ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

AJOVY 225 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One pre-filled syringe contains 225 mg fremanezumab.

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

Clear to opalescent, colourless to slightly yellow solution with a pH of 5.5 and an osmolality of 300-450 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AJOVY is indicated for prophylaxis of migraine in adults who have at least 4 migraine days per month.

4.2 Posology and method of administration

The treatment should be initiated by a physician experienced in the diagnosis and treatment of migraine.

Posology

Treatment is intended for patients with at least 4 migraine days per month when initiating treatment with fremanezumab.

Two dosing options are available:

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

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

When initiating treatment with fremanezumab, concomitant migraine preventive treatment may be continued if considered necessary by the prescriber (see section 5.1).

The treatment benefit should be assessed within 3 months after initiation of treatment. Any further decision to continue treatment should be taken on an individual patient basis. Evaluation of the need to continue treatment is recommended regularly thereafter.

Missed dose
If a fremanezumab 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.

Special Populations

Elderly
There is limited data available on the use of fremanezumab in patients ≥65 years of age. Based on the results of population pharmacokinetic analysis, no dose adjustment is required (see section 5.2).

Renal or hepatic impairment
No dose adjustment is necessary in patients with mild to moderate renal impairment or hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy of AJOVY in children and adolescents below the age of 18 years have not yet been established. No data are available.

Method of administration

Subcutaneous use.

AJOVY is for subcutaneous injection only. It should not be administered by the intravenous or intramuscular route. AJOVY can be injected into areas of the abdomen, thigh, or upper arm that are not tender, bruised, red, or indurated. For multiple injections, injection sites should be alternated.

Patients may self-inject if instructed in subcutaneous self-injection technique by a healthcare professional. For further instructions on administration, see section 6.6.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability

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

Hypersensitivity

Hypersensitivity reactions were reported with fremanezumab in less than 1% of patients in clinical trials. If a hypersensitivity reaction occurs, discontinuation of fremanezumab administration should be considered and appropriate therapy should be initiated.

Major cardiovascular diseases

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

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e., is essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

No formal clinical drug interaction studies have been performed with AJOVY. No pharmacokinetic drug interactions are expected based on the characteristics of fremanezumab. Furthermore, concomitant use of acute migraine treatments (specifically analgesics, ergots, and triptans) and migraine preventive medicinal products during the clinical studies did not affect the pharmacokinetics of fremanezumab.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data from the use of AJOVY in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of AJOVY during pregnancy.

Breast-feeding

It is unknown whether fremanezumab is excreted in human milk. Human IgG is known to be excreted in breast milk during the first days after birth, which is decreasing to low concentrations soon afterwards; consequently, a risk to breast-fed infants cannot be excluded during this short period. Afterwards, use of fremanezumab could be considered during breast-feeding only if clinically needed.

Fertility

There are no fertility data in humans. Available non-clinical data do not suggest an effect on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

A total of over 2,500 patients (more than 1,900 patient years) have been treated with AJOVY in registration studies. More than 1,400 patients were treated for at least 12 months.

Commonly reported adverse drug reactions (ADRs) were local reactions at the injection site (pain [24%], induration [17%], erythema [16%] and pruritus [2%]).

Tabulated list of adverse reactions

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

The following ADRs have been identified in the AJOVY clinical development programme (Table 1).

Table 1: Adverse reactions in clinical studies

MedDRA System Organ Class	Frequency	Adverse Reaction
General disorders and administration site conditions	Very common	Injection site pain
		Injection site induration
		Injection site erythema
	Common	Injection site pruritus
	Uncommon	Injection site rash

Description of selected adverse reactions

Injection site reactions
The most frequently observed local reactions at the injection site were pain, induration and erythema. All 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. All injection site reactions resolved, mostly within a few hours or days. Injection site reactions generally did not necessitate discontinuation of the medicinal product.

Immunogenicity
In 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 neutralising antibodies. To date, 1,494 patients have completed 12 months of treatment with fremanezumab in the ongoing long-term Study 3. ADA were detected in 2% of the patients (38 out of 1,888). The safety and efficacy of fremanezumab were not affected by ADA development.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Doses up to 2,000 mg have been administered intravenously in clinical trials without dose-limiting toxicity. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse effects and given appropriate symptomatic treatment if necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Not yet assigned. ATC code: Not yet assigned.

Mechanism of action

Fremanezumab is a humanised IgG2Δa/kappa monoclonal antibody derived from a murine precursor. Fremanezumab selectively binds the calcitonin gene-related peptide (CGRP) ligand and blocks both CGRP isoforms (α-and β-CGRP) from binding to the CGRP receptor. While the precise mechanism of action by which fremanezumab prevents migraine attacks is unknown, it is believed that prevention of migraine is obtained by its effect modulating the trigeminal system. CGRP levels have been shown to increase significantly during migraine and return to normal with headache relief.

