PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrAJOVY™

Fremanezumab

Solution for Subcutaneous Injection
225 mg in 1.5 mL (150 mg/mL)

Professed Standard

Anti-calcitonin Gene-related Peptide (anti-CGRP)

Distributed by:
Teva Canada Limited
Toronto, Ontario M1B 2K9

Manufactured for:
Teva Canada Innovation
Montreal, Quebec H2Z 1S8

Submission Control No: 226828

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

PrAJOVY™ (fremanezumab) is indicated for the prevention of migraine in adults who have at least 4 migraine days per month.

PrAJOVY™ should be initiated by health professionals experienced in the diagnosis and treatment of migraine.

1.1 Pediatrics

Pediatrics (< 18 years of age):
Safety and efficacy of AJOVY in patients below the age of 18 have not been studied.

Health Canada has not authorized AJOVY for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): Clinical studies of AJOVY did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. (See WARNINGS AND PRECAUTIONS, Geriatrics)

2 CONTRAINDICATIONS

AJOVY (fremanezumab) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING .

3 DOSAGE AND ADMINISTRATION

3.1 DOSING CONSIDERATIONS

AJOVY is administered subcutaneously through single dose prefilled syringes. AJOVY is intended for patient self-administration. Administration should be performed by an individual who has been trained to administer the product. (See Administration and Instructions for Use leaflet)

3.2 Recommended Dose and Dosage Adjustment

Two subcutaneous dosing options of AJOVY are available to administer the recommended dosage (See Part II – Clinical Trials):

- 225 mg (1 subcutaneous injection) once a month (monthly dosing), or
- 675 mg (3 separate subcutaneous injections of 225 mg one after another) every 3 months (quarterly dosing).

The dose regimen must be followed as prescribed. Patients should be advised that monthly dosing consists of a single subcutaneous injection.

When switching dosage options, the first dose of the new regimen should be given on the next scheduled dosing date of the prior regimen.

The treatment benefit should be assessed within 3 months after initiation of the 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. (See PART II. CLINICAL TRIALS).

Health Canada has not authorized AJOVY for pediatric use.

3.3 Administration

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 24 hours or longer. (See STORAGE, STABILITY AND DISPOSAL).
- Follow aseptic injection technique every time AJOVY is administered.
- Inspect AJOVY for particles or discolouration prior to administration. Do not use if the solution is cloudy, discoloured, or contains particles. (See DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).
- 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

3.4 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.

4 OVERDOSAGE

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 management of a suspected drug overdose, contact your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous injection	Solution for injection in Pre-filled syringe 225 mg/1.5 mL (150 mg/mL)	Disodium ethylenediaminetetraacetic acid dehydrate (EDTA), L-histidine, polysorbate 80, sucrose, and Water for Injection.

AJOVY is a sterile, preservative-free, clear to opalescent, colorless to slightly yellow solution practically free from particles.

The prefilled syringe cap is not made with natural rubber latex. The syringe cap is made from natural latex-free material.

AJOVY is supplied as carton of one 225 mg/1.5 mL (150 mg/mL) single-dose pre-filled syringe.

Pack sizes of 1 carton containing one single dose pre-filled syringe.

6 DESCRIPTION

AJOVY contains fremanezumab, a fully humanized IgG2Δa/kappa monoclonal antibody specific for calcitonin gene-related peptide (CGRP) ligand. Fremanezumab 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.

7 WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions
Serious hypersensitivity reactions, including rash, angioedema, and anaphylactic reactions, were reported with the CGRP- class products including AJOVY in clinical trials and in post-market experience.

These reactions may occur within minutes, although some may occur up to one month after administration.

If a hypersensitivity reaction occurs, consider discontinuing AJOVY, and institute appropriate therapy.

Patients with Hepatic or Renal Impairment
No safety data are available in these populations. Fremanezumab as a monoclonal antibody is not expected to undergo hepatic metabolism or renal clearance. Patients with severe hepatic impairment

and severe renal impairment (eGFR <30 mL/min/1.73 m^2) have not been studied in AJOVY clinical trials. (See PART II: CLINICAL TRIALS)

Patients with Cardiovascular Diseases
No safety data are available in these populations. Patients with significant cardiovascular disease, vascular ischemia, or thrombotic events, such as cerebrovascular accident, transient ischemic attacks, deep vein thrombosis, or pulmonary embolism were excluded from the clinical trials. (See PART II:CLINICAL TRIALS)

Special Populations

7.1.1 Pregnant Women

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*)*. This should be taken into consideration for women who are pregnant or plan to become pregnant while using AJOVY. (See Non-Clinical Toxicology).

7.1.2 Breast-feeding

It is unknown if the drug is excreted in human milk. Because many drugs are excreted in human milk, precaution should be exercised.

There are no data on the presence of fremanezumab 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.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): Safety and efficacy of AJOVY in patients below the age of 18 have not been established.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): Clinical studies of AJOVY did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

8 ADVERSE REACTIONS

Adverse Reaction Overview

Hypersensitivity reactions, including rash, pruritus and urticaria were reported with fremanezumab in less than 1% of patients 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. Hypersensitivity reactions, including urticaria, pruritus, rash and swelling/edema have also been reported with fremanezumab in post-marketing experience.

Very common reported adverse drug reactions (ADRs) from the clinical trials were local reactions at the injection site pain, induration, erythema and pruritus.

The adverse reactions that most commonly led to discontinuations were injection site reactions.

Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety of AJOVY was evaluated in 2512 patients with migraine who received at least one dose of AJOVY 225 mg monthly or AJOVY 675 mg quarterly for at least six 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 Trials*)*. 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 were injection site reactions. The adverse reactions that most commonly led to discontinuations were injection site reactions .

Patients with significant cardiovascular disease, vascular ischemia, or thrombotic events, such as cerebrovascular accident, transient ischemic attacks, deep vein thrombosis, or pulmonary embolism were excluded from the clinical trials. (See PART II: CLINICAL TRIALS)

Table 2 - Adverse Reactions Occurring with an Incidence of ≥ 1% and Greater Than Placebo in Studies 1 and 2

System Organ Class Preferred Term	AJOVY 225 mg monthly N=290 n= (%)	AJOVY 675 mg quarterly N=667 n= (%)	Placebo N=668 n= (%)
Injection site reactions*	43	45	38

*Injection site reactions include multiple related adverse event terms, such as injection site pain, induration, and erythema

Table 3 Treatment Emergent adverse events occurring with an incidence of ≥ 1 % in the Placebo controlled studies 1 and 2

System Organ Class Preferred Term	AJOVY 225 mg monthly N=290 n= (%)	AJOVY 675 mg quarterly N=667 n= (%)	Placebo N=668 n= (%)
Patients with at least 1 AE	192 (66)	458 (69)	411 (62)
Gastrointestinal disorders			
Nausea	4 (1)	11 (2)	16 (2)
Diarrhoea	2 (<1)	5 (<1)	8 (1)
General disorders and administration site conditions			
Injection site pain	87 (30)	200 (30)	180 (27)
Injection site induration	71 (24)	131 (20)	113 (17)
Injection site erythema	52 (18)	135 (20)	101 (15)
Injection site haemorrhage	3 (1)	16 (2)	16 (2)
Injection site pruritus	4 (1)	10 (1)	2 (<1)
Fatigue	2 (<1)	9 (1)	9 (1)
Injection site rash	3 (1)	5 (<1)	0
Injection site swelling	3 (1)	4 (<1)	0
Infections and infestations			
Upper respiratory tract infection	16 (6)	29 (4)	180 (27)
Nasopharyngitis	11 (4)	30 (4)	113 (17)
Urinary tract infection	7 (2)	14 (2)	101 (15)
Bronchitis	6 (2)	9 (1)	16 (2)
Sinusitis	4 (1)	12 (2)	2 (<1)
Influenza	2 (<1)	8 (1)	9 (1)
Gastroenteritis	4 (1)	4 (<1)	0
Cystitis	3 (1)	1 (<1)	0
Herpes zoster	3 (1)	0	180 (27)
Injury, poisoning and procedural complications			
Ligament sprain	1 (<1)	3 (<1)	2 (<1)
Investigations			
Blood creatine phosphokinase increased	1 (<1)	3 (<1)	7 (1)
Alanine aminotransferase increased	1 (<1)	3 (<1)	1 (<1)
Aspartate aminotransferase increased	1 (<1)	3 (<1)	1 (<1)
Musculoskeletal and connective tissue disorders			
Back pain	3 (1)	11 (2)	9 (1)
Musculoskeletal pain	3 (1)	4 (<1)	0
Arthralgia	3 (1)	2 (<1)	1 (<1)

System Organ Class Preferred Term	AJOVY 225 mg monthly N=290 n= (%)	AJOVY 675 mg quarterly N=667 n= (%)	Placebo N=668 n= (%)
Nervous system disorders			
Dizziness	3 (1)	9 (1)	9 (1)
Paraesthesia	2 (<1)	9 (1)	4 (<1)
Migraine	1 (<1)	6 (<1)	11 (2)
Respiratory, thoracic and mediastinal disorders			
Cough	1 (<1)	8 (1)	6 (<1)
Skin and subcutaneous tissue disorders			
Pruritus	0	8 (1)	1 (<1)

Injection site reactions

The most frequently observed local reactions at the injection site were pain, induration and erythema. Most local injection site reactions were transient and 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. Most injection site reactions resolved, generally within a few hours or days. If the intensity of Injection site reactions is severe, discontinuation of fremanezumab should be considered.

Immunogenicity

In 3-month placebo-controlled studies, 0.4 % of patients (6 out of 1,701) treated with fremanezumab developed anti-drug antibodies (ADA). The antibody responses were of low titer. One of these 6 patients developed neutralizing antibodies. With 12 months of treatment, ADA were detected in 2.3% of the patients (38 out of 1,888) with 0.95% of the patients developing neutralizing antibodies.

8.3 Less Common Clinical Trial Adverse Reactions

From all clinical trials with AJOVY in adult patients with chronic and episodic migraine, the following less common adverse events of <1% have been observed. Causality to AJOVY has not been established.

Cardiac disorders (palpitations, angina pectoris).
Eyes disorders (vision blurred, diplopia, eye irritations).
Gastrointestinal disorders (nausea, diarrhea, constipation, vomiting, abdominal distension).
General disorders (chest pain, malaise).
Hepatobiliary disorders (weight increased, Gamma-glutamyltransferase increased).
Musculocutaneous and connective tissue disorders (pain, myalgia).
Nervous system disorders (migraine, headache, somnolence).
Psychiatric disorders (insomnia, anxiety, depression, suicidal ideation).
Skin disorders (rash, urticaria)
Vascular disorder (hypertension)

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

None.

8.5 Post-Market Adverse Reactions

The following adverse reactions are based on post-marketing spontaneous reports. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate the frequency.

