens. Median accumulation ratio, based on once-monthly and once-quarterly dosing regimens, is approximately 2.3 and 1.2, respectively.

Distribution

Fremanezumab-vfrm has an apparent volume of distribution of approximately 6 liters, suggesting minimal distribution to the extravascular tissues.

Metabolism

Similar to other monoclonal antibodies, fremanezumab-vfrm is degraded by enzymatic proteolysis into small peptides and amino acids.

Elimination

Fremanezumab-vfrm apparent clearance was approximately 0.141 L/day. Fremanezumab-vfrm was estimated to have a half-life of approximately 31 days.

Specific Populations

A population PK analysis assessing effects of age, race, sex, and weight was conducted on data from 2287 subjects. No dose adjustments are recommended for AJOVY.

Patients with Hepatic or Renal Impairment

Hepatic/renal impairment is not expected to affect the pharmacokinetics of fremanezumab. A population PK analysis of integrated data from the AJOVY clinical studies did not reveal a difference in the pharmacokinetics of fremanezumab in patients with mild hepatic impairment, relative to those with normal hepatic function. There were only 4 patients with moderate hepatic impairment, and no patient with severe hepatic impairment in fremanezumab clinical studies. No dedicated hepatic/renal impairment studies were conducted to assess the effect of hepatic or renal impairment on the pharmacokinetics of fremanezumab.

Drug Interactions

Fremanezumab is not metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely. Additionally, the effects of medications for the acute treatment (specifically analgesics, ergots, and triptans) and preventive treatment of migraine were evaluated in a population PK model, and found not to influence fremanezumab exposure.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies of fremanezumab-vfrm were not conducted.

Mutagenesis

Genetic toxicology studies of fremanezumab-vfrm were not conducted.

Impairment of Fertility

When fremanezumab-vfrm (0, 50, 100, or 200 mg/kg) was administered to male and female rats by weekly subcutaneous injection prior to and during mating and continuing in females throughout organogenesis, no adverse effects on male or female fertility were observed. The highest dose tested was associated with plasma exposures (AUC) approximately 2 times that in humans at a dose of 675 mg.

14 CLINICAL STUDIES

The efficacy of AJOVY was evaluated as a preventive treatment of episodic or chronic migraine in two multicenter, randomized, 3-month, double-blind, placebo-controlled studies (Study 1 and Study 2, respectively).

Episodic Migraine

Study 1 (NCT 02629861) included adults with a history of episodic migraine (patients with <15 headache days per month). All patients were randomized (1:1:1) to receive subcutaneous injections of either AJOVY 675 mg every three months (quarterly), AJOVY 225 mg monthly, or placebo monthly, over a 3-month treatment period. Patients were allowed to use acute headache treatments during the study. A subset of patients (21%) was allowed to use one additional concomitant preventive medication.

The study excluded patients with a history of significant cardiovascular disease, vascular ischemia, or thrombotic events, such as cerebrovascular accident, transient ischemic attacks, deep vein thrombosis, or pulmonary embolism.

The primary efficacy endpoint was the mean change from baseline in the monthly average number of migraine days during the 3-month treatment period. 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 the number of migraine days during the first month of the treatment period.

In Study 1, a total of 875 patients (742 females, 133 males), ranging in age from 18 to 70 years, were randomized. A total of 791 patients completed the 3-month double-blind phase. The mean migraine frequency at baseline was approximately 9 migraine days per month, and was similar across treatment groups.

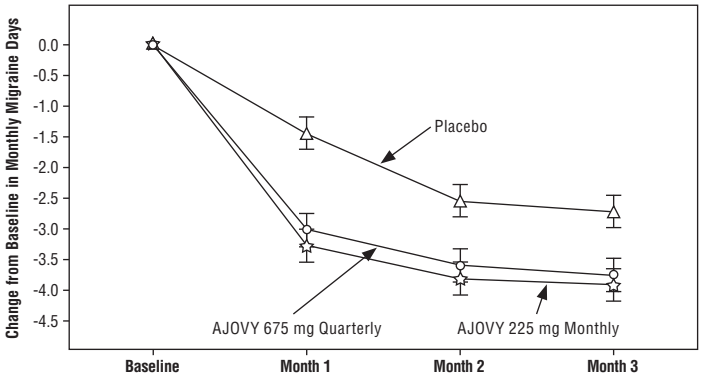
Both monthly and quarterly dosing regimens of AJOVY demonstrated statistically significant improvements for efficacy endpoints compared to placebo over the 3-month period, as summarized in Table 2.