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

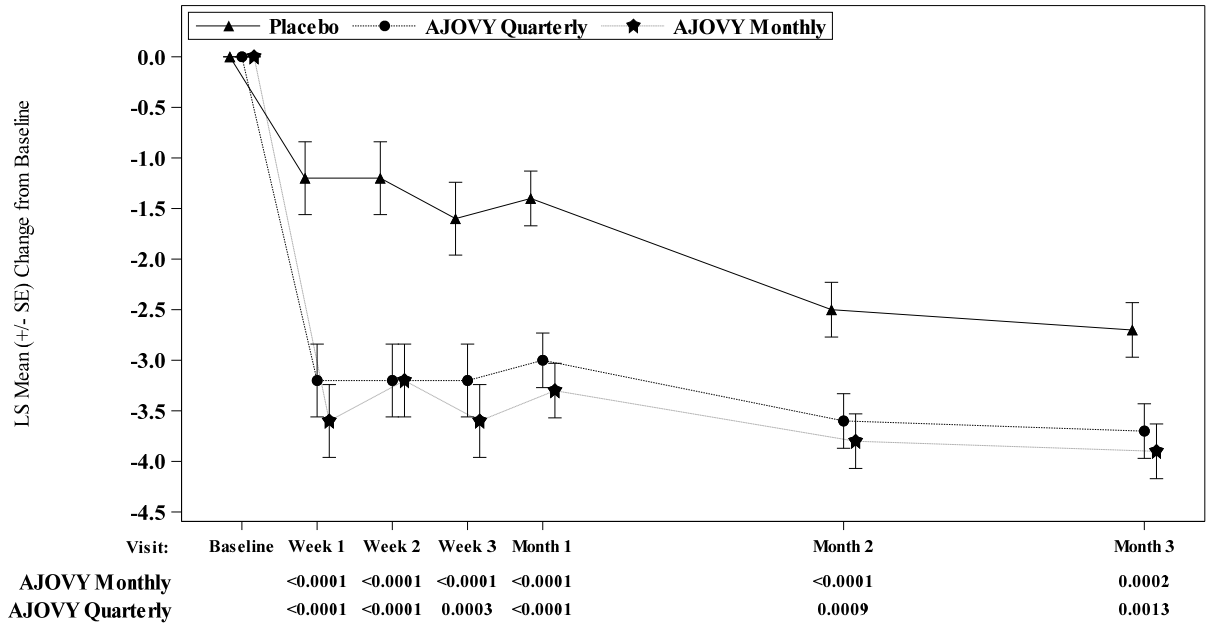
Clinical efficacy and safety

The efficacy of fremanezumab was assessed in two randomised, 12-week, double-blind, placebo-controlled phase III studies in adult patients with episodic (Study 1) and chronic migraine (Study 2). The patients enrolled had at least a 12-month history of migraine (with and without aura) according to the International Classification of Headache Disorders (ICHD-III) diagnostic criteria. Elderly patients (>70 years), patients using opioids or barbiturates on more than 4 days per month, and patients with pre-existing myocardial infarction, cerebrovascular accident, and thromboembolic events were excluded.

Episodic migraine study (Study 1)
The efficacy of fremanezumab was evaluated in episodic migraine in a randomised, multicentre, 12-week, placebo-controlled, double-blind study (Study 1). Adults with a history of episodic migraine (less than 15 headache days per month) were included in the study. A total of 875 patients (742 females, 133 males) were randomised into one of three arms: 675 mg fremanezumab every three months (quarterly, n=291), 225 mg fremanezumab once a month (monthly, n=290), or monthly administration of placebo (n=294) administered via subcutaneous injection. Demographics and baseline disease characteristics were balanced and comparable between the study arms. Patients had a median age of 42 years (range: 18 to 70 years), 85% were female, and 80% were white. The mean migraine frequency at baseline was approximately 9 migraine days per month. Patients were allowed to use acute headache treatments during the study. A sub-set of patients (21%) was also allowed to use one commonly used concomitant, preventive medicinal product (beta-blockers, calcium channel blocker/benzocycloheptene, antidepressants, anticonvulsants). Overall, 19% of the patients had previously used topiramate. A total of 791 patients completed the 12-week double-blind treatment period.

The primary efficacy endpoint was the mean change from baseline in the monthly average number of migraine days during the 12-week treatment period. Key secondary endpoints were the achievement of at least 50% reduction from baseline in monthly migraine days (50% responder rate), mean change from baseline in the patient reported MIDAS score, and change from baseline in monthly average number of days of acute headache medicinal product use. Both monthly and quarterly dosing regimens of fremanezumab demonstrated statistically significant and clinically meaningful improvement from baseline compared to placebo for key endpoints (see Table 2). The effect also occurred from as early as the first month and sustained over the treatment period (see Figure 1).