Isolated cases of serious hypersensitivity reactions including angioedema and anaphylaxis have been reported in the post-marketing experience.

9 DRUG INTERACTIONS

No formal clinical drug interaction studies have been performed with AJOVY. 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. Furthermore, concomitant use of acute migraine treatments (specifically analgesics, ergots and triptans) and preventive treatment of migraine were found not to influence fremanezumab exposure

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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

10.2 Pharmacodynamics

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

10.3 Pharmacokinetics

Absorption:
After single subcutaneous administrations of 225 mg, 675 mg and 900mg fremanezumab, median time to maximum concentrations (t_{max}) in healthy subjects was 5 to 7 days. Dose proportionality, based on population pharmacokinetics, was observed from 225 mg to 900 mg. The absolute bioavailability was 54% and 57% for doses at 225 mg and 900 mg, respectively. Steady state was achieved by approximately 168 days (about 6 months) following 225 mg monthly and 675 mg quarterly dosing regimens. Median accumulation ratio, based on once monthly and once quarterly dosing regimens, is approximately 2.4 and 1.2, respectively.

Distribution:

The apparent volume of distribution was approximately 6 L following subcutaneous administration of fremanezumab.

Metabolism:
Similar to other monoclonal antibodies, fremanezumab is expected to be degraded by enzymatic proteolysis into small peptides and amino acids.

Elimination:
Based on a population pharmacokinetic analysis, the estimated apparent clearance was 0.14 L/day (23% CV) and the estimated half-life was 30 days (21% CV) following subcutaneous administration of fremanezumab.

Special Populations and Conditions
Based on a population pharmacokinetic analysis assessing age, race, gender, and weight was conducted on data from 2,546 subjects, no dose adjustments are required for fremanezumab.

Patients with Hepatic or Renal Impairment

Hepatic/renal impairment is not expected to affect the pharmacokinetics of fremanezumab. No dedicated hepatic/renal impairment studies were conducted to assess the effect of hepatic or renal impairment on the pharmacokinetics of fremanezumab. Population pharmacokinetic analysis did not reveal a difference in the pharmacokinetics of fremanezumab in patients with hepatic or renal impairment relative to those with normal hepatic or renal function. Patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) have not been studied in AJOVY clinical trials.

11 STORAGE, STABILITY AND DISPOSAL

- Store refrigerated at 2°C to 8°C in the original outer carton to protect from light until time of use.
- If necessary, AJOVY may be kept in the original carton at room temperature up to 25°C (for a maximum of 24 hours. After removal from the refrigerator, AJOVY must be used within 24 hours or discarded.
- Do not freeze. Do not expose to extreme heat or direct sunlight. Do not shake.
- Disposal: Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

12 SPECIAL HANDLING INSTRUCTIONS

- The detailed instructions for use provided at the end of the package leaflet must be followed step-by-step carefully.
- The prefilled syringe is for single use only.
- AJOVY should not be used if the solution is cloudy or discoloured or contains particles.
    - AJOVY should not be used if the solution has been frozen.
- The prefilled syringe should not be shaken.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: fremanezumab

Chemical name: Immunoglobulin G2, anti-(human alpha-calcitonin gene-related peptide/beta-calcitonin gene-related peptide

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

Molecular mass
Approximately 148 kDa

Structural formula: fremanzumab is composed of 2 heavy chains, each predicted to contain 448 amino acids residues and 2 light chains containing 214 amino acid residues.

Physicochemical properties: AJOVY (fremanezumab) injection is a sterile, preservative-free, clear to opalescent, colorless to slightly yellow solution for subcutaneous administration with a pH of 5.5.

Product Characteristics
Fremanezumab is a fully humanized IgG2Δa/kappa monoclonal antibody specific for calcitonin gene-related peptide (CGRP) ligand. Fremanezumab 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.

Each prefilled syringe delivers 1.5 mL of solution containing 225 mg fremanezumab, 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.

14 CLINICAL TRIALS

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).

Table 3 - Summary of trial design and patient demographics for clinical trials in Migraine Prevention

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Study 1 TV48125-CNS-30050 (Efficacy and safety) Episodic migraine	Randomized, double-blind, placebo-controlled, parallel-group study	3-month treatment period[a]: sc PBO monthly (PBO/PBO/PBO) sc fremanezumab at 675 mg followed by monthly doses of PBO (675 mg/PBO/PBO) sc fremanezumab 225 mg monthly (225/225/225 mg)	Enrolled: 875 Treated: 874 Completed: 791	18-70	M: 133(15 %) F: 742 (85%)
Study 2 TV48125-CNS-30049 (Efficacy and safety) Chronic migraine	Randomized, double-blind, placebo-controlled, parallel-group study	3-month treatment period[a]: sc PBO monthly (PBO/PBO/PBO) sc fremanezumab at 675 mg followed by monthly doses of PBO (675 mg/PBO/PBO) sc fremanezumab 225 mg monthly with a starting dose of 675 mg (675/225/225 mg)	Enrolled: 1130 Treated: 1130 Completed: 1034	18-71	M: 139 (12%) F: 991 (88%)

a In order to maintain blinding throughout the study, the number of injections at each visit was the same for all patients regardless of the treatment group to which they were randomized.

14.1 Episodic Migraine - Study 1

14.1.1 Trial Design and Study Demographics

AJOVY was evaluated for the preventive treatment of episodic migraine in Study 1 which 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. Randomization was stratified based on sex, country, and baseline preventive migraine medication use (yes, no). The total number of patients who received concomitant migraine preventive medication during the study was pre-specified not to exceed 30% of the total sample size of the study. Overall, 21% of randomized patients received concomitant migraine preventive medication during the study.

