PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]**ANDEMBRY®**

garadacimab injection

Prefilled Syringes and Prefilled Pens

200 mg solution for Subcutaneous Injection

Monoclonal antibody inhibitor of activated FXII

[ATC Code B06AC07]

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Date of Initial Authorization:
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RECENT MAJOR LABEL CHANGES

N/A

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ANDEMBRY (garadacimab injection) is indicated for routine prevention of attacks of hereditary angioedema (HAE) in adult and pediatric patients (aged 12 years and older).

ANDEMBRY is not intended for acute treatment of HAE attacks.

1.1 Pediatrics

Adolescents (≥ 12 years): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of ANDEMBRY in pediatric patients age 12 years and older has been established. Therefore, Health Canada has authorized an indication for pediatric use above 12 years age group (see 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment).

Pediatrics (<12 years): The safety and efficacy of ANDEMBRY in pediatric patients below the age of 12 have not been established.

1.2 Geriatrics

The safety and efficacy of ANDEMBRY were evaluated in two phase 3 studies with patients (N=13) aged 65 years of age or older with HAE (see 7.1.4 Geriatrics). No overall differences in safety or efficacy were observed compared to patients 18 to 65 years of age.

2 CONTRAINDICATIONS

ANDEMBRY 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 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

This medicinal product should be initiated under the supervision of a healthcare professional experienced in the management of patients with HAE.

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of ANDEMBRY is an initial loading dose of 400 mg administered subcutaneously as two 200 mg injections on the first day of treatment followed by a monthly dose of 200 mg.

Special Populations

Pediatric population

The dosing for pediatric population age 12 and older is same as adults and no dose adjustment is required.

Health Canada has not authorized an indication for children aged less than 12 years.

Geriatric population

The safety and efficacy of garadacimab is not expected to be affected by age. No dose adjustment is required for patients above 65 years of age (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics).

Hepatic impairment

No studies have been conducted in patients with hepatic impairment. Based on population pharmacokinetic analysis, hepatic impairment is not expected to affect exposure to garadacimab. No dose adjustment is required in patients with hepatic impairment (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics).

Renal impairment

No studies have been conducted in patients with renal impairment. Based on population pharmacokinetic analysis, renal impairment is not expected to affect exposure to garadacimab. No dose adjustment is required in patients with renal impairment (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics).

4.4 Administration

- ANDEMBRY is intended for subcutaneous administration only.
- Each ANDEMBRY unit (prefilled syringe with needle safety device (**Figure 1**) or prefilled pen (**Figure 2**)) is intended for single use only and is provided as a ready-to-use solution .
- The injection should be restricted to the recommended injection sites: the abdomen, the thighs, and the upper outer arms (see **PATIENT MEDICATION INFORMATION** - Instruction for Use: step by step guide, **Figure E** for prefilled pen or **Figure F** for prefilled syringe). Rotation of the injection site is recommended.
- ANDEMBRY may be self-administered or administered by a caregiver only after training on subcutaneous injection technique by a healthcare professional.

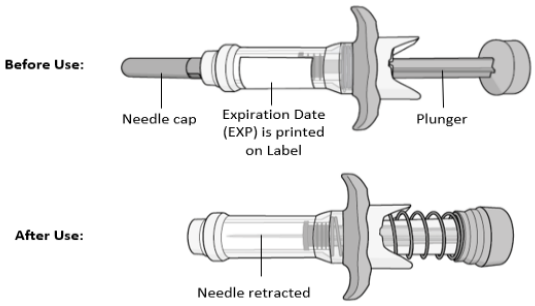


Figure 1

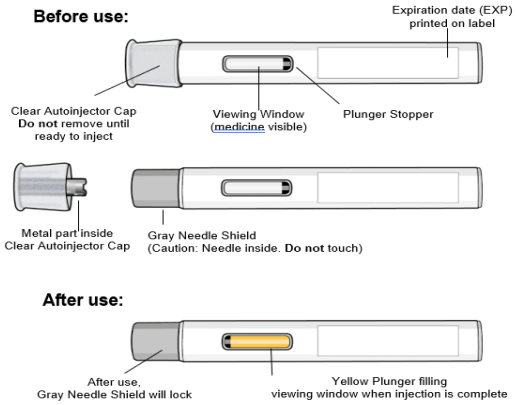


Figure 2

Instruction for Prefilled pen/Prefilled syringe

Assemble Supplies

Supplies needed for the Prefilled pen (see Figure 3)/Prefilled syringe (see Figure 4)

Included in the carton box:

- 1 Single-dose Prefilled pen or 1 Prefilled syringe

Required supplies but not included in the carton box:

- 1 Alcohol pad
- 1 Cotton ball or gauze pad
- 1 sharps container or puncture-resistant container for disposal (see **PATIENT MEDICATION INFORMATION** - Instruction for Use: step by step guide **Step 11. Disposing of the Prefilled Pen** or **Step 12. Disposing of the Syringe**)

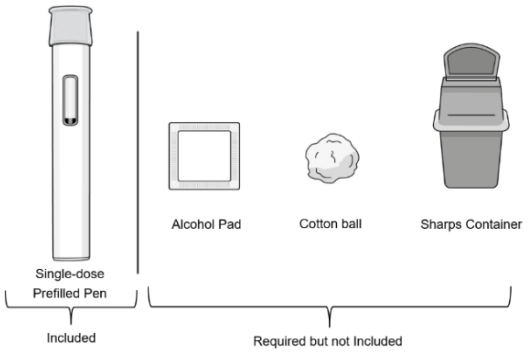


Figure 3

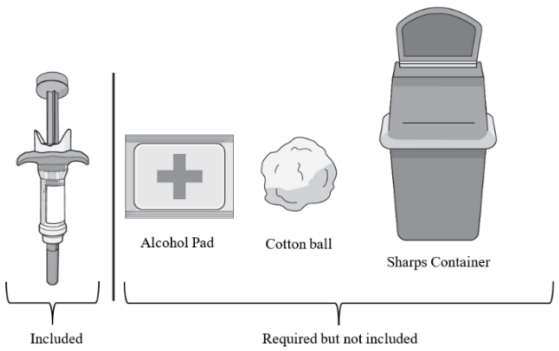


Figure 4

For detailed instructions on the preparation and administration of ANDEMBRY see **PATIENT MEDICATION INFORMATION**.