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



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

Table 2: Key Efficacy Outcomes in Study 1 in Episodic Migraine

Efficacy Endpoint	**Placebo** (n=290)	**Fremanezumab 675 mg quarterly** (n=288)	**Fremanezumab 225 mg monthly** (n=287)
MMD			
Mean change[a] (95% CI)	-2.2 (-2.68, -1.71)	-3.4 (-3.94, -2.96)	-3.7 (-4.15, -3.18)
TD (95% CI)[b]	-	-1.2 (-1.74, -0.69)	-1.4 (-1.96, -0.90)
Baseline (SD)	9.1 (2.65)	9.2 (2.62)	8.9 (2.63)
P-value (vs. placebo)[a]	-	*p<0.0001*	*p<0.0001*
MHD			
Mean change[a] (95% CI)	-1.5 (-1.88, -1.06)	-3.0 (-3.39, -2.55)	-2.9 (-3.34, -2.51)
TD (95% CI)[b]	-	-1.5 (-1.95, -1.02)	-1.5 (-1.92, -0.99)
Baseline (SD)	6.9 (3.13)	7.2 (3.14)	6.8 (2.90)
P-value (vs. placebo)[a]	-	*p<0.0001*	*p<0.0001*
50% Responder Rate MMD			
Percentage [%]	27.9%	44.4%	47.7%
P-value (vs. placebo)	-	*p<0.0001*	*p<0.0001*
75% Responder Rate MMD			
Percentage [%]	9.7%	18.4%	18.5%
P-value (vs. placebo)	-	*p=0.0025*	*p=0.0023*
MIDAS total			
Mean change[a] (95% CI)	-17.5 (-20.62, -14.47)	-23.0 (-26.10, -19.82)	-24.6 (-27.68, -21.45)
Baseline (SD)	37.3 (27.75)	41.7 (33.09)	38 (33.30)
P-value (vs. placebo)[a]	-	*p=0.0023*	*p<0.0001*
MAHMD			
Mean change[a] (95% CI)	-1.6 (-2.04, -1.20)	-2.9 (-3.34, -2.48)	-3.0 (-3.41, -2.56)
	-	-1.3 (-1.73, -0.78)	-1.3 (-1.81, -0.86)

TD (95% CI)[b] Baseline (SD)	7.7 (3.60)	7.7 (3.70)	7.7 (3.37)
P-value (vs. placebo)[a]	-	*p<0.0001*	*p<0.0001*

CI = confidence interval; MAHMD = monthly acute headache medication days; MHD = monthly headache days of at least moderate severity; MIDAS = Migraine Disability Assessment; MMD = monthly migraine days; SD = standard deviation; TD = treatment difference

[a] For all endpoints mean change and CIs are 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] Treatment difference is based on the MMRM analysis with treatment, gender, region, and baseline preventive medication use (yes/no), month, and treatment month as fixed effects and corresponding baseline value and years since onset of migraine as covariates.

In patients on one other concomitant, migraine preventive medicinal product, the treatment difference for the reduction of monthly migraine days (MMD) observed between fremanezumab 675 mg quarterly and placebo was -1.8 days (95% CI: -2.95, -0.55) and between fremanezumab 225 mg monthly and placebo -2.0 days (95% CI: -3.21, -0.86).