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.

Headache information was captured daily throughout study participation using the electronic headache diary device. 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 (90.4%) patients completed the 3-month double-blind phase.

Study Results

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 4.

Table 4: Key Efficacy Outcomes in Episodic Migraine – Study 1 Based on FAS

Efficacy Endpoint	**Placebo (n=290)**	**Fremanezumab 675 mg quarterly (n=288)**	**Fremanezumab 225 mg monthly (n=287)**
Monthly Migraine Days (MMD)			
Baseline MMD	9.1	9.2	8.9
LS mean change from baseline[a]	-2.2	-3.4	-3.7
LS mean difference from placebo (95% CI)[a]	-	-1.2 (-1.74, -0.69)	-1.4 (-1.96, 0.90)
P-value (vs. placebo)[a]	-	*p<0.0001*	*p<0.0001*
50% Responder Rate MMD			
Percentage [%]	27.9%	44.4%	47.7%
Estimated difference from placebo (95%) CI)	-	16.5 (8.8, 24.2)	19.8 (12.1, 27.6)
P-value (vs. placebo)[b]	-	*p<0.0001*	*p<0.0001*
Monthly Acute Headache Medication Days (MAHMD)			
Baseline MAHMD	7.7	7.7	7.7
LS mean change from baseline[a]	-1.6	-2.9	-3.0
LS mean difference from placebo (95% CI)[a]	-	-1.3 (-1.73, -0.78)	-1.3 (-1.81, -0.86)
P-value (vs. placebo)[a]	-	*p<0.0001*	*p<0.0001*

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

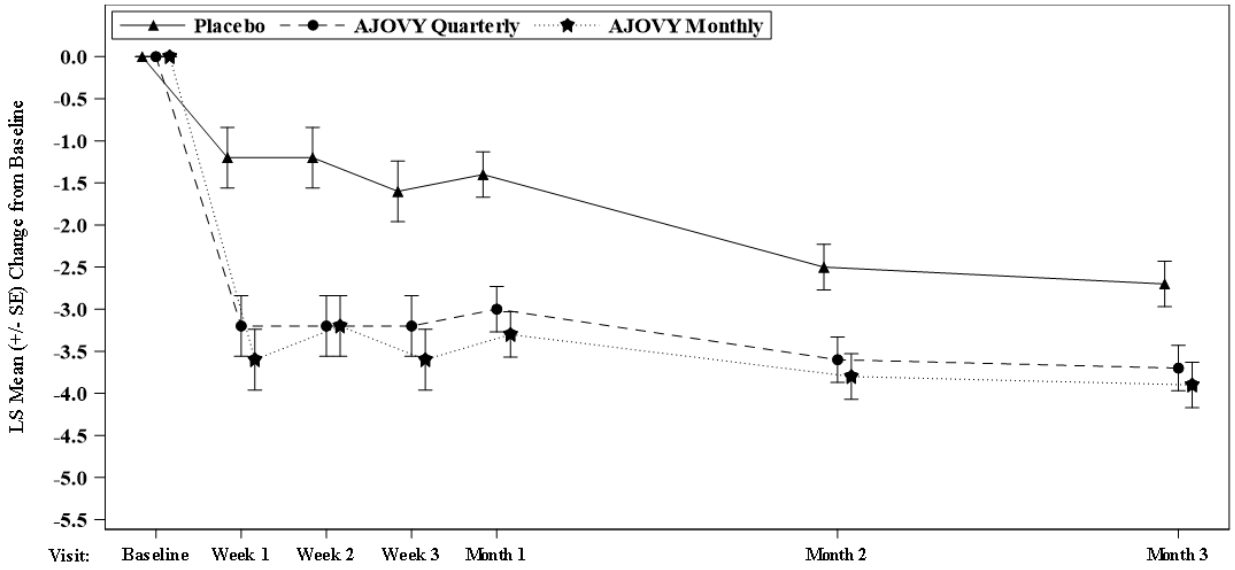
A fixed-sequence (hierarchical) testing procedure was implemented to control the type 1 error rate at 0.05.

[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 was based on the Cochran-Mantel-Haenszel test stratified by baseline preventive medication use (yes/no). The early discontinued patients were considered as non-responders for overall analysis.

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

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



Note: Least squares (LS) mean and standard error (SE) of the mean are presumed in the figure.

Chronic Migraine - Study 2

14.2.1 Trial Design and Study Demographics

Study 2 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. Randomization was stratified based on sex, country, and baseline preventive migraine medication use (yes, no). The total number of patients who received concomitant migraine preventive medication during the study was pre-specified not to exceed 30% of the total sample size of the study. Overall, 21% of randomized patients received concomitant migraine preventive medication during the study.

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.

Headache information was captured daily throughout study participation using the electronic headache diary device. 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 (91.5%) patients completed the 3-month double-blind phase.

14.2.1 Study results

Both monthly and quarterly dosing regimens of AJOVY treatment demonstrated statistically significant improvement for key efficacy outcomes compared to placebo, as summarized in Table 5.