4.5 Missed Dose

If a dose of ANDEMBRY is missed, administer the dose as soon as possible, and then administer the next dose according to the original schedule. If you're unsure about when to take the missed dose, especially if it's close to the time for your next scheduled dose, consult your healthcare professional.

5 OVERDOSE

No cases of overdose were reported in clinical studies. There is no available information to identify potential signs and symptoms of overdose.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, healthcare professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous administration	Solution for injection, 200 mg / 1.2 mL	L-arginine monohydrochloride, L-histidine, L-proline, Polysorbate 80, Water for injection

ANDEMBRY is supplied as a sterile, preservative-free solution for subcutaneous administration in the following two presentations.

- 200 mg/1.2 mL solution in a single-dose prefilled glass syringe with needle safety device (**Figure 1**) or
- 200 mg/1.2 mL solution in a single-dose prefilled pen (**Figure 2**)

ANDEMBRY is supplied as a sterile, preservative-free solution for subcutaneous administration. ANDEMBRY is supplied as either a single-dose prefilled pen or as a single-dose 1.2 mL prefilled glass syringe with needle safety device. Enclosed within the prefilled pen is a single-dose 1.2 mL prefilled glass syringe.
The solution of ANDEMBRY is slightly opalescent to clear, brownish-yellow to yellow liquid, with a pH of approximately 6.1. The solution has an osmolality of approximately 470 mOsm/kg.

Each 1.2 mL prefilled glass syringe delivers 1.2 mL (200 mg) of garadacimab. Each of these contain as nominal quantity per prefilled glass syringe: garadacimab (200 mg), L-arginine monohydrochloride (37.9 mg), L-histidine (3.7 mg), L-proline (19.3 mg), polysorbate 80 (0.24 mg), and water for injection, USP.

7 WARNINGS AND PRECAUTIONS

General

Acute HAE attacks

ANDEMBRY is not intended for treatment of acute HAE attacks. In case of breakthrough HAE attack, individualised treatment should be initiated with an approved rescue medicine.

Normal C1-INH HAE (nC1-INH)

Some subcategories of normal C1-INH HAE (nC1-INH) may not respond to treatment with garadacimab due to alternative pathways that do not include FXII activation. It is recommended to perform genetic testing, if available, according to the current HAE guidelines. Consideration should be given to discontinuing treatment in patients with nC1-INH who have shown insufficient reduction in attacks after 3 months of treatment.

Coagulation disorders & thromboembolism

ANDEMBRY has not been studied in patients with clinically significant bleeding due to coagulopathy or with thromboembolism. There were no garadacimab-related bleeding and thromboembolic events in the clinical studies.

Interference with coagulation test

ANDEMBRY can prolong activated partial thromboplastin time (aPTT) due to an interaction of garadacimab with the aPTT assay (see 9.7 Drug-Laboratory Test Interactions).

Reproductive Health: Female and Male Potential

Fertility

Effect on fertility has not been evaluated in humans.

Sensitivity/Resistance

Hypersensitivity

Severe hypersensitivity reactions have not been observed but may theoretically occur. The signs and symptoms of hypersensitivity reactions may include hives (local and generalized), tightness of the chest, difficulty breathing, wheezing, hypotension, and/or anaphylaxis during or after injection of ANDEMBRY. In case of severe hypersensitivity, discontinue ANDEMBRY administration and institute appropriate treatment.

7.1 Special Populations

7.1.1 Pregnancy

There are no studies with ANDEMBRY in pregnant women. The extent of exposure in pregnancy during clinical trials was very limited. As a precautionary measure, it is preferable to avoid the use of garadacimab during pregnancy.

A pre- and postnatal development study conducted in pregnant rabbits administered subcutaneous doses of garadacimab resulted in confirmed exposure to the developing fetus. At parturition, fetal plasma garadacimab concentrations can exceed maternal plasma concentrations (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

7.1.2 Breastfeeding

It is unknown whether ANDEMBRY is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, and decrease to low concentrations soon afterwards. Because human IgGs are known to be excreted in human milk, precaution should be exercised. A risk to the breast-fed child cannot be excluded.

7.1.3 Pediatrics

Adolescents (≥12 years): The safety and efficacy of ANDEMBRY have been established in pediatric patients with HAE aged 12 years and older. The use of ANDEMBRY for this indication was evaluated in 11 pediatric patients (≥12 to 17 years) in phase 3 studies. Efficacy and safety results in adolescents were similar to the adult population.

Pediatrics (<12 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use under the age of 12.

7.1.4 Geriatrics

The safety and efficacy of ANDEMBRY were evaluated in two phase 3 studies with patients (N=13) aged 65 years of age or older with HAE. No overall differences in safety or efficacy were observed compared to patients 18 to 65 years of age.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

One hundred and sixty-six (166) unique subjects with HAE were exposed to at least one dose of ANDEMBRY 200 mg in one (1) Phase 2 and two (2) Phase 3 clinical trials. The most commonly observed adverse reactions from pooled data from these 3 trials associated with ANDEMBRY were injection site erythema (7.8%), injection site bruising (1.8%), injection site pruritus (3.6%), injection site urticaria (1.2%), headache (11.4%), and abdominal pain (6.6%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, 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 may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The safety of ANDEMBRY is primarily based on a 6-month, randomized, double-blind, parallel-group and placebo-controlled study (Trial 1) in 64 adult and pediatric patients (aged 12 years and older) with Type I or II HAE (see 14 CLINICAL TRIALS). A total of 39 patients with HAE aged 12 years and older received at least one dose of ANDEMBRY. Overall, 59.4% of patients were female and 85.9% of patients were Caucasian with a mean age of 41.2 years.

Table 2 below summarizes treatment-emergent adverse events (TEAEs) in ≥5% of patients treated with ANDEMBRY.

Table 2 – Treatment-emergent adverse events (TEAEs) in ≥5% of patients treated with ANDEMBRY (garadacimab) in Trial 1

System organ class/preferred term	Garadacimab 200 mg (N = 39) n (%) E	Placebo (N = 25) n (%) E
Any TEAE	25 (64.1) 75	15 (60.0) 54
Infection and infestation		
Upper respiratory tract infection	4 (10.3) 4	2 (8.0) 2
Nasopharyngitis	3 (7.7) 3	1 (4.0) 1
Nervous system disorders		
Headache	3 (7.7) 9	4 (16.0) 4

n = number of patients with at least one event; E = number of events

Safety data from all patients treated with ANDEMBRY in a phase 3 open-label extension study with a median exposure of 13.8 months were consistent with data in Table 2.