Table 2: Efficacy Endpoints in Study 1

Study 1 Efficacy Endpoint	AJOVY 225 mg Monthly (N=287)	AJOVY 675 mg Quarterly (N=288)	Placebo (N=290)
Monthly migraine days (MMD)			
Baseline migraine days	8.9	9.2	9.1
Change from baseline	-3.7	-3.4	-2.2
Difference from placebo	-1.5	-1.2	
p-value	<0.001	<0.001	
≥50% MMD responders			
% responders	47.7%	44.4%	27.9%
Difference from placebo	19.8%	16.5%	
p-value	<0.001	<0.001	
Monthly acute headache medication days			
Change from baseline	-3.0	-2.9	-1.6
Difference from placebo	-1.4	-1.3	
p-value	<0.001	<0.001	

Figure 1 displays the mean change from baseline in the average monthly number of migraine days in Study 1.

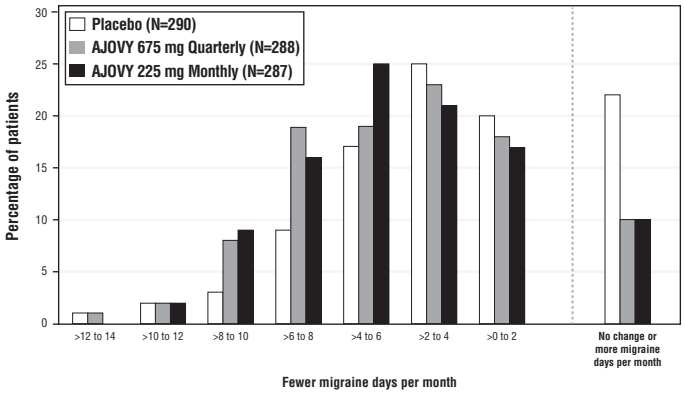
Figure 1: Change from Baseline in Monthly Migraine Days in Study 1[a]



[a] LS (least-square) means and standard error of the mean are presented.

Figure 2 shows the distribution of change from baseline in mean monthly migraine days in bins of 2 days by treatment group in Study 1. A treatment benefit over placebo for both doses of AJOVY is seen across a range of changes from baseline in monthly migraine days.

Figure 2: Distribution of Change from Baseline in Mean Monthly Migraine Days by Treatment Group in Study 1



Chronic Migraine

Study 2 (NCT 02621931) included adults with a history of chronic migraine (patients with ≥15 headache days per month). All patients were randomized (1:1:1) to receive subcutaneous injections of either AJOVY 675 mg starting dose followed by 225 mg monthly, 675 mg every 3 months (quarterly), or placebo monthly, over a 3-month treatment period. Patients were allowed to use acute headache treatments during the study. A subset of patients (21%) was allowed to use one additional concomitant, preventive medication.

The study excluded patients with a history of significant cardiovascular disease, vascular ischemia, or thrombotic events, such as cerebrovascular accident, transient ischemic attacks, deep vein thrombosis, or pulmonary embolism.

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 3-month treatment period. The secondary endpoints were the mean change from baseline in the monthly average number of migraine days during the 3-month treatment period, the proportion of patients reaching at least 50% reduction in the monthly average number of headache days of at least moderate severity 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 the number of headache days of at least moderate severity during the first month of treatment.

In Study 2, a total of 1130 patients (991 females, 139 males), ranging in age from 18 to 70 years, were randomized. A total of 1034 patients completed the 3-month double-blind phase.

Both monthly and quarterly dosing regimens of AJOVY treatment demonstrated statistically significant improvement for key efficacy outcomes compared to placebo, as summarized in Table 3.

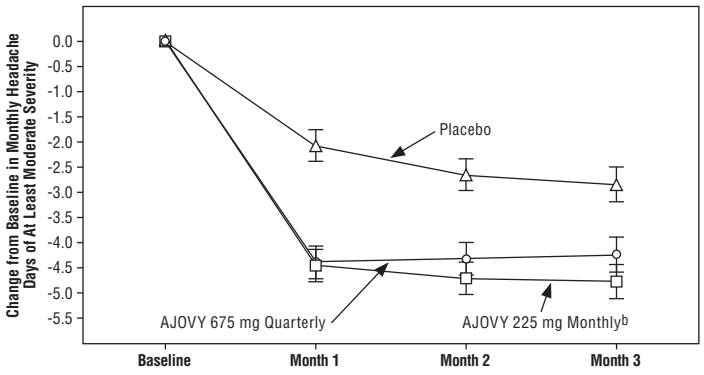
Table 3: Efficacy Endpoints in Study 2

Study 2 Efficacy Endpoint	AJOVY 225 mg[a] Monthly (N=375)	AJOVY 675 mg Quarterly (N=375)	Placebo (N=371)
Baseline headache days of any severity[b]	20.3	20.4	20.3
Baseline headache days of at least moderate severity[c]	12.8	13.2	13.3
Change from baseline in the monthly average number of headache days of at least moderate severity	-4.6	-4.3	-2.5
Difference from placebo	-2.1	-1.8	
p-value	<0.001	<0.001	
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	-4.6	-2.3
Percentage of patients with ≥ 50% reduction 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

[a] In Study 2, patients received a 675 mg starting dose.
[b] Used for chronic migraine diagnosis.
[c] Used for primary endpoint analysis.