Table 5: Key Efficacy Outcomes in Chronic Migraine – Study 2 Based on FAS

Efficacy Endpoint	**Placebo (n=371)**	**Fremanezumab 675 mg quarterly (n=375)**	**Fremanezumab 225 mg monthly with 675 mg starting dose (n=375)**
Monthly Headache Days of At Least Moderate Severity (MHD)			
Baseline MHD	13.3	13.2	12.8
LS mean change from baseline[a]	-2.5	-4.3	-4.6
LS mean difference from placebo (95% CI)[a]	-	-1.8 (-2.45, -1.13)	-2.1 (-2.77, -1.46)
P-value (vs. placebo)[a]	-	*p<0.0001*	*p<0.0001*
Monthly Migraine Days (MMD)			
Baseline MMD	16.3	16.2	16.0
LS mean change from baseline[a]	-3.2	-4.9	-5.0

LS mean difference from placebo (95% CI)[a]	-	-1.7 (-2.44, -0.92)	-1.9 (-2.61, -1.09)
P-value (vs. placebo)[a]	-	*p<0.0001*	*p<0.0001*
50% Responder Rate MHD Percentage [%] Estimated difference from placebo (95%) CI)	 18.1% -	 37.6% 19.5 (13.2, 25.7)	 40.8% 22.9 (16.5, 29.2)
P-value (vs. placebo)[b]	-	*p<0.0001*	*p<0.0001*
Monthly Acute Headache Medication Days (MAHMD) Baseline MAHMD LS mean change from baseline[a] LS mean difference from placebo (95% CI)[a]	 13.0 -1.9 -	 13.1 -3.7 -1.7 (-2.40, -1.09)	 13.1 -4.2 -2.3 (-2.95, -1.64)
P-value (vs. placebo)[a]	-	*p<0.0001*	*p<0.0001*

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.

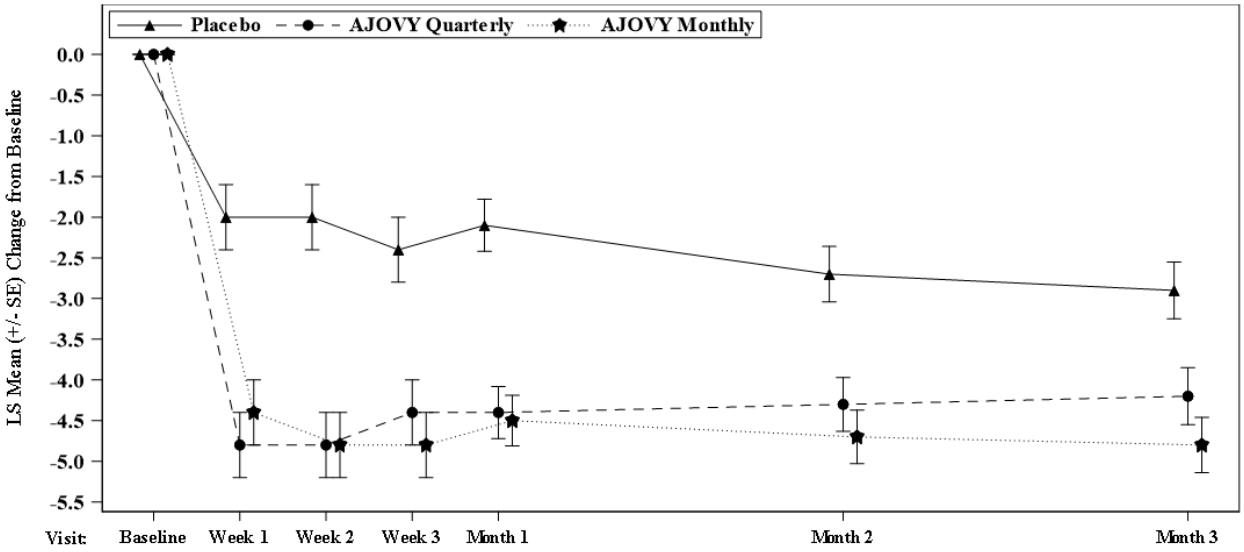
CI = confidence interval

A fixed-sequence (hierarchical) testing procedure was implemented to control the type 1 error rate at 0.05.

[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 was based on the Cochran-Mantel-Haenszel test stratified by baseline preventive medication use (yes/no). The early discontinued patients were considered as non-responders for overall analysis.

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



Note: Least squares (LS) mean and standard error (SE) of the mean are presumed in the figure.

NON-CLINICAL TOXICOLOGY

15.1 Safety Pharmacology

Safety pharmacology endpoints were evaluated in the general toxicology studies (up to 300 mg/kg/week) and in an additional stand-alone single dose study (100 mg/kg) in conscious telemetered cynomolgus monkeys, as well as single dose respiratory and CNS studies in rats (up to 300 mg/kg). No treatment-related effects were identified after single or repeated administrations up to 6 months via once weekly administration at doses of up to 300 mg/kg.

15.2 General Toxicology

The safety of fremanezumab was evaluated in repeat-dose toxicity studies in rats and monkeys for the duration of 3 months, and in chronic toxicity studies in cynomolgus monkeys for the duration of 6 months. Both the iv and sc routes were tested following once weekly dosing.

In rats, the no-observed-adverse-effect-level (NOAEL) was the highest dose tested in the 3-month repeat dose study (300 mg/kg sc) and safety margins (based on AUC) were 21 times higher than the exposure in humans at the recommended clinical sc dose regimen of 225 mg once monthly.

In monkeys, in the 6-month chronic toxicity study, at the NOAEL dose of 300 mg/kg/weekly, safety margins (based on AUC) were at least 158 times higher than the human exposure at the 225 mg once monthly sc dose.