Description of selected adverse reactions

Injection site reactions

In Trial 1, 3 incidents of injection site reactions of mild severity were observed in 2 (5.1%) patients who received ANDEMBRY. Temporal relationship (began within 1-3 days after investigational product administration) was identified for all three injection site reactions. All three injection site reactions were assessed as related to ANDEMBRY.

In a Phase 3 open-label extension study (Trial 2), 161 patients with HAE were administered ANDEMBRY 200 mg subcutaneously every month; 57 patients had rolled over from Trial 1. Injection site reactions (e.g., injection site bruising, injection site erythema, injection site haematoma, injection site pruritus, injection site urticaria) were reported in 16 (10%) patients.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

While limited, the safety profile in pediatric patients 12 years of age and older (n=6) was similar to that of the adult population.

8.5 Post-Market Adverse Reactions

Not Applicable.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No drug interactions have been established.

9.3 Drug-Behaviour Interactions

The interaction of Andembry with individual behavioural risks (e.g. cigarette smoking, cannabis use, and/or alcohol consumption) has not been studied.

9.4 Drug-Drug Interactions

No dedicated drug interaction studies have been conducted in humans. Garadacimab has only been studied as a monotherapy and not in combination with other products indicated for long-term prophylaxis of HAE.

There is very limited clinical data on the use of concomitant antiplatelet/anticoagulant medication with garadacimab. Garadacimab inhibits the activity of activated FXII. FXII activation initiates the intrinsic pathway of the coagulation cascade. The impact on the concomitant use of anticoagulants which inhibit the extrinsic pathway is unknown.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Coagulation Tests

Garadacimab can prolong activated partial thromboplastin time (aPTT) due to an interaction of garadacimab with the aPTT assay. The reagents used in the aPTT laboratory test initiate intrinsic coagulation through the activation of FXII in the contact system, therefore inhibition of plasma FXIIa by garadacimab can prolong aPTT in this assay. None of the increases in aPTT in patients treated with garadacimab were associated with bleeding adverse events. There were no clinically relevant differences in international normalized ratio (INR) between treatment groups.

Interference with D-Dimer test

Reductions in mean D-dimer values were observed in patients treated with garadacimab, including some patients with values below the lower limit of normal. The clinical relevance of this observation is unclear.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Garadacimab is a fully human IgG4/lambda recombinant monoclonal antibody which binds to the catalytic domain of activated Factor XII (FXIIa and βFXIIa) and potently inhibits its catalytic activity. FXII is the first factor activated in the contact activation pathway and initiates the inflammatory bradykinin-producing kallikrein-kinin system. The inhibition of FXIIa prevents the activation of prekallikrein to kallikrein and the generation of bradykinin, which is associated with inflammation and swelling in HAE attacks, thus potentially reducing the cascade of events leading to an HAE attack.

10.2 Pharmacodynamics

Concentration-dependent inhibition of FXIIa-mediated kallikrein activity was demonstrated after subcutaneous administration of ANDEMBRY in patients with HAE.

10.3 Pharmacokinetics

Table 3 provides Garadacimab pharmacokinetics and steady-state exposure, based on population pharmacokinetic (PK) analysis, in HAE patients given 400 mg (2 x 200 mg) subcutaneous loading dose followed by 200 mg once monthly subcutaneously in Trial 1. Following subcutaneous administration of ANDEMBRY, peak plasma concentration is reached within ~6 days, and terminal elimination half-life is ~19 days. Steady state garadacimab exposure was achieved after the initial subcutaneous administration of loading dose of 400 mg (2 x 200 mg).

Table 3 – Mean (SD) Pharmacokinetic Parameters of Garadacimab Following Subcutaneous Administration (Trial 1)

Pharmacokinetic Parameters	Garadacimab 200 mg once monthly (N=39)
CL/F (L/h)	0.0217 (0.00793)
V_c/F (L)	7.42 (4.20)
$AUC_{tau,ss}$ (mcg·h/mL)	10300 (3380)
$C_{max,ss}$ (mcg/mL)	21.2 (6.58)
$C_{min,ss}$ (mcg/mL)	9.30 (3.73)
t_{max} (h)	137 (91.0, 175)*
$t_{1/2}$ (h)	445 (97.4)

CL/F: apparent clearance; V_c/F: apparent volume of distribution; $AUC_{tau,ss}$ area under the curve over the dosing interval at steady-state; $C_{max,ss}$: maximum concentration at steady-state; $C_{min,ss}$: minimum concentration at steady-state; t_{max}: time to maximum concentration; $t_{1/2}$: terminal elimination half-life.
*Median (range) presented for t_{max}

Absorption

Following subcutaneous administration, the time to maximum concentration is approximately 6 days. The site of subcutaneous injection (thigh, arm, or abdomen) did not affect the absorption of garadacimab. The absorption rate of garadacimab was 0.00824/h. The mean absolute bioavailability of garadacimab in HAE patients was 39.5% on the basis of the population pharmacokinetic analysis.

Distribution

The mean (SD) apparent volume of distribution of garadacimab in patients with HAE was 7.42 litres (4.20). Garadacimab is a monoclonal antibody and is not expected to bind to plasma proteins.

Metabolism

Similar to other monoclonal antibodies, garadacimab is expected to be degraded by enzymatic proteolysis into small peptides and amino acids. Therefore, specific metabolism studies were not conducted with garadacimab.

Elimination

Garadacimab has a mean (SD) apparent clearance of 0.0217 L/h (0.00793) and a terminal elimination half-life of approximately 19 days.

- **Special Populations and Conditions**

  Population pharmacokinetic analyses showed that age, gender, and race did not meaningfully influence the pharmacokinetics of garadacimab after correcting for body weight. Body weight was identified as an important covariate describing the variability of clearance and volume of distribution, resulting in higher exposure in lighter patients. However, this difference is not clinically relevant and no dose adjustments are recommended for any of these demographics.