Figure 3 displays the mean change from baseline in the average monthly number of headache days of at least moderate severity in Study 2.

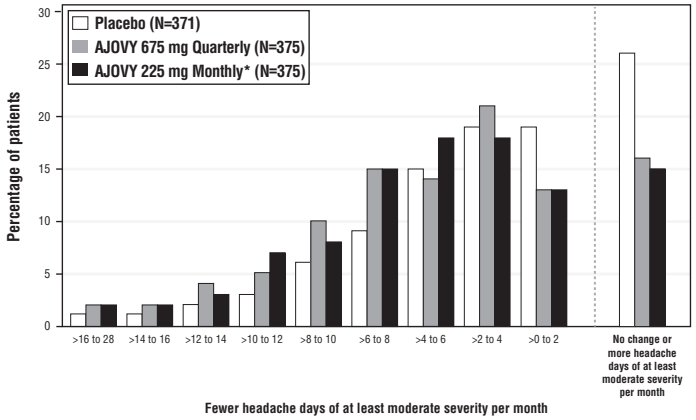
Figure 3: Change from Baseline in Monthly Headache Days of At Least Moderate Severity in Study 2[a]



[a] LS (least-square) means and standard error of the mean are presented.
[b] In Study 2, patients received a 675 mg starting dose.

Figure 4 shows the distribution of change from baseline in monthly headache days of at least moderate severity at month 3 in bins of 3 days by treatment group. A treatment benefit over placebo for both dosing regimens of AJOVY is seen across a range of changes from baseline in headache days.

Figure 4: Distribution of Mean Change from Baseline in Monthly Headache Days of At Least Moderate Severity by Treatment Group in Study 2



*In Study 2, patients received a 675 mg starting dose.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

AJOVY (fremanezumab-vfrm) injection is a sterile, preservative-free, clear to opalescent, colorless to slightly yellow solution for subcutaneous administration.

AJOVY is not made with natural rubber latex.

AJOVY is supplied as follows:

Prefilled Autoinjector

- Pack of 1 autoinjector: 225 mg/1.5 mL single-dose prefilled autoinjector
  NDC 51759-202-10
- Pack of 3 autoinjectors: 3 x 225 mg/1.5mL single-dose prefilled autoinjectors
  NDC 51759-202-22

Prefilled Syringe

- Pack of 1 syringe: 225 mg/1.5 mL single-dose prefilled syringe
  NDC 51759-204-10

16.2 Storage and Handling

- Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original outer carton to protect from light.
- If necessary, AJOVY may be kept in the original carton at room temperature up to 30°C (86°F) for a maximum of 7 days. After removal from the refrigerator, AJOVY must be used within 7 days or discarded. Once stored at room temperature, do not place back in the refrigerator.
- Do not freeze.
- Do not expose to extreme heat or direct sunlight.
- Do not shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Information on Preparation and Administration

Provide guidance to patients and caregivers on proper subcutaneous administration technique, including aseptic technique, and how to use the single-dose prefilled syringe *[see Dosage and Administration (2.2)]*. Instruct patients and/or caregivers to read and follow the Instructions for Use each time they use AJOVY.

Instruct patients prescribed the regimen of 675 mg every 3 months to administer the dosage as three consecutive subcutaneous injections of 225 mg each *[see Dosage and Administration (2.1)]*.

Hypersensitivity Reactions

Inform patients about the signs and symptoms of hypersensitivity reactions and that these reactions can occur up to 1 month after administration. Advise patients to contact their healthcare provider immediately if signs or symptoms of hypersensitivity reactions occur *[see Warnings and Precautions (5.1)]*.

Pregnancy

Advise women that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to AJOVY during pregnancy *[see Use in Specific Populations (8.1)]*.

Manufactured by:
Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454
US License No. 2016

AJO-010

AJOVY® (fremanezumab-vfrm) injection

Patient Information
AJOVY® (a-JO-vee)
(fremanezumab-vfrm) injection
for subcutaneous use

What is AJOVY?

AJOVY is a prescription medicine used for the preventive treatment of migraine in adults.

It is not known if AJOVY is safe and effective in children.

Who should not use AJOVY?

Do not use AJOVY if you are allergic to fremanezumab-vfrm or any of the ingredients in AJOVY. See the end of this leaflet for a complete list of the ingredients in AJOVY.