Other studies in rats and monkeys via sc dosing were of shorter duration and therefore, safety margins were slightly lower than the values mentioned above, ranging from 18 to 48 times higher than the clinical exposure at the 225 mg once monthly sc dose. In one study in monkeys via iv dosing, the

NOAEL (10 mg/kg) and corresponding safety margin (approximately 4-fold higher) were lower due to incidental findings which were not reproducible in the chronic toxicity study

Other studies in rats and monkeys via sc dosing were of shorter duration and therefore, safety margins were slightly lower than the values mentioned above, ranging from 18 to 48 times higher than the clinical exposure at the 225 mg once monthly sc dose. In one study in monkeys via iv dosing, the NOAEL (10 mg/kg) and corresponding safety margin (approximately 4-fold higher) were lower due to incidental findings (perivasculitis of the ciliary vessel of the eye) which were not reproducible in the chronic toxicity study.

15.3 Carcinogenicity

Animal studies have not been performed to evaluate the carcinogenic potential of fremanezumab**.**

15.4 Genotoxicity

No studies have been performed to evaluate the genotoxic potential of fremanezumab.

15.5 Reproductive and Developmental Toxicology

When fremanezumab (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 calculated safety margins of approximately 43-fold and 9-fold in male and female rats, respectively, based on AUC over the human exposure following 225 mg once monthly sc dosing.

Administration of fremanezumab (0, 10, 50, or 100 mg/kg) weekly by subcutaneous injection to pregnant rabbits throughout the period of organogenesis produced no adverse effects on embryo-fetal development. The highest dose tested was associated with a calculated safety margin (based on AUC) of 20-fold relative to the human exposure administered a monthly sc dose of 225 mg.

Administration of fremanezumab (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. Exposure at the NOAEL (based on AUC) was 14 times higher than the human exposure at 225 mg monthly sc dose.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

AJOVY™
fremanezumab injection for subcutaneous use

Read this carefully before you start taking **AJOVY™** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **AJOVY™**.

What is AJOVY™ used for?

AJOVY™ is a prescription medicine used for the prevention of migraine in adults who have at least 4 migraine days per month.
It has not been studied in children younger than18 years of age, and it is not known if **AJOVY™** is safe and effective in children. Health Canada has not authorized **AJOVY™** for pediatric use.

How does AJOVY™ work?

AJOVY™ works by blocking the activity of a molecule called calcitonin gene-related peptide (CGRP). Increased CGRP levels in the blood may cause migraine attacks.

What are the ingredients in AJOVY™ ?

Medicinal ingredient: fremanezumab

Non-medicinal ingredients:
Disodium ethylenediaminetetraacetic acid dihydrate (EDTA)
L-histidine,
polysorbate80,
sucrose, and
water for Injection

AJOVY™ comes in the following dosage forms:

Solution for subcutaneous injection in a prefilled syringe containing 225mg/1.5mL(150mg/mL) for a single use.

Do not use AJOVY™ if:

Do not use **AJOVY™** if you are allergic to fremanezumab- or any of the ingredients in AJOVY. See the "What are the ingredients of AJOVY" above for a complete list of the ingredients in **AJOVY™**.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take AJOVY™ . Talk about any health conditions or problems you may have, including if you:

- If you have severe kidney disease
- If you have severe liver disease

- are pregnant or plan to become pregnant. It is not known if **AJOVY™** will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if **AJOVY™** passes into your breast milk. Talk to your healthcare professional about the best way to feed your baby while using **AJOVY™**
- **Talk to your doctor, pharmacist or nurse right away if you get:**
- Severe injection site reactions such as area of swelling, bleeding
- Severe allergic reaction such as trouble breathing, swelling of the lips and tongue, itching or severe rash after injecting AJOVY .

  These reactions may occur within minutes, although some may occur up to one month after administration.

- **Tell your doctor if you have or have had cardiovascular disease (problems with the heart and blood vessels) before using this medication, because AJOVY has not been studied in patients with certain cardiovascular diseases.**

Tell your healthcare professional 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 to take 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 professional tells you to use it.
- AJOVY is injected under your skin (subcutaneously).
- Your healthcare professional should show you or your caregiver how to prepare and inject your first dose of AJOVY
- Your healthcare professional will tell you how much AJOVY to use and when to use it. See Usual Dose section for more information.
  - Your healthcare professional 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 syringes. You will give 3 separate injections, one after another, one time every 3 months.
- If you are giving 3 injections of AJOVY for your prescribed dose, you may use the same body site for all 3 injections. Do NOT use the same spot for all 3 injections
- **Do not** inject AJOVY in the same injection site that you inject other medicine.
- If your doctor decided to change the frequency of injections, the new dose regimen should be given on the next scheduled dosing date of the old dose regimen.

If you have questions about your schedule, ask your healthcare professional.

Usual dose:
AJOVY comes as single-use (1 time) pre-filled syringe containing a single-dose. Your healthcare professional will prescribe the dose that is best for you.

- If your healthcare professional prescribes the 225 mg monthly dose for you, take 1 injection every month, using a prefilled syringe.
- If your healthcare professional prescribes the 675 mg every 3 months dose for you, take 3 separate injections one after another. Use different prefilled syringe for each injection. You will take these injections once every 3 months.

It is important to follow dose regimen as prescribed by your doctor!

Be aware that that monthly dose consists of a single subcutaneous injection.

Overdose:

If you think you have taken too much AJOVY contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
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 adjust 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 professional.

What are possible side effects from using AJOVY ?
These are not all the possible side effects you may feel when taking AJOVY. If you experience any side effects not listed here, contact your healthcare professional.