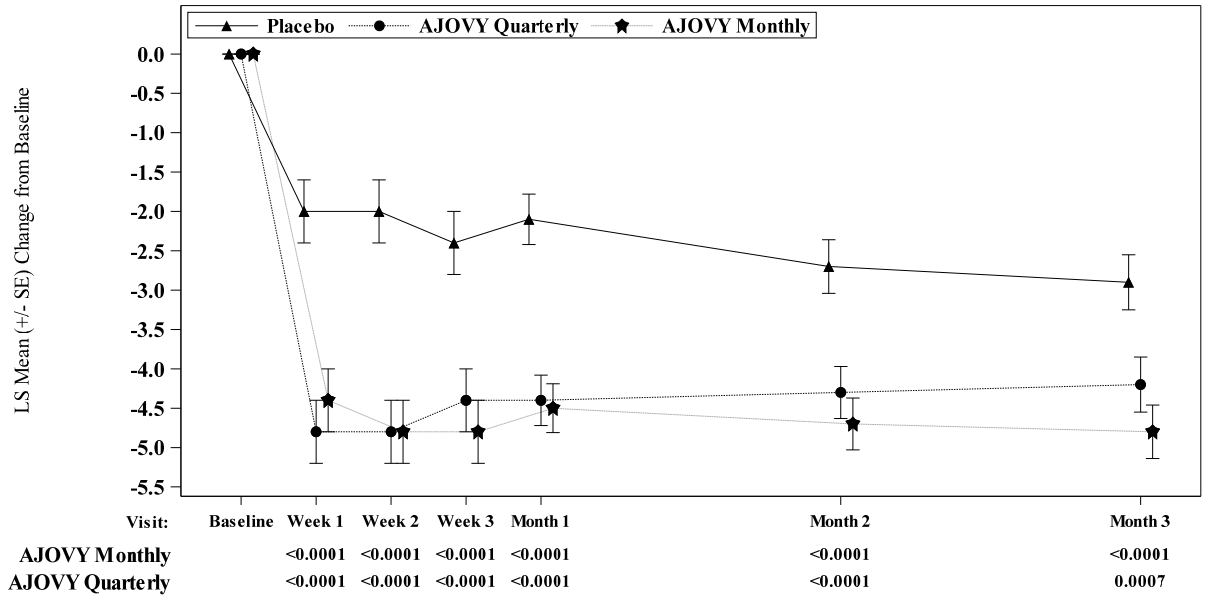
In patients who had previously used topiramate the treatment difference for the reduction of monthly migraine days (MMD) observed between fremanezumab 675 mg quarterly and placebo was -2.3 days (95% CI: -3.64, -1.00) and between fremanezumab 225 mg monthly and placebo -2.4 days (95% CI: -3.61, -1.13).

Chronic migraine study (Study 2)

Fremanezumab was evaluated in chronic migraine in a randomised, multicentre, 12-week, placebo-controlled, double-blind study (Study 2). The study population included adults with a history of chronic migraine (15 headache days or higher per month). A total of 1,130 patients (991 females, 139 males) were randomised into one of three arms: 675 mg fremanezumab starting dose followed by 225 mg fremanezumab once a month (monthly, n=379), 675 mg fremanezumab every three months (quarterly, n=376), or monthly administration of placebo (n=375) administered via subcutaneous injection. Demographics and baseline disease characteristics were balanced and comparable between the study arms. Patients had a median age of 41 years (range: 18 to 70 years), 88% were female, and 79% were white. The mean headache frequency at baseline was approximately 21 headache days per month (of which 13 headache days were of at least moderate severity). Patients were allowed to use acute headache treatments during the study. A sub-set of patients (21%) was also allowed to use one commonly used concomitant, preventive medicinal product (beta-blockers, calcium channel blocker/benzocycloheptene, antidepressants, anticonvulsants). Overall, 30% of the patients had previously used topiramate and 15% onabotulinumtoxin A. A total of 1,034 patients completed the 12-week double-blind treatment period.

The primary efficacy endpoint was the mean change from baseline in the monthly average number of headache days of at least moderate severity during the 12-week treatment period. Key secondary endpoints were the achievement of at least 50% reduction from baseline in monthly headache days of at least moderate severity (50% responder rate), mean change from baseline in the patient reported HIT-6 score, and change from baseline in monthly average number of days of acute headache medicinal product use. Both monthly and quarterly dosing regimens of fremanezumab demonstrated statistically significant and clinically meaningful improvement from baseline compared to placebo for key endpoints (see Table 3). The effect also occurred from as early as the first month and sustained over the treatment period (see Figure 2).

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



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

Table 3: Key Efficacy Outcomes in Study 2 in Chronic Migraine

Efficacy Endpoint	**Placebo** (n=371)	**Fremanezumab 675 mg quarterly** (n=375)	**Fremanezumab 225 mg monthly with 675 mg starting dose** (n=375)
MHD			
Mean change[a] (95% CI)	-2.5 (-3.06, -1.85)	-4.3 (-4.87, -3.66)	-4.6 (-5.16, -3.97)
TD (95% CI)[b]	-	-1.8 (-2.45, -1.13)	-2.1 (-2.77, -1.46)
Baseline (SD)	13.3 (5.80)	13.2 (5.45)	12.8 (5.79)
P-value (vs. placebo)[a]	-	*p<0.0001*	*p<0.0001*
MMD			
Mean change[a] (95% CI)	-3.2 (-3.86, -2.47)	-4.9 (-5.59, -4.20)	-5.0 (-5.70, -4.33)
TD (95% CI)[b]	-	-1.7 (-2.44, -0.92)	-1.9 (-2.61, -1.09)
Baseline (SD)	16.3 (5.13)	16.2 (4.87)	16.0 (5.20)
P-value (vs. placebo)[a]	-	*p<0.0001*	*p<0.0001*
50% Responder Rate MHD			
Percentage [%]	18.1%	37.6%	40.8%
P-value (vs. placebo)	-	*p<0.0001*	*p<0.0001*
75% Responder Rate MHD			
Percentage [%]	7.0%	14.7%	15.2%
P-value (vs. placebo)	-	*p=0.0008*	*p=0.0003*
HIT-6 total			
Mean change[a] (95% CI)	-4.5 (-5.38, -3.60)	-6.4 (-7.31, -5.52)	-6.7 (-7.71, -5.97)
Baseline (SD)	64.1 (4.79)	64.3 (4.75)	64.6 (4.43)
P-value (vs. placebo)[a]	-	*p=0.0001*	*p<0.0001*
MAHMD			
Mean change[a] (95% CI)	-1.9 (-2.48, -1.28)	-3.7 (-4.25, -3.06)	-4.2 (-4.79, -3.61)
	-	-1.7 (-2.40, -1.09)	-2.3 (-2.95, -1.64)