Before you use AJOVY, tell your healthcare provider if you:

- are pregnant or plan to become pregnant. It is not known if AJOVY will harm your unborn baby.
  Pregnancy Registry: There is a registry for women who become pregnant during treatment with AJOVY. The purpose of this registry is to collect information about the safety of AJOVY during pregnancy. Contact the registry as soon as you learn that you are pregnant, or ask your doctor to contact the registry for you. You or your doctor can get information and enroll you in the registry by calling 1-833-927-2605 or visiting www.tevamigrainepregnancyregistry.com.
- are breastfeeding or plan to breastfeed. It is not known if AJOVY passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby while using AJOVY.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of your medicines with you to show your healthcare provider and pharmacist when you get a new medicine.

How should I use AJOVY?

- See the detailed "Instructions for Use" for information on how to prepare and inject a dose of AJOVY.
- Use AJOVY exactly as your healthcare provider tells you to use it.
- AJOVY is given by injection under your skin (subcutaneously).
- Your healthcare provider should show you or your caregiver how to prepare and inject your dose of AJOVY before you or your caregiver give your AJOVY the first time.
- Your healthcare provider will tell you how much AJOVY to use and when to use it.
  - Your healthcare provider will tell you if you should use AJOVY 225 mg one time every month or AJOVY 675 mg one time every 3 months.
  - If your prescribed dose is AJOVY 675 mg every 3 months, you must use 3 separate autoinjectors or 3 separate syringes. You will give 3 separate injections one time every 3 months.
- If you are giving 3 injections of AJOVY for your prescribed dose, you may use the same injection area for all 3 injections, but not the same spot.
- **Do not** inject AJOVY in the same injection site that you inject other medicine.
- If you are switching from using AJOVY one time every month to one time every 3 months or if you are switching from using AJOVY one time every 3 months to one time every month, give the first dose of AJOVY on the day it was due to be given on your old schedule.
- If you miss a dose of AJOVY, take it as soon as possible. If you need to take the dose late, you will need to change your schedule: if you take 225 mg of AJOVY, inject your next dose 1 month after the late dose. If you take 675 mg of AJOVY, inject your next dose 3 months after the late dose. If you have questions about your schedule, ask your healthcare provider.

continued

What are the possible side effects of AJOVY?

AJOVY may cause serious side effects, including:

- **Allergic reactions.** Allergic reactions, including itching, rash, and hives, can happen within hours and up to 1 month after receiving AJOVY. Call your healthcare provider or get emergency medical help right away if you have any of the following symptoms of an allergic reaction:
  - swelling of your face, mouth, tongue, or throat
  - trouble breathing

The most common side effects of AJOVY include:

- injection site reactions

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of AJOVY. For more information, ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store AJOVY?

- Store AJOVY in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Keep AJOVY in the carton it comes in to protect from light.
- If needed, AJOVY may be stored at room temperature up to 86°F (30°C) in the carton it comes in for up to 7 days. Do not use AJOVY if it has been out of the refrigerator for 7 days or longer. Throw away (dispose of) AJOVY in a sharps disposal or puncture-resistant container if it has been out of the refrigerator for 7 days or longer. Once stored at room temperature, do not place back in the refrigerator.
- **Do not** freeze. If AJOVY freezes, throw it away in a sharps disposal container.
- Keep AJOVY out of extreme heat and direct sunlight.
- **Do not** shake AJOVY.

Keep AJOVY prefilled autoinjector and AJOVY prefilled syringe out of the reach of small children.

General information about the safe and effective use of AJOVY.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use AJOVY for a condition for which it was not prescribed. Do not give AJOVY to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about AJOVY that is written for health professionals.

What are the ingredients in AJOVY?

Active ingredient: fremanezumab-vfrm

Inactive ingredients: disodium ethylenediaminetetraacetic acid dihydrate (EDTA), L-histidine, L-histidine hydrochloride monohydrate, polysorbate-80, sucrose, and Water for Injection.

AJOVY prefilled syringe and prefilled autoinjector are not made with natural rubber latex.

Manufactured by: Teva Pharmaceuticals USA, Inc., North Wales, PA 19454
US License No. 2016
AJOPL-005
For more information, go to www.AJOVY.com or call 1-888-483-8279.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 9/2021

AJOVY® (fremanezumab-vfrm) injection

Instructions for Use

AJOVY® (a-JO-vee) (fremanezumab-vfrm) injection prefilled autoinjector, for subcutaneous use

For subcutaneous injection only.

Read and follow the **Instructions for Use** for your AJOVY prefilled autoinjector before you start using it and each time you get a refill.

Important:

- AJOVY prefilled autoinjector is for single-time (one-time) use only. Put AJOVY in a FDA-cleared sharps disposal or puncture-resistant container right away after use. Do not throw away (dispose of) your used sharps disposal container in your household trash.
- Before injecting, let AJOVY sit at room temperature for 30 minutes.
- Keep AJOVY prefilled autoinjector out of the reach of small children.
- After you remove the protective cap from AJOVY, to prevent infection, **do not** touch the needle.
- **Do not** inject AJOVY in your veins (intravenously).
- **Do not** re-use your AJOVY prefilled autoinjector as this could cause injury or infection.
- **Do not** share your AJOVY prefilled autoinjector with another person. You may give another person an infection or get an infection from them.