- **Pediatrics**

  Based on population pharmacokinetic analyses that included pediatric patients (12 to 17 years, N=11), age does not have a clinically meaningful impact on the PK of garadacimab and no dose adjustments are recommended.

  Pharmacokinetics of garadacimab in pediatric patients below the age of 12 has not been investigated.

- **Geriatrics**

  Based on population pharmacokinetic analyses that included elderly patients (≥65 years, N=13), age does not have a clinically meaningful impact on the PK of garadacimab and no dose adjustments are recommended.

- **Hepatic Insufficiency**

  No dedicated studies have been conducted to evaluate the PK of garadacimab in hepatic impairment patients. Based on population pharmacokinetic analysis, hepatic impairment had no effect on the PK of garadacimab.

- **Renal Insufficiency**

  No dedicated studies have been conducted to evaluate the PK of garadacimab in renal impairment patients. Based on population pharmacokinetic analysis, renal impairment (estimated GFR: ≥90 mL/min/1.73m^2 [normal, N=145], 60 to <90 mL/min/1.73m^2 [mild, N=26], and 30 to <60 mL/min/1.73m^2 [moderate, N=2]) had no effect on the PK of garadacimab.

- **Concomitant medications**

  Based on population PK analyses, the use of analgesic, antibacterial, antihistamine, anti-inflammatory and anti-rheumatic medications had no effect on the PK of garadacimab.

  Based on population PK analyses, for breakthrough HAE attacks, use of rescue medications such as plasma-derived and recombinant C1-INH or icatibant had no effect on the PK of garadacimab.

10.4 Immunogenicity

All therapeutic proteins have the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies in the studies described below with the incidences of antibodies in other studies or to other products may be misleading.

In Trial 1, treatment with garadacimab has been associated with development of low-titre treatment emergent anti-drug antibodies (ADA) in 1 (2.6%) of treated subjects during the 6-month period. In Trial 2, 5 (2.9%) treated subjects including 1 subject rolled over from Trial 1 developed low-titre treatment emergent ADAs.

The development of ADA against garadacimab did not affect pharmacokinetics (PK), pharmacodynamics (PD), safety or clinical response.

A standalone neutralizing antibody assay has not been developed. The potential impact of neutralizing antibodies on garadacimab exposure, efficacy, pharmacodynamics, and safety has not been assessed.

11 STORAGE, STABILITY AND DISPOSAL

- Store in a refrigerator (+2^{o}C to +8^{o}C). Do not freeze.
- Keep the solution (prefilled syringe with needle safety device or prefilled pen) in the outer carton in order to protect from light.
- The solution (prefilled syringe with needle safety device or prefilled pen) may be stored at room temperature up to +25°C for up to 2 months, but not beyond the expiry date. Do not return ANDEMBRY to refrigerated storage after storage at room temperature up to +25 °C.
- Discard any unused product after each infusion in accordance with local requirements.

12 SPECIAL HANDLING INSTRUCTIONS

The ANDEMBRY prefilled syringe/prefilled pen is for single-use only. There are no special handling instructions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: garadacimab
Chemical name: IgG4/lambda or IgG4/**λ**-light chain
Molecular formula and molecular mass: Garadacimab has a molecular weight of approximately 148 kDa.
Physicochemical properties: slightly opalescent to clear, brownish-yellow to yellow liquid.
Pharmaceutical standard: FXIIa inhibitor monoclonal antibody

Product Characteristics:

Garadacimab is a recombinant, fully human, monoclonal antibody (IgG4/**λ**-light chain) produced by recombinant DNA technology in Chinese Hamster Ovarian (CHO) cells.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Hereditary Angioedema (HAE)

Table 4 – Summary of patient demographics for clinical trials in HAE Attacks

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex (%)
Phase 3-Trial 1 (NCT04656418)	multicenter, randomized, double-blind, placebo-controlled parallel group study	garadacimab 200 mg SC Q4W after an initial 400 mg SC loading dose or placebo for a 6-month treatment period	39 (garadacimab 200 mg) 25 (placebo)	41.2 years (12-69)	M (40.6%) / F (59.4%)
Phase 3-Trial 2 (NCT04739059)	multicenter, open-label extension study	garadacimab 200 mg monthly after an initial 400 mg loading dose. Planned Study duration: 4.6 years	161 (garadacimab 200 mg)	42.3 years (13-73)	M (37.3%) / F (62.7%)

M = male; F = female; SC = subcutaneous

Trial 1 (NCT04656418):

The efficacy of ANDEMBRY for the prevention of hereditary angioedema attacks in patients 12 years of age and older with Type I or II HAE was demonstrated in a phase 3, multicenter, randomized, double-blind, placebo-controlled parallel group study.

The study included 64 adult and pediatric patients (12 years of age and older) who experienced at least 2 attacks during the up to 2-month run-in period. Patients were randomized into 2 parallel treatment arms in a 3:2 ratio (garadacimab 200 mg monthly after an initial 400 mg loading dose or volume-match placebo) for a 6-month treatment period. Patients were required to discontinue other prophylactic HAE medications prior to entering the study. All patients were allowed to use on-demand medications for treatment of HAE attacks during the study.

Overall, 87.5% of patients had Type I HAE. A family history of HAE was reported for 89.1%, a history of laryngeal edema attacks for 59.4% of patients and 32.8% were on prior prophylaxis. During the study run-in period, attack rates of ≥3 attacks/month were observed in 59.4% of patients overall.

The primary endpoint was the difference in time-normalized number of investigator-confirmed attacks of HAE (Day 1 to 182) between ANDEMBRY and placebo. The key secondary endpoints were the percent reduction in the time-normalized number of HAE attacks (Day 1 to 182); the number of attack-free subjects through Day 91; and the percentage of subjects rating therapy as “good” or better (ie, “excellent”) through the SGART at Day 182.

The results for the primary and key secondary endpoints in the Intent-to-Treat (ITT) population are presented below in **Table 5**.