TD (95% CI)[b] Baseline (SD)	13.0 (6.89)	13.1 (6.79)	13.1 (7.22)
P-value (vs. placebo)[a]	-	*p<0.0001*	*p<0.0001*

CI = confidence interval; HIT-6 = Headache Impact Test; MAHMD = monthly acute headache medication days; MHD = monthly headache days of at least moderate severity; MMD = monthly migraine days; SD = standard deviation; TD = treatment difference

[a] For all endpoints mean change and CIs are 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] Treatment difference is based on the MMRM analysis with treatment, gender, region, and baseline preventive medication use (yes/no), month, and treatment month as fixed effects and corresponding baseline value and years since onset of migraine as covariates.

In patients on one other concomitant, migraine preventive medicinal product, the treatment difference for the reduction of monthly headache days (MHD) of at least moderate severity observed between fremanezumab 675 mg quarterly and placebo was -1.3 days (95% CI: -2.66, 0.03) and between fremanezumab 225 mg monthly with 675 mg starting dose and placebo -2.0 days (95% CI: -3.27, -0.67).

In patients who had previously used topiramate the treatment difference for the reduction of monthly headache days (MHD) of at least moderate severity observed between fremanezumab 675 mg quarterly and placebo was -2.7 days (95% CI: -3.88, -1.51) and between fremanezumab 225 mg monthly with 675 mg starting dose and placebo -2.9 days (95% CI: -4.10, -1.78). In patients who had previously used onabotulinumtoxin A the treatment difference for the reduction of monthly headache days (MHD) of at least moderate severity observed between fremanezumab 675 mg quarterly and placebo was -1.3 days (95% CI: -3.01, -0.37) and between fremanezumab 225 mg monthly with 675 mg starting dose and placebo -2.0 days (95% CI: -3.84, -0.22).

Approximately 52% of the patients in the study had acute headache medication overuse. The observed treatment difference for the reduction of monthly headache days (MHD) of at least moderate severity between fremanezumab 675 mg quarterly and placebo in these patients was -2.2 days (95% CI: -3.14, -1.22) and between fremanezumab 225 mg monthly with 675 mg starting dose and placebo -2.7 days (95% CI: -3.71, -1.78).

Long-term study (Study 3)

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

Intrinsic and extrinsic factors

The efficacy and safety of fremanezumab was demonstrated regardless of age, gender, race, use of concomitant preventive medicinal products (beta-blockers, calcium channel blocker/benzocycloheptene, antidepressants, anticonvulsants), use of topiramate or onabotulinumtoxin A for migraine in the past, and acute headache medication overuse.
There is limited data available on the use of fremanezumab in patients ≥65 years of age (2% of the patients).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with AJOVY in one or more subsets of the paediatric population in prevention of migraine headaches (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

After single subcutaneous administrations of 225 mg and 675 mg fremanezumab, median time to maximum concentrations (t_{max}) in healthy subjects was 5 to 7 days. The absolute bioavailability of fremanezumab after subcutaneous administration of 225 mg and 900 mg in healthy subjects was 55% (±SD of 23%) to 66% (±SD of 26%). Dose proportionality, based on population pharmacokinetics, was observed between 225 mg to 675 mg. 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

Assuming the model-derived estimated bioavailability of 66% (±SD of 26%) holds for the patient population, the volume of distribution for a typical patient was 3.6 L (35.1% CV) following subcutaneous administration of 225 mg, 675 mg and 900 mg of fremanezumab.

Biotransformation

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

Elimination

Assuming the model-derived estimated bioavailability of 66% (±SD of 26%) holds for the patient population, central clearance for a typical patient was 0.09 L/day (23.4% CV) following subcutaneous administration of 225 mg, 675 mg and 900 mg of fremanezumab. The formed small peptides and amino acids may be re-used in the body for de novo synthesis of proteins or are excreted by the kidney. Fremanezumab has an estimated half-life of 30 days.