You may give AJOVY yourself. If you feel uncomfortable, you should not get your first dose of AJOVY until you or your caregiver receive training from a healthcare provider on the right way to use AJOVY.

Storage Conditions:

- Store AJOVY in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Keep AJOVY in the carton it comes in to protect from light.
- If needed, AJOVY may be stored at room temperature up to 86°F (30°C) in the carton it comes in for up to 7 days. Do not use AJOVY if it has been out of the refrigerator for 7 days or longer. Throw away (dispose of) AJOVY in a sharps disposal or puncture-resistant container if it has been out of the refrigerator for 7 days or longer. Once stored at room temperature, do not place back in the refrigerator.
- **Do not** freeze. If AJOVY freezes, throw it away in a sharps disposal container.
- Keep AJOVY out of extreme heat and direct sunlight.

Do not shake AJOVY.

AJOVY prefilled autoinjector (Before use). See Figure A.

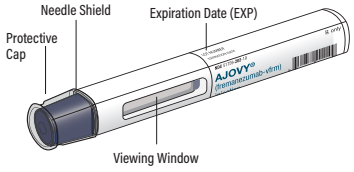


Figure A

AJOVY prefilled autoinjector (After use). See Figure B.

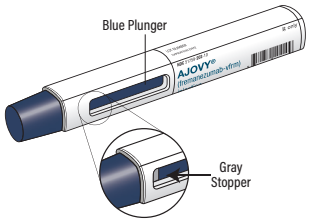


Figure B

- The blue plunger moves down the viewing window during the injection. The blue plunger fills the window when the injection is complete. **Note**: When the blue plunger has filled the viewing window you will still be able to see the gray stopper, as shown in Figure B.
- When injecting AJOVY, hold the prefilled autoinjector so that your hand does not cover the viewing window.

Read this before you inject.

Step 1. Check the dose your healthcare provider has prescribed.

AJOVY comes as a single-dose (one time) prefilled autoinjector. Your healthcare provider will prescribe the dose that is best for you.

- If your healthcare provider has prescribed 225 mg of AJOVY each month for you, give 1 injection each month, using a 225 mg prefilled AJOVY autoinjector.
- If your healthcare provider has prescribed 675 mg of AJOVY every 3 months for you, give 3 separate injections, one after another, using a different 225 mg prefilled AJOVY autoinjector for each injection. Give these injections 1 time every 3 months.

Before you inject, always check the label of your single-dose prefilled autoinjector to make sure you have the correct medicine and the correct dose of AJOVY. If you are not sure of your dose, ask your healthcare provider.

How do I inject AJOVY?

Step 2. Remove the prefilled autoinjector from the carton.

- You may need to use more than 1 prefilled autoinjector depending on your prescribed dose.
- **Remove** the autoinjector from the carton (see Figure C).
- **Do not** shake the prefilled autoinjector at any time, as this could affect the way the medicine works.

Important: If there are any unused autoinjectors left in the carton, **put the carton and unused autoinjectors back in the refrigerator.**

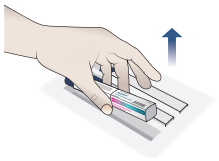


Figure C

Step 3. Gather the supplies you will need to inject AJOVY.

- Gather the following supplies (see Figure D) and the number of AJOVY 225 mg prefilled autoinjectors you will need to give your prescribed dose:
  - If your dose is 225 mg, you will need 1 AJOVY 225 mg prefilled autoinjector.
  - If your dose is 675 mg, you will need 3 AJOVY 225 mg prefilled autoinjectors.
  - Alcohol swabs (not supplied).
  - Gauze pads or cotton balls (not supplied).
  - Sharps disposal or puncture-resistant container (not supplied).

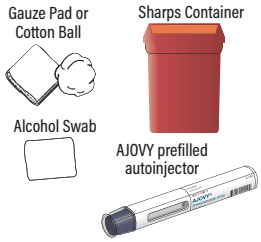


Figure D

Step 4. Let AJOVY reach room temperature.

- **Place** the supplies you have gathered on a clean, flat surface.
- **Wait** for 30 minutes to allow the medicine to reach room temperature.
- **Do not** leave the prefilled autoinjector in direct sunlight.
- **Do not** warm up the AJOVY prefilled autoinjector using a heat source such as hot water or a microwave.

AJOVY® (fremanezumab-vfrm) injection

Step 5. Wash your hands.

- **Wash your hands** with soap and water and dry well with a clean towel. Be careful not to touch your face or hair after washing your hands.

Step 6. Look closely at your AJOVY prefilled autoinjector.