Table 5 – Results of Primary and Key Secondary Efficacy Endpoints at 6 months in Subjects with HAE in Trial 1 (NCT04656418)

	ANDEMBRY 200 mg N = 39	Placebo N = 24[a]
Primary Endpoint		
Time-normalized Number of HAE Attacks Per Month		
Number of HAE Attacks during Treatment Period	63	264
Adjusted LS mean[b] (95% CI)	0.22 (0.11, 0.47)	2.07 (1.49, 2.87)
HAE attacks ratio[b] (95% CI)	0.11 (0.05, 0.24)	
p-value*	< 0.001	
	ANDEMBRY 200 mg N = 39	**Placebo N = 24[a]**
Secondary Endpoints		
Patients who were attack free from day 1 through the end of month 3		
Percentage of patients	71.8%	8.3%
p-value*	< 0.001	
Good or Excellent Responses to the Subject's Global Assessment of Response to Therapy (SGART)		
Percentage of patients	81.6%	33.3%
p-value*	< 0.001	

CI = confidence interval; HAE = hereditary angioedema; ITT = intention-to-treat; LS = least squares; N = number of patients in the ITT Analysis Set; SD = standard deviation

[a] Twenty-five (N=25) subjects were originally randomized into the placebo arm; however, one patient had a Treatment Period of less than 30 Days and was therefore not included in the efficacy analyses.

[b] Generalized linear model for count data (Poisson regression model) adjusted for baseline attack rate.

* A hierarchical testing procedure controls for the overall alpha level of 5%.

Additional non-hierarchically tested secondary endpoints from day 1 to 182 were the mean (median) time-normalised number of HAE attacks requiring on-demand treatment, 0.23 (0.0) in subjects treated with ANDEMBRY compared to 1.86 (1.35) in the placebo group, and the mean (median) time-normalised number of moderate to severe HAE attacks, 0.13 (0.0) in subjects treated with ANDEMBRY compared to 1.35 (0.83) in the placebo group. The proportion of patients who remained attack free from the first dose to the end of trial (day 1 to 182) was 62% compared to 0% in the placebo group.

The proportion of subjects who achieved an improvement in quality of life as evaluated by the Angioedema Quality of Life (AE-QoL) questionnaire (minimal clinically important difference ≥6 for the AE-QoL total score), which measures functioning, fatigue/mood, fear/shame, and nutrition, was 87.9% for the ANDEMBRY® and 55.0% for the placebo.

While very limited, the efficacy profile in pediatric patients with HAE 12 years of age and older (n=6) appeared similar to that of the adult population.

Trial 2 (NCT04739059).

Trial 2 is a phase 3, multicenter, open-label extension study designed to investigate long-term safety and efficacy of ANDEMBRY that enrolled a total of 161 patients. The 161 patients are from: Trial 1 (n=57), a phase 3, multicenter, randomized, double-blind, placebo-controlled parallel group study; a phase 2 (n=35), multicenter, randomized, placebo-controlled, parallel-arm study; and the remaining patients (n=69) are newly enrolled and naïve to treatment with ANDEMBRY.

At the time of the interim analysis 2 (data cut of 13-FEB-2023), for the 36 garadacimab-treated patients from Trial 1 who rolled over into the open-label extension study, the median duration of

exposure was 11.6 months (range: 4.9 to 16.3 months) and the associated mean (SD) time-normalized number of HAE attacks per month was 0.11 (0.316) attacks/month.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: Garadacimab was administered at doses of 0 (vehicle), 3, 10, 30, or 100 mg/kg by intravenous (IV) bolus injection twice per week, or 0 (vehicle), 60, or 200 mg/kg by subcutaneous (SC) injection twice per week, in mice for up to 4 weeks and in cynomolgus monkeys for up to 26 weeks. Animals showed increased activated partial thromboplastin times. Some mice and monkeys developed clinical signs of anaphylaxis and were euthanized. One monkey developed skeletal muscle lesions related to the immune response to a heterologous protein. A NOAEL was not determined in mice. The NOAELs in monkeys were 30 mg/kg/occasion by IV and 60 mg/kg/occasion by SC administration (equal to 31.5 and 37-fold the recommended human dose of 200 mg SC once monthly based on area under the curve [AUC]) due to anaphylaxis observed at higher doses.

Genotoxicity: Animal studies have not been conducted to evaluate the genotoxic potential of garadacimab.

Carcinogenicity: Animal studies have not been conducted to evaluate the carcinogenic potential of garadacimab.

Reproductive and Developmental Toxicology: Garadacimab was administered to male rabbits at doses of 0 (vehicle), 10, 30, or 100 mg/kg intravenously once every three days beginning 27 days before cohabitation, during cohabitation and continuing until 8 days post-cohabitation. In a separate study, female rabbits were administered garadacimab at the same doses beginning 12 days before cohabitation and continuing until gestational day (GD) 7. Male and female fertility were unaffected based upon a lack of adverse findings on mating, fecundity, fertility indices, maternal reproductive parameters, embryo survival or sperm assessment in sexually mature rabbits that received garadacimab up to doses of 100 mg/kg (resulting in approximately 83- and 103-fold the exposure in females and males, respectively, at the recommended human dose of 200 mg SC once monthly based on AUC).

In the embryofetal development study, pregnant rabbits were administered garadacimab at doses of 0 (vehicle), 10, 30, or 100 mg/kg intravenously once every 3 days from GD 6 to 18. No effects on embryofetal development were reported at doses up to 100 mg/kg (resulting in approximately 104-fold the exposure at the recommended human dose of 200 mg SC once monthly based on AUC).

In a pre- and post-natal development study, pregnant rabbits were administered garadacimab at doses of 0 (vehicle), 10, 30, or 100 mg/kg subcutaneously, or 100 mg/kg intravenously, once every 5 days, from GD 7 until weaning on lactation day 38. Maternal garadacimab treatment had no effect on embryo-fetal development, postnatal development, survival, growth, neurobehavioral, and reproductive performances of offspring through 6 months of age. The maternal and developmental NOAELs were 100 mg/kg by SC or IV injection (53- and 76-fold the exposure at the recommended human dose of 200 mg SC once monthly based on AUC, respectively).

Garadacimab crossed the placenta in rabbits. At GD 29, fetal plasma garadacimab concentrations were 40.8 to 136.6% of maternal concentrations after subcutaneous administration of 10 to 100 mg/kg and were equal to maternal concentrations after intravenous administration of 100 mg/kg.