Special populations

A population pharmacokinetic analysis looking at age, race, gender, and weight was conducted on data from 2,546 subjects. Approximately twice as much exposure is expected in the lowest body weight quartile (43.5 to 60.5 kg) compared to the highest body weight quartile (84.4 to131.8 kg). However, body weight did not have an observed effect on the clinical efficacy based on the exposure-response analyses in episodic and chronic migraine patients. No dose adjustments are required for fremanezumab. No data on exposure-efficacy relationship in subjects with body weight >132 kg is available.

Renal or hepatic impairment
Since monoclonal antibodies are not known to be eliminated via renal pathways or metabolised in the liver, renal and hepatic impairment are not expected to impact the pharmacokinetics of fremanezumab. Patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) have not been studied. Population pharmacokinetic analysis of integrated data from the AJOVY clinical studies did not reveal a difference in the pharmacokinetics of fremanezumab in patients with mild to moderate renal impairment or hepatic impairment relative to those with normal renal or hepatic function (see section 4.2).

5.3 Preclinical safety data

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine
L-histidine hydrochloride monohydrate
Sucrose
Disodium ethylenediaminetetraacetic acid (EDTA) dihydrate
Polysorbate 80
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Keep the pre-filled syringe(s) in the outer carton in order to protect from light.
AJOVY may be stored unrefrigerated for up to 24 hours at a temperature up to 25°C. AJOVY must be discarded if it has been out of the refrigerator for longer than 24 hours.

6.5 Nature and contents of container

1.5 mL solution in a 2.25 mL Type I glass syringe with plunger stopper (bromobutyl rubber) and needle.

Pack sizes of 1 or 3 pre-filled syringes. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Instructions for use

The detailed instructions for use provided at the end of the package leaflet must be followed step-by-step carefully.
The pre-filled 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 pre-filled syringe should not be shaken.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

TEVA GmbH
Graf-Arco-Str. 3
89079 Ulm
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1358/001
EU/1/19/1358/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 March 2019

10. DATE OF REVISION OF THE TEXT

28 March 2019

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

CELLTRION Inc.
20 Academy -ro 51 beon-gil
Yeonsu-gu
22014 Incheon
Republic of Korea

Name and address of the manufacturer(s) responsible for batch release

Merckle GmbH
Graf-Arco-Str. 3
89079 Ulm
Germany

Teva Pharmaceuticals Europe B.V.
Swensweg 5
2031 GA Haarlem
Netherlands

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription. (see Annex I: Summary of Product Characteristics, section 4.2)

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.
The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.
An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new

information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

AJOVY 225 mg solution for injection in pre-filled syringe
fremanezumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pre-filled syringe contains 225 mg fremanezumab.

3. LIST OF EXCIPIENTS

Excipients: L-histidine, L-histidine hydrochloride monohydrate, sucrose, disodium ethylenediaminetetraacetic acid (EDTA) dihydrate, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled syringe of 1.5 mL solution
3 pre-filled syringes of 1.5 mL solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use
For single use only.

OPEN HERE
LIFT HERE

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light.
Keep the pre-filled syringes in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

TEVA GmbH
Graf-Arco-Str. 3
89079 Ulm
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1358/001 1 pre-filled syringe
EU/1/19/1358/002 3 pre-filled syringes

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

AJOVY

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

AJOVY 225 mg injection
fremanezumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1.5 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

AJOVY 225 mg solution for injection in pre-filled syringe
fremanezumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What AJOVY is and what it is used for

What AJOVY is
AJOVY is a medicine containing the active substance fremanezumab, a monoclonal antibody, a type of protein that recognises and attaches to a specific target in the body.

How AJOVY works
A substance in the body called calcitonin gene-related peptide (CGRP) plays an important role in migraine. Fremanezumab attaches to CGRP and prevents it from working. This reduction in CGRP's activity reduces migraine attacks.

What AJOVY is used for
AJOVY is used to prevent migraine in adults who have at least 4 migraine days per month.

What are the benefits of using AJOVY
AJOVY reduces the frequency of migraine attacks and days with headache. This medicine also decreases the disability associated with migraine and it reduces the need for medicines used to treat migraine attacks.

2. What you need to know before you use AJOVY

Do not use AJOVY
Do not use this medicine if you are allergic to fremanezumab or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse if you get any symptoms of an allergic reaction, e.g. trouble breathing, swelling of the lips and tongue, or severe rash, after injecting AJOVY.

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

Children and adolescents
AJOVY is not recommended for children and adolescents below the age of 18 years because it has not been studied in this age group.

Other medicines and AJOVY
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

Pregnancy and breast-feeding
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. It is preferable to avoid the use of AJOVY during pregnancy as the effects of this medicine in pregnant women are not known.

If you are breast-feeding or are planning to breast-feed, talk to your doctor or pharmacist before using this medicine. You and your doctor should decide if you will use AJOVY while breast-feeding.