Note: You may see air bubbles in the prefilled autoinjector. This is normal. **Do not** remove the air bubbles from the prefilled autoinjector before giving your injection.

Injecting AJOVY with these air bubbles will not harm you.

• **Check that the liquid medicine in the prefilled autoinjector viewing window is clear and colorless to slightly yellow before you give your injection.** (See Figure E). If the liquid has any particles in it, or is discolored, cloudy, or frozen, do not use the prefilled autoinjector. Call your healthcare provider or pharmacist.	• **Do not** use the prefilled autoinjector if it has any visible damage, such as cracks or leaks. See disposal instructions in Step 12.
• **Check** that AJOVY appears on the prefilled autoinjector.	• **Do not** use if you have been given the wrong medicine.
• **Check** the expiration date (EXP) printed on the prefilled autoinjector label.	• **Do not** use the prefilled autoinjector if the expiration date (EXP) has passed.

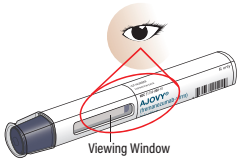


Figure E

Step 7: Choose your injection area.

- **Choose** an injection area from the following areas (see Figure F):
  - your **stomach area** (abdomen), avoid about 2 inches around the belly button.
  - the **front of your thighs**, an area that is at least 2 inches above the knee and 2 inches below the groin.
  - the **back of your upper arms**, in the fleshy area of the upper back portion.

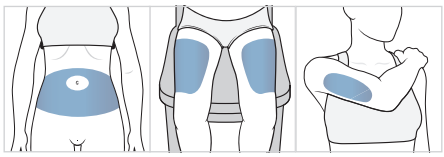


Figure F

Note: There are some injection areas on your body that are hard to reach (like the back of your arm). You may need help from someone who has been instructed on how to give your injection if you cannot reach certain injection areas.

Step 8. Clean your injection area.

- **Clean** the chosen injection area using a new alcohol swab. Let your skin dry.
- **Do not** inject AJOVY into an area that is tender, red, bruised, callused, tattooed, hard, or that has scars or stretch marks.
- **Do not** inject AJOVY in the same injection site that you inject other medicine.
- If you want to use the same injection area for the 3 separate injections needed for the 675 mg dose, make sure the second and third injections are not at the same spot you used for the other injections.

Step 9. Remove protective cap and do not replace.

- **Pick up** the prefilled autoinjector in 1 hand.
- **Hold** the prefilled autoinjector as shown in Figure G and **pull the protective cap straight off** with your other hand. **Do not** twist.

- **Throw away** the protective cap right away.
- **Do not** put the protective cap back on the prefilled autoinjector, to avoid injury and infection.

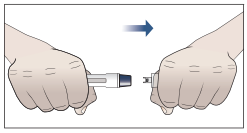


Figure G

Step 10. Give your injection.

- **10.1 Place** the prefilled autoinjector at a 90 degree angle against your skin at the injection site you have cleaned (see Figure H).

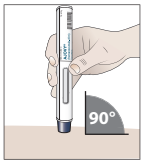
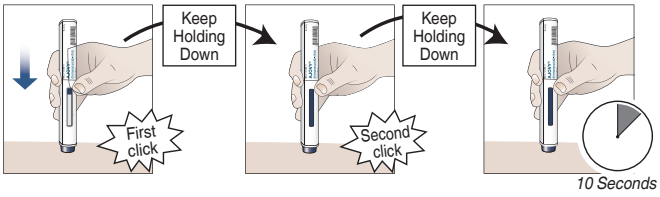


Figure H

10.2 Press down on the prefilled autoinjector and keep holding it down against the skin **for about 30 seconds.**
Do not remove pressure until the 3 steps below are complete.

1. **You hear the first "click"** (this means the injection has started and the blue plunger starts to move).	2. **You hear a second "click"** (about 15 seconds after the first click. The plunger will be moving to the bottom of the viewing window as the medicine is being injected.)	3. **You wait another 10 seconds.** (to make sure all the medicine is injected).



10.3 Check that the blue plunger has filled the viewing window **and remove** the autoinjector from the skin by lifting the prefilled autoinjector straight up (see Figure I).

Note: When the blue plunger has filled the viewing window **you will be able to see the gray stopper**.

As the prefilled autoinjector is lifted from the skin, the needle shield returns to the original (before use) position and locks into place, covering the needle.

Do not try to put the protective cap back on the used prefilled autoinjector as it is no longer needed.

Do not try to re-use the prefilled autoinjector.

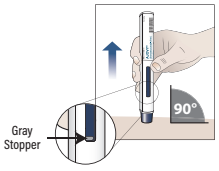


Figure I

Step 11. Apply pressure to the injection site.

- Use a clean, dry cotton ball, or gauze pad to **gently press on the injection site** for a few seconds.
- **Do not** rub the injection site.
- **Do not** re-use the prefilled autoinjector.