Juvenile Toxicity: No dedicated juvenile toxicity studies have been performed for garadacimab.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]ANDEMBRY®

garadacimab injection

This Patient Medication Information is written for the person who will be taking ANDEMBRY. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about ANDEMBRY, talk to a healthcare professional.

What is ANDEMBRY used for?

ANDEMBRY is a medicine used in patients aged 12 years and older with Hereditary Angioedema (HAE) to prevent angioedema attacks.

ANDEMBRY should not be used to treat an acute HAE attack. In the event of an acute attack, seek medical attention.

How does ANDEMBRY work?

HAE is a disorder that causes recurrent episodes of swelling, known as HAE attacks, throughout your body due to proteins in your blood called bradykinin. Too much bradykinin causes your body to swell. Your body also produces another protein called Factor XII (FXII) which in turn produces bradykinin. Blood levels of activated FXII (FXIIa) have been shown to increase in patients during HAE attacks. The active substance in ANDEMBRY, garadacimab, attaches to FXII and prevents it from working and limiting the production of bradykinin, which would potentially limit swelling and HAE attacks.

What are the ingredients in ANDEMBRY?

Medicinal ingredients: garadacimab

Non-medicinal ingredients: L-arginine monohydrochloride, L-histidine, L-proline, polysorbate 80, water for injection.

ANDEMBRY comes in the following dosage forms:

ANDEMBRY is a sterile, preservative-free, slightly opalescent to clear, brownish-yellow to yellow solution available in the following presentations:

- 200 mg/1.2 mL solution in a single-dose prefilled glass syringe with needle safety device (**Figure 1**) or
- 200 mg/1.2 mL solution in a single-dose prefilled pen (**Figure 2**)

Parts of the Prefilled Syringe with needle safety device / Prefilled Pen:

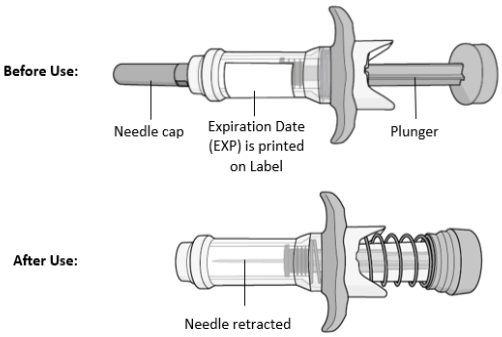


Figure 1

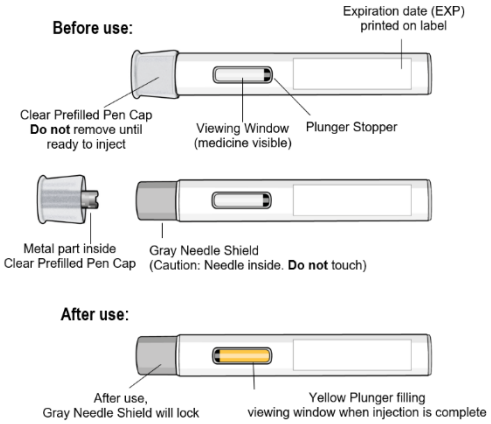


Figure 2

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

- are pregnant or planning to become pregnant. It is not known if ANDEMBRY can harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if ANDEMBRY passes into your breastmilk. Talk to your healthcare provider about the best way to feed your baby while using ANDEMBRY.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

- No interaction studies have been performed.

How to take ANDEMBRY:

- Keep the prefilled syringe/ prefilled pen in its original carton box until use, to protect it from light.
- **Do not** remove the clear prefilled pen cap or the needle cap until you are ready to inject the medicine.
- For prefilled syringe: **Do not** recap the prefilled syringe.
- For prefilled pen: **Do not** put the Clear Prefilled Pen Cap back on the prefilled pen after it has been removed because this could start the injection and cause injury.
- **Do not** reuse the same prefilled syringe/prefilled pen. The prefilled syringe /prefilled pen. contains 1 dose and is for single-use only.
- The prefilled syringe/prefilled pen is for subcutaneous (under the skin) injection only.
- **Do not** use the prefilled syringe/prefilled pen if it looks damaged, has cracks, or is leaking medicine, or has been dropped. In these cases, throw away the prefilled syringe/prefilled pen and use a new one.
- **Do not** inject through clothing.
- For prefilled pen: **Do not** touch or try to remove the gray needle shield at any time.
- **Keep ANDEMBRY and all medicines out of reach of children.**

Instructions for administration:

These medical devices (prefilled syringe or prefilled pen) work differently than other injection devices. Read the instruction for use carefully and each time you get a new device. There may be new information. This information does not this information does not replace talking to your healthcare provider about your medical condition or treatment.

In adolescent patients, administer ANDEMBRY under the supervision of an adult. **Make sure you have been trained by your healthcare provider before you use this prefilled syringe / prefilled pen for the first time.**

Assemble Supplies

Supplies needed for the Prefilled pen (see Figure 3)/Prefilled syringe (see Figure 4)

Included in the carton box:

- 1 Single-dose Prefilled pen or 1 Prefilled syringe

Required supplies but not included in the carton box:

- 1 Alcohol pad
- 1 Cotton ball or gauze pad
- 1 sharps container or puncture-resistant container for disposal (see Instruction for Use: step by step guide **Step 11. under Prefilled Pen** or **Step 12. under Syringe** respectively)

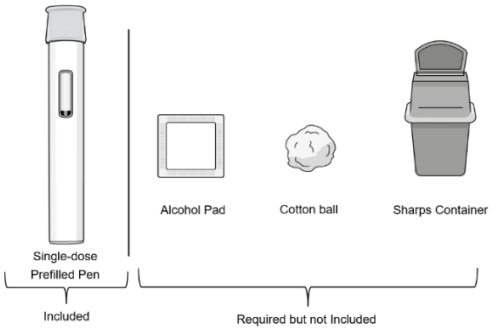


Figure 3

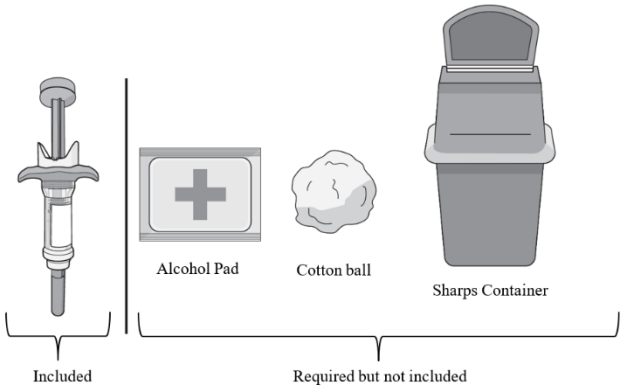


Figure 4

NOTE: FOR "INSTRUCTIONS FOR USE" – PLEASE REFER TO END OF THE PATIENT MEDICATION INFORMATION

Usual dose:

The recommended dose of ANDEMBRY is an initial loading dose of 400 mg given as two 200 mg injections on the first day of treatment followed by one 200 mg injection given once a month.

Overdose:

No cases of overdose were reported in clinical studies. There is no available information to identify potential signs and symptoms of overdose.

If you think you, or a person you are caring for, have taken too much ANDEMBRY, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no symptoms.

Missed Dose:

If a dose of ANDEMBRY is missed, administer the dose as soon as possible, and then administer the next dose according to the original schedule. If you're unsure about when to take the missed dose, especially if it's close to the time for your next scheduled dose, consult your healthcare professional.

What are possible side effects from using ANDEMBRY?

These are not all the possible side effects you may have when taking ANDEMBRY. If you experience any side effects not listed here, tell your healthcare professional. Allergic reactions may happen with **ANDEMBRY**. Call your healthcare provider or get emergency help right away if you have any of the following symptoms:

- hives
- tightness of the chest
- difficulty breathing
- wheezing
- hypotension
- anaphylaxis

The most common side effects of **ANDEMBRY** are:

- Injection site reactions (redness, itchiness, and bruising), headache and abdominal pain

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell 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 (canada.ca/drug-device-reporting) 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.

We recommend that CSL Behring Canada be copied when reporting suspected side effects, at the following address:

AdverseReporting@CSLBehring.com

Storage:

- Keep out of reach and sight of children.
- Store in a refrigerator (2^{o}C to 8^{o}C).
- Do not freeze.
- Keep the solution (prefilled syringe with needle safety device or prefilled pen) in the outer carton in order to protect from light.
- The solution (prefilled syringe with needle safety device or prefilled pen) may be stored at room temperature up to 25°C for up to 2 months, but not beyond the expiry date. Do not return **ANDEMBRY** to refrigerated storage after storage at room temperature up to 25 °C.

Instructions for Use: step by step guide for Prefilled Pen

Preparing for an Injection

Do not remove the clear Prefilled Pen cap until immediately before the injection.

Step 1. Let the Prefilled Pen Reach Room Temperature

- Remove the prefilled pen from the carton box and place it laying down on a clean flat surface.
- Wait **30 minutes** for the medicine to reach room temperature if it was stored in the refrigerator (see **Figure A**).
- Injecting the medicine cold could be uncomfortable.
- **Do not** try to speed up the warming process in any way. For example, **do not** warm it in a microwave, in hot water, or leave it in direct sunlight.

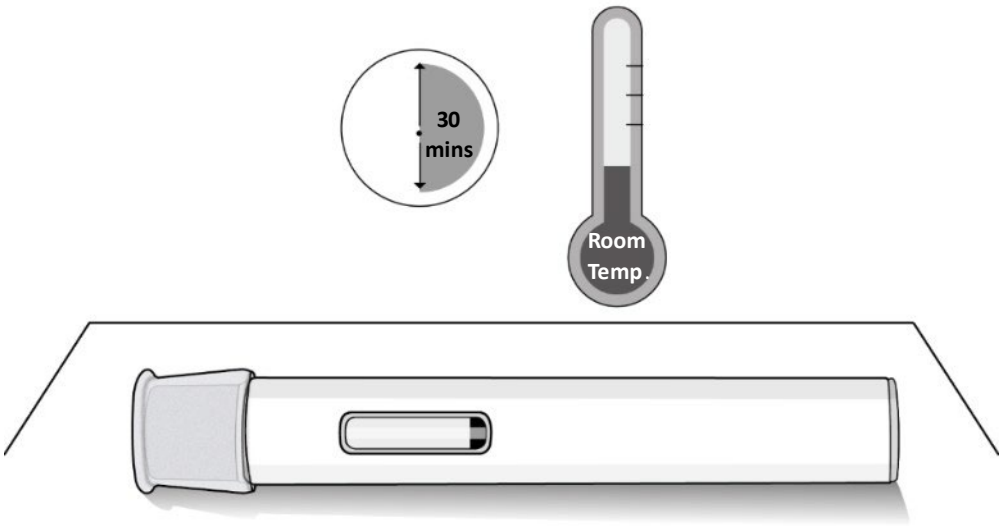


Figure A

Step 2. Check the Expiration Date

- Check the expiration date on the prefilled pen label (see **Figure B**).
- **Do not use** the prefilled pen if the expiration date has passed.
- **Do not use** the prefilled pen if stored at room temperature for longer than 2 months.
- If the expiration date has passed or if stored at room temperature for longer than 2 months, then safely dispose of the prefilled pen and get a new one (see **Step 11. Disposing of the Prefilled Pen**).

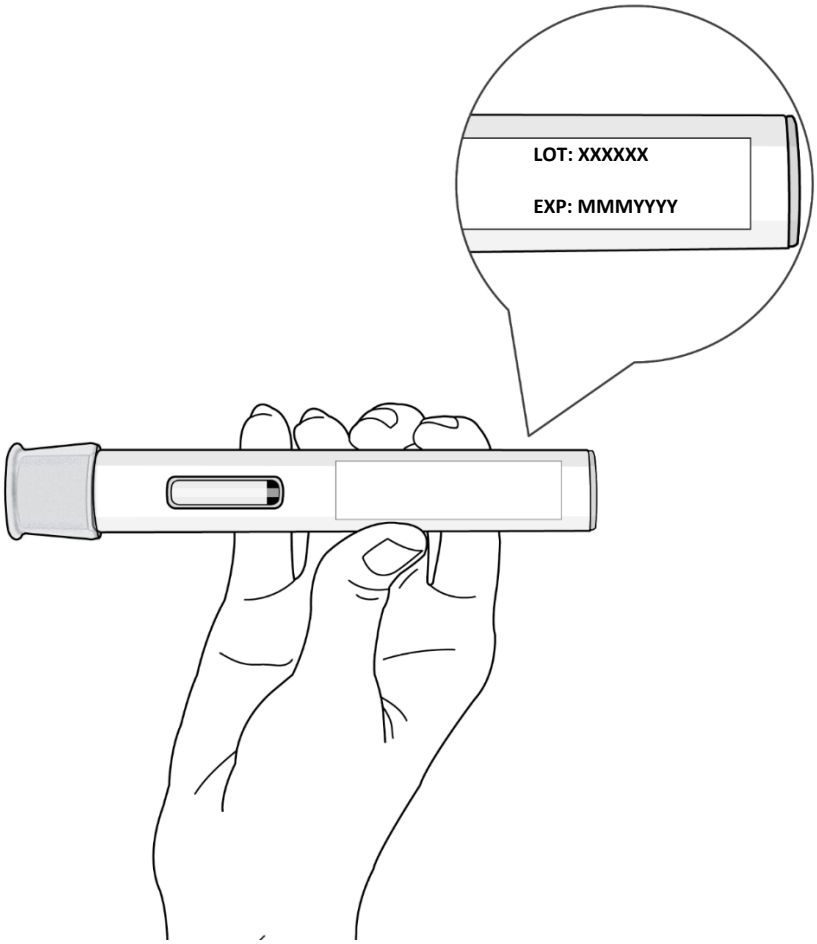


Figure B

Step 3. Inspect the Prefilled Pen and the medicine

- **Check** the prefilled pen **for damage**.
- **Check the medicine** through the viewing window of the prefilled pen (see **Figure C**).
- It is normal to see air bubbles, **do not** try to remove the air bubbles**.**
- The medicine should be slightly opalescent to clear, brownish-yellow to yellow liquid.
- **Do not use** the prefilled pen, safely dispose and a get a new one (see **Step 11. Disposing of the Prefilled Pen**) **if**:
    - The medicine is discoloured or contains particles
    - The prefilled pen looks damaged or has cracks
    - The prefilled pen is leaking
    - The prefilled pen has been dropped on a hard surface, even if it does not look damaged

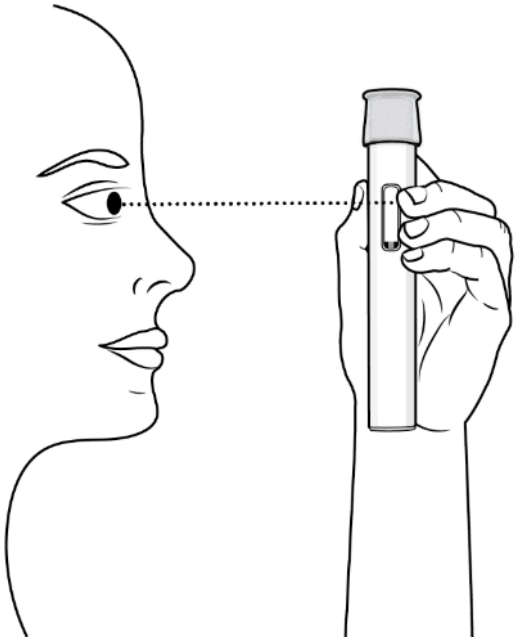


Figure C

Choose and Prepare an Injection Site

Step 4. Clean your Hands

- Wash your hands well with soap and water or use hand sanitizer (see **Figure D**).

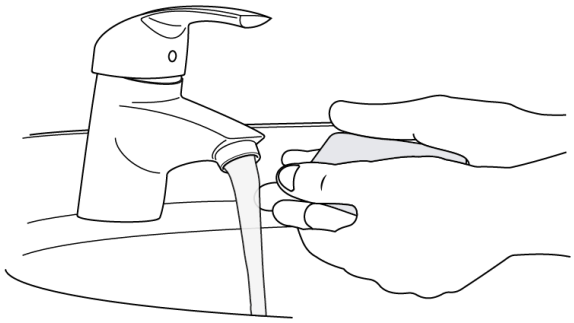


Figure D

Step 5. Select the Injection Site

- Inject into the **thigh or belly (abdomen) area**, but stay 1 inch (2 cm) away from the belly button (navel) (see **Figure E**)
- If somebody else (caregiver) gives you the injection, they can also use the upper arm. **Do not** try to inject into the upper arm yourself.
- Change (rotate) your injection sites with each injection.
- **Do not Inject** into areas where the skin is tender, red, hard, or injured, or into belly button, moles, scars or bruises or stretch marks.

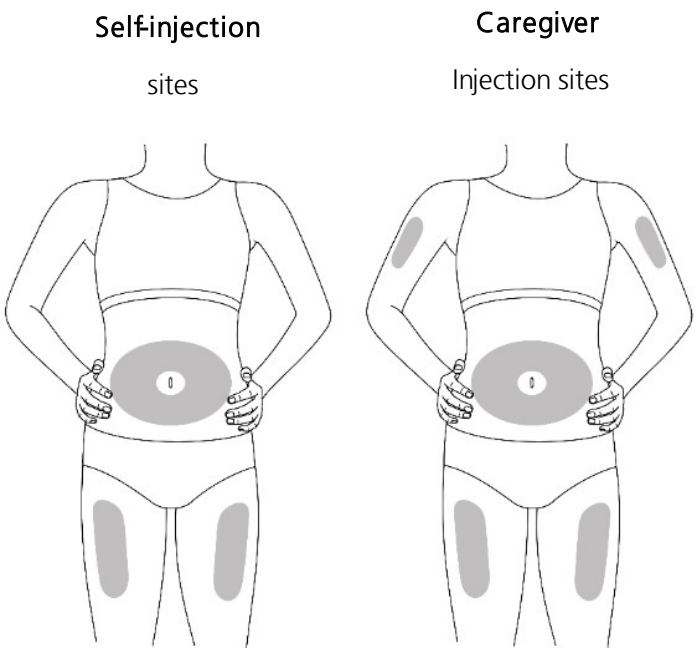


Figure E

Step 6. Prepare the Injection Site

- Clean the injection site with an alcohol pad (see **Figure F**).
- Let your skin dry on its own.
- **Do not** touch this area again before injecting.
- **Do not** fan or blow on the skin area that you cleaned.