Driving and using machines
This medicine is not expected to have any effect on your ability to drive or use machines.

AJOVY contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, i.e. is essentially “sodium-free”.

3. How to use AJOVY

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

AJOVY is given by injection under your skin (subcutaneous injection). Your doctor or nurse will explain to you or your caregiver how to give the injection. Do not inject AJOVY until you or your caregiver have been trained by your doctor or nurse.

Read the “Instructions for Use” for the pre-filled syringe carefully before using AJOVY.

How much and when to inject
Your doctor will discuss and decide with you the most appropriate dosing schedule. There are two alternative recommended dosing options:
- one injection (225 mg) once a month (monthly dosing) or
- three injections (675 mg) every 3 months (quarterly dosing)

If your dose is 675 mg, inject the three injections one after another, each in a different place.

Use a reminder method such as notes in a calendar or diary to help you remember your next dose so that you do not miss a dose or have a dose too soon after the last one.

If you use more AJOVY than you should
If you have used more AJOVY than you should, tell your doctor.

If you forget or miss to use AJOVY
If you have missed a dose of AJOVY, inject your missed dose as soon as you can. Do not take a double dose to make up for a forgotten dose. If you are not sure when to inject AJOVY, talk to your doctor, pharmacist or nurse.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following mild to moderate, short-lasting skin reactions around the injection area can occur:

Very common (may affect more than 1 in 10 people)
Pain, hardening or redness 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 the injection site

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store AJOVY

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the syringe label and on the outer carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C). Do not freeze.
Keep the pre-filled syringe in the outer carton to protect the medicine from light.

This medicine may be removed from the refrigerator and stored at a temperature below 25°C for a maximum period of up to 24 hours. The medicine must be discarded if it has been out of the refrigerator for longer than 24 hours.

Do not use this medicine if you notice that the outer carton has been tampered with, the syringe is damaged, or the medicine is cloudy, discoloured, or contains particles.

The syringe is for single use only.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What AJOVY contains
- The active substance is fremanezumab.
  Each pre-filled syringe contains 225 mg of fremanezumab.
- The other ingredients (excipients) are L-histidine, L-histidine hydrochloride monohydrate, sucrose, disodium ethylenediaminetetraacetic acid (EDTA) dihydrate, polysorbate 80 and water for injections.

What AJOVY looks like and contents of the pack
AJOVY is a solution for injection (injection) in a pre-filled syringe with a fixed injection needle in a blister. AJOVY is a clear, colourless to slightly yellow solution. Each pre-filled syringe contains 1.5 mL solution.

AJOVY is available in packs containing 1 or 3 pre-filled syringes. Not all pack sizes may be available in your country.

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Manufacturer
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This leaflet was last revised in March 2019.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Instructions for Use

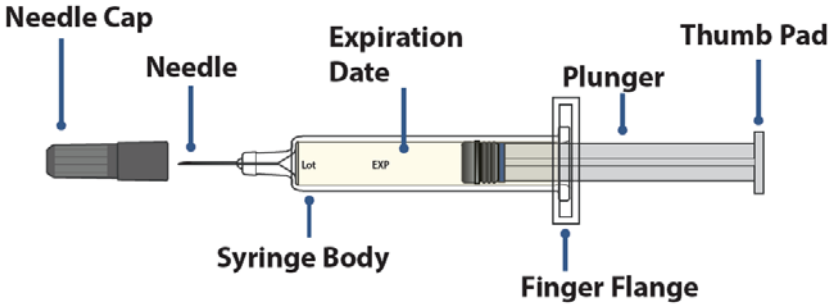
AJOVY 225 mg solution for injection in pre-filled syringe
fremanezumab

Before you use the AJOVY pre-filled syringe, read and carefully follow the step-by-step instructions.

Important information:

- The AJOVY pre-filled syringe is for single use only.
- Each AJOVY pre-filled syringe contains 225 mg of fremanezumab. Depending on your dose you will need to use 1 pre-filled syringe or 3 pre-filled syringes.
- AJOVY is injected under your skin (subcutaneous injection).You should not inject yourself until you have been trained by your doctor or nurse.
- Carefully read the AJOVY package leaflet to learn more about your medicine.
- **Do not** pull back on the plunger at any time as this can break the pre-filled syringe.
- **Do not** shake the pre-filled syringe.
- **Put the carton back in the refrigerator immediately**, if you have any unused pre-filled syringes in the carton.