AJOVY® (fremanezumab-vfrm) injection

Step 12. Dispose of your prefilled autoinjector right away.

- Put your used prefilled autoinjectors in a FDA-cleared sharps disposal container right away after use.
- **Do not throw away (dispose of) prefilled autoinjectors in your household trash. Do not recycle your used sharps disposal container.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used autoinjectors. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal
- **Do not** dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. **Do not** recycle your used sharps disposal container.

Injection Complete

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454
US License No. 2016

AJOIFU-AI-004

Approved: 10/2020

Instructions for Use

AJOVY® (a-JO-vee)
(fremanezumab-vfrm) injection
prefilled syringe, for subcutaneous use

For subcutaneous injection only.

Read and follow the **Instructions for Use** for your AJOVY prefilled syringe before you start using it and each time you get a refill.

Important:

- AJOVY prefilled syringe is for single-time (one-time) use only. Put AJOVY in a FDA-cleared sharps disposal or puncture-resistant container right away after use. Do not throw away (dispose of) your used sharps disposal container in your household trash.
- Before injecting, let AJOVY sit at room temperature for 30 minutes.
- Keep AJOVY prefilled syringe out of the reach of small children.
- After you remove the needle cap from AJOVY, to prevent infection, **do not** touch the needle.
- **Do not** pull back on the plunger at any time, as this can break the prefilled syringe.
- **Do not** inject AJOVY in your veins (intravenously).
- **Do not** re-use your AJOVY prefilled syringe, as this could cause injury or infection.
- **Do not** share your AJOVY prefilled syringe with another person. You may give another person an infection or get an infection from them.

You may give AJOVY yourself. If you feel uncomfortable, you should not get your first dose of AJOVY until you or your caregiver receive training from a healthcare provider on the right way to use AJOVY.

Storage Conditions:

- Store AJOVY in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Keep AJOVY in the carton it comes in to protect from light.
- If needed, AJOVY may be stored at room temperature up to 86°F (30°C) in the carton it comes in for up to 7 days. Do not use AJOVY if it has been out of the refrigerator for 7 days or longer. Throw away (dispose of) AJOVY in a sharps disposal or puncture-resistant container if it has been out of the refrigerator for 7 days or longer. Once stored at room temperature, do not place back in the refrigerator.
- **Do not** freeze. If AJOVY freezes, throw it away in a sharps disposal container.
- Keep AJOVY out of extreme heat and direct sunlight.
- **Do not** shake AJOVY.

AJOVY prefilled syringe (Before use). See Figure A.

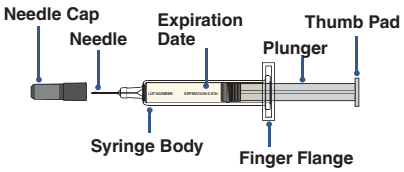


Figure A

AJOVY prefilled syringe (After use). See Figure B.

Figure B

STOP

Read this before you inject.

Step 1. Check the dose your healthcare provider has prescribed.

AJOVY comes as a single-dose (one time) prefilled syringe. Your healthcare provider will prescribe the dose that is best for you.

- If your healthcare provider has prescribed 225 mg of AJOVY each month for you, give 1 injection each month using a 225 mg prefilled AJOVY syringe.
- If your healthcare provider has prescribed 675 mg of AJOVY every 3 months for you, give 3 separate injections, one after another, using a different 225 mg prefilled AJOVY syringe for each injection. Give these injections 1 time every 3 months.

Before you inject, always check the label of your single-dose prefilled syringe to make sure you have the correct medicine and the correct dose of AJOVY. If you are not sure of your dose, ask your healthcare provider.

How do I inject AJOVY?

Step 2. Remove the prefilled syringe from the carton.

- You may need to use more than 1 prefilled syringe depending on your prescribed dose.
- **Hold** the prefilled syringe (as shown in Figure C).
- **Remove** the syringe from the carton.
- **Do not** shake the prefilled syringe at any time, as this could affect the way the medicine works.

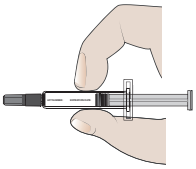


Figure C

AJOVY® (fremanezumab-vfrm) injection

Step 3. Gather the supplies you will need to inject AJOVY.

- **Gather** the following supplies (see Figure D) and the number of AJOVY 225 mg prefilled syringes you will need to give your prescribed dose:
  - If your dose is 225 mg, you will need 1 AJOVY 225 mg prefilled syringe.
  - If your dose is 675 mg, you will need 3 AJOVY 225 mg prefilled syringes.
  - alcohol swabs (not supplied).
  - gauze pads or cotton balls (not supplied).
  - sharps disposal or puncture-resistant container (not supplied).