Very common (may affect more than 1 in 10 people)
The following mild to moderate, short-lasting skin reactions around the injection area can occur: Pain, localized hardening in the skin-raised red or purple skin patches, redness of the skin, severe itching at the injection site

Common (may affect up to 1 in 10 people)
Itching at the injection site

Uncommon (may affect up to 1 in 100 people)
Rash at injection site. Hives, rash, dizziness, fatigue, gastrointestinal discomfort, joint pain, back pain.

If you have a troublesome symptom or side effect that is not listed above, or becomes bad

enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting ((https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store refrigerated at 2°C to 8°C in the original outer carton to protect from light until time of use.
- If necessary, AJOVY may be kept in the original carton at room temperature up to 25°C (for a maximum of 24 hours. After removal from the refrigerator, AJOVY must be used within 24 hours or discarded.
- Do not freeze. Do not expose to extreme heat or direct sunlight. Do not shake.

Keep out of reach and sight of children.

If you want more information about AJOVY™

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website at http//hc-sc.gc.ca/index-eng.php; the manufacturer's website at http//www.tevacanadainnovation.ca or by calling Toll free number 1-833-302-0121

This leaflet was prepared by Teva Canada Innovation.

Last Revised:

Instructions for Use AJOVY™ (fremanezumab) injection 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.

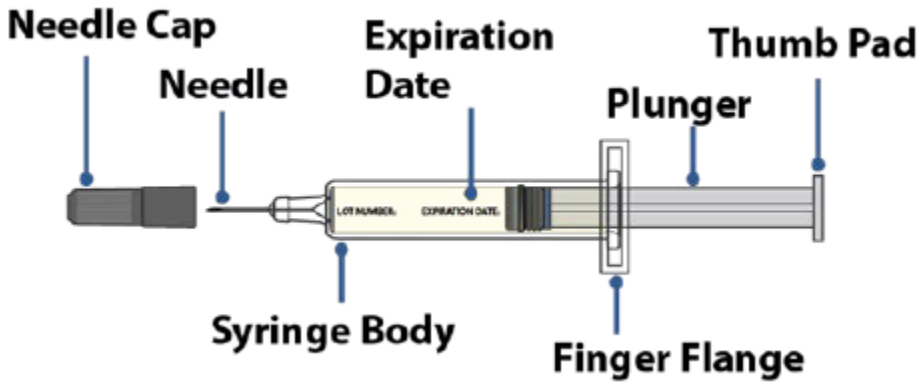
Important:

- AJOVY prefilled syringe is for one-time use only. Put AJOVY in sharps disposal 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 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 25 °C in the carton it comes in for up to 24 hours. Do not use AJOVY if it has been out of the refrigerator for 24 hours or longer. Throw away AJOVY in a sharps disposal container if it has been out of the refrigerator for 24 hours or longer.
- **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 the syringe out of the reach of children.

AJOVY prefilled syringe (Before use). See Figure A. Appearance of the syringe before use



A AJOVY prefilled syringe

After use: See Figure B.

Figure B Appearance of the syringe after use

How do I inject AJOVY?

Read this before you inject.

Step 1. Check your prescription.

AJOVY comes as a single-dose (1 time) prefilled syringe. Your healthcare provider will prescribe the dose that is best for you.

- If your healthcare professional prescribes the 225 mg monthly dose for you, take 1 injection monthly, using a prefilled syringe.
- If your healthcare professional prescribes the 675 mg every 3 months dose for you, take 3 separate injections one after another, using a different prefilled syringe for each injection. You will take these injections once 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 professional.

Step 2. Remove the prefilled syringe from the carton.

- You may need to use more than 1 prefilled syringe based 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.

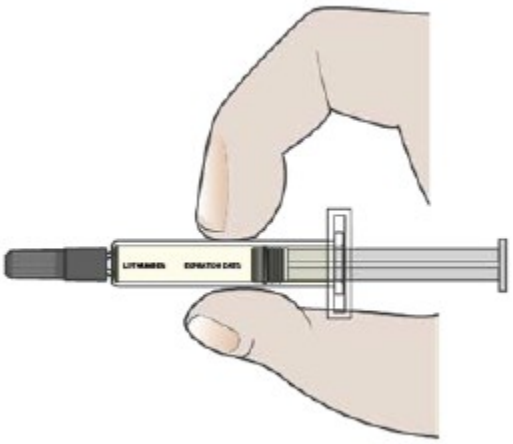


Figure C How to manipulate the syringe

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).

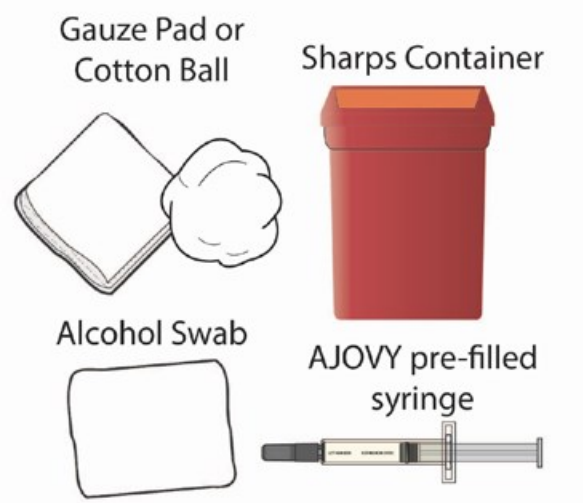


Figure D Supplies needed for the injection of AJOVY

Tell your pharmacist or healthcare provider if you do not already have a sharps or puncture-resistant container.

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, as this could damage the liquid medicine.
- **Do NOT** warm up the AJOVY prefilled syringe using hot water, a microwave, or any other way than instructed, as this could damage the liquid medicine.

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 professional or pharmacist.
- **Check** that AJOVY appears on the prefilled syringe.
- **Check** the expiration date printed on the prefilled syringe label.
- **Do NOT** use the prefilled syringe if it has any visible damage, such as cracks or leaks. See disposal instructions in Step 12.
- **Do NOT use** if you have been given the wrong medicine.
- **Do NOT** use the prefilled syringe if the expiration date has passed.

The above checks are all important to make sure the medicine is safe to use.

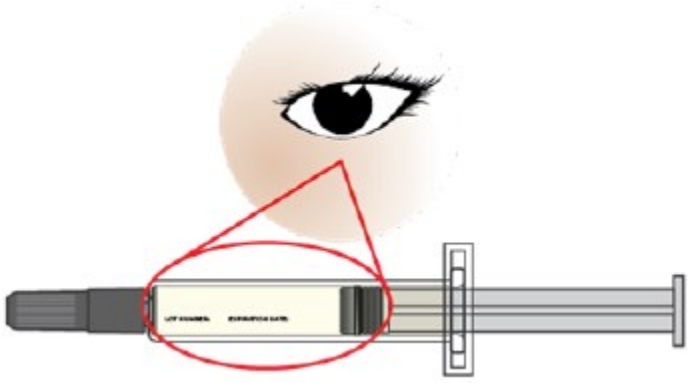


Figure E Checking the content of the prefilled syringe

Step 7. Choose your injection area.

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

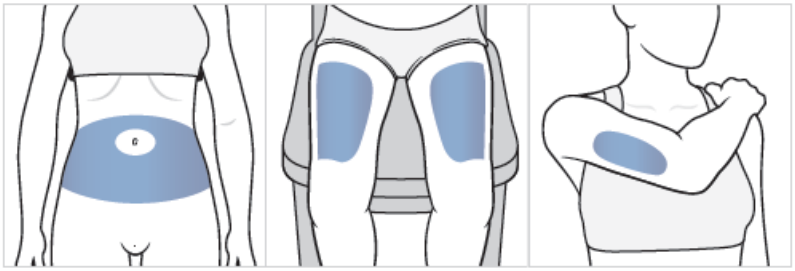


Figure F Injection areas

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
- **Wait** 10 seconds to allow the skin to dry before injecting.
- **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 body site for the three 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.

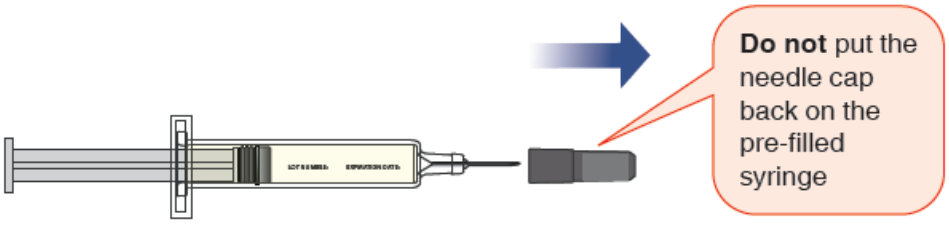
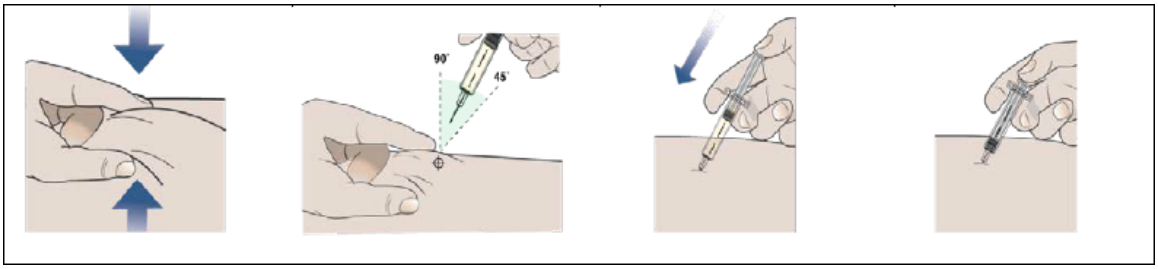


Figure G Removing the needle cap

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 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.

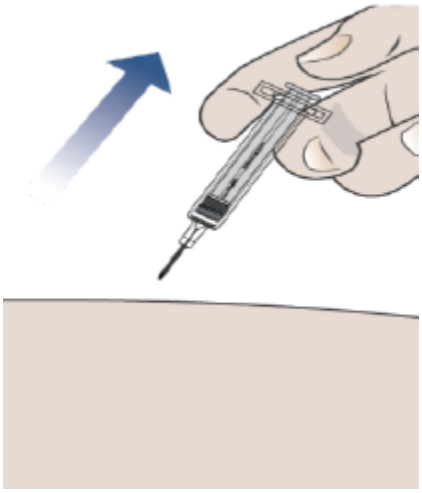


Figure H Removing the needle

Step 12. Apply pressure at 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 Health Canada -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 Health Canada -cleared sharps disposal container, you may use a household container that is:
  o made of a heavy-duty plastic,
  o can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  o upright and stable during use,
  o leak-resistant, and
  o 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 provincial or local laws about how you should throw away used syringes.
- **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