Parts of the AJOVY pre-filled syringe



Step 1: Getting ready for an injection

a) Gather the following supplies for your injection:
- 1 or 3 AJOVY pre-filled syringes to enable 1 or 3 injections depending on your dose
- 1 alcohol swab per injection
- 1 gauze pad or cotton ball per injection
- 1 sharps disposal or puncture-resistant container

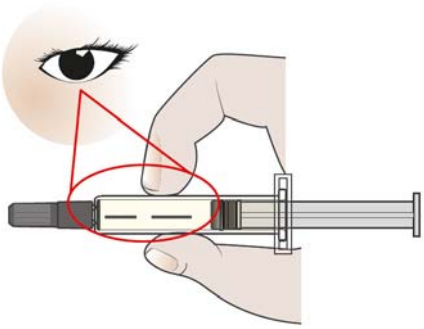
b) Place the supplies you have gathered on a clean, flat surface.

c) Wait for 30 minutes to let AJOVY reach room temperature to reduce discomfort during injection.
- **Do not** leave the pre-filled syringe in direct sunlight.
- **Do not** warm up the pre-filled syringe using a microwave or any other heat source.

d) Wash your hands with soap and water and dry well with a clean towel.

e) Inspect your AJOVY pre-filled syringe.
- Check the syringe label. Make sure the name AJOVY appears on the label.
- Check that the medicine inside the syringe looks clear and is colourless to slightly yellow.
- You may see small air bubbles in the pre-filled syringe. This is normal.

- **Do not** use the pre-filled syringe if you see any of the following:
  - The syringe looks damaged.
  - The expiration date has passed.
  - The medicine is cloudy, discoloured, or contains particles.



f) Choose your injection area.

- **Choose** an injection area from the following areas:
  - Your **stomach area** (abdomen), avoid about 5 cm around the belly button
  - The **front of your thighs**, about 5 cm above the knee and 5 cm below the groin
  - The **back of your upper arms**, in the fleshy areas of the upper back portion
- If multiple injections are required, they may be given in the same or different area (abdomen, thigh, upper arm), but you should avoid injecting in exactly the same place.

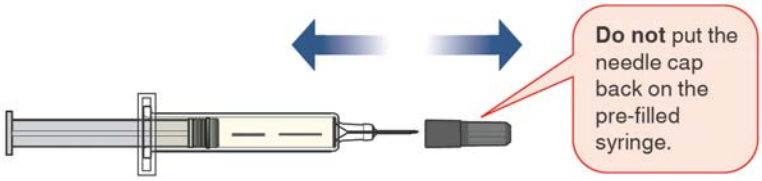
g) Clean your injection area.

- 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, hot, bruised, hardened, tattooed or that has scars or stretch marks.

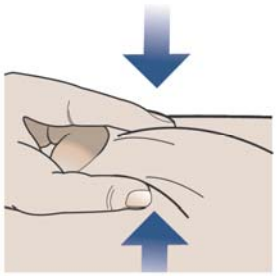
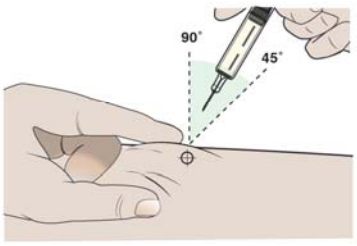
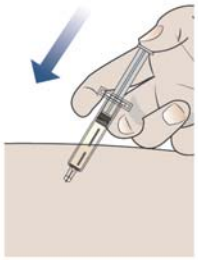
Step 2: How to inject

a) Pull the needle cap straight off and throw it away.

- **Do not** put the needle cap back on the pre-filled syringe, to avoid injury and infection.
- **Do not** touch the needle.

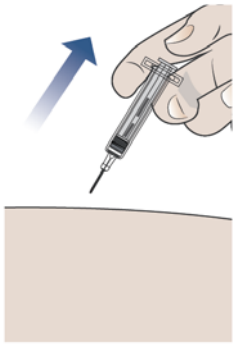


b) Inject by following the 4 steps below.

1. Gently pinch up at least 2.5 cm of the skin that you have cleaned.	2. Insert the needle into the pinched skin at a 45° to 90° angle.	3. Slowly push the plunger in.	4. Push the plunger all the way down as far as it will go to inject all of the medicine.
			

c) Remove the needle from your skin.

- After you have injected all of the medicine, pull the needle straight out.
- **Do not** put the cap back on the needle at any time to avoid injury and infection.



d) 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 or re-use the pre-filled syringe.

Step 3: Disposal of the pre-filled syringe

a) Dispose of your pre-filled syringe right away.

- Put your used pre-filled syringes (with the needle still attached) in a sharps disposal container right away after use.
- **Do not** throw away (dispose of) loose needles, syringes, or pre-filled syringes with your household waste.
- **Do not** recycle used sharps disposal container.

b) Ask your doctor, pharmacist or nurse how to throw away the container.

If your dose is 675 mg, repeat steps 1 e) to 3 a) with the second and third pre-filled syringe to inject the full dose.