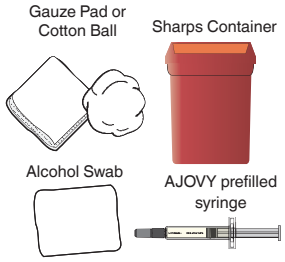


Figure D

Step 4. Let AJOVY reach room temperature.

- **Place** the supplies you have gathered on a clean, flat surface.
- **Wait** for 30 minutes to allow the medicine to reach room temperature.
- **Do not** leave the prefilled syringe in direct sunlight.
- **Do not** warm up the AJOVY prefilled syringe using a heat source such as hot water or a microwave.

Step 5. Wash your hands.

- **Wash your hands** with soap and water and dry well with a clean towel. Be careful not to touch your face or hair after washing your hands.

Step 6. Look closely at your AJOVY prefilled syringe.

Note: You may see air bubbles in the prefilled syringe. This is normal. **Do not** remove the air bubbles from the prefilled syringe before giving your injection. Injecting AJOVY with these air bubbles will not harm you.

• **Check that the liquid medicine in the prefilled syringe is clear and colorless to slightly yellow before you give your injection** (see Figure E). If the liquid has any particles in it, or is discolored, cloudy, or frozen, do not use the prefilled syringe. Call your healthcare provider or pharmacist.	• **Do not** use the prefilled syringe if it has any visible damage, such as cracks or leaks. See disposal instructions in Step 12.
• **Check** that AJOVY appears on the prefilled syringe.	• **Do not use** if you have been given the wrong medicine.
• **Check** the expiration date (EXP) printed on the prefilled syringe label.	• **Do not** use the prefilled syringe if the expiration date (EXP) has passed.

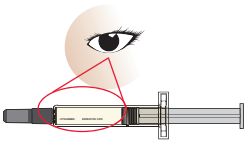


Figure E

Step 7. Choose your injection area.

- **Choose** an injection area from the following areas (see Figure F):
  - your **stomach area** (abdomen), avoid about 2 inches around the belly button.
  - the **front of your thighs**, an area that is at least 2 inches above the knee and 2 inches below the groin.
  - the **back of your upper arms**, in the fleshy area of the upper back portion.

Figure F

Note: There are some injection areas on your body that are hard to reach (like the back of your arm). You may need help from someone who has been instructed on how to give your injection if you cannot reach certain injection areas.

Step 8. Clean your injection area.

- **Clean** the chosen injection area using a new alcohol swab. Let your skin dry.
- **Do not** inject AJOVY into an area that is tender, red, bruised, callused, tattooed, hard, or that has scars or stretch marks.
- **Do not** inject AJOVY in the same injection site that you inject other medicine.
- If you want to use the same injection area for the 3 separate injections needed for the 675 mg dose, make sure the second and third injections are not at the same spot you used for the other injections.

Step 9. Remove needle cap and do not replace.

- **Pick up** the body of the prefilled syringe with 1 hand.
- **Pull** the needle cap **straight off** with your other hand (see Figure G). **Do not** twist.
- **Throw away** the needle cap right away.
- **Do not** put the needle cap back on the prefilled syringe, to avoid injury and infection.

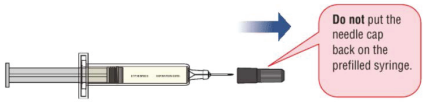
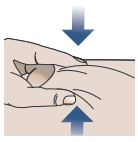
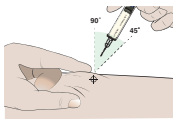
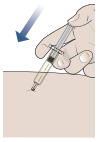


Figure G

Step 10. Give your injection following the 4 steps below.

1. Use your free hand to **gently pinch up** at least 1 inch of the skin that you have cleaned.	2. **Insert the needle** into the pinched skin at a 45 to 90 degree angle.	3. When the needle is all the way into your skin, **use your thumb to push the plunger**.	4. **Push the plunger slowly all the way down** as far as it will go to inject all of the medicine.
			

Step 11. Remove the needle from your skin.

- After you have injected all of the medicine, **pull the needle straight out** (see Figure H).
- **Do not** recap the needle at any time to avoid injury and infection.

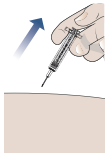


Figure H

AJOVY® (fremanezumab-vfrm) injection

Step 12. Apply pressure to the injection site.

- Use a clean, dry cotton ball or gauze to **gently press on the injection site** for a few seconds.
- **Do not** rub the injection site.
- **Do not** re-use the prefilled syringe.

Step 13. Dispose of your prefilled syringe right away.

- Put your used prefilled syringes, needles, and sharps in a FDA-cleared sharps disposal container right away after use.
- **Do not throw away (dispose of) loose needles, syringes, or prefilled syringes in your household trash. Do not recycle your used sharps disposal container.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal
- **Do not** dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. **Do not** recycle your used sharps disposal container.

Injection Complete

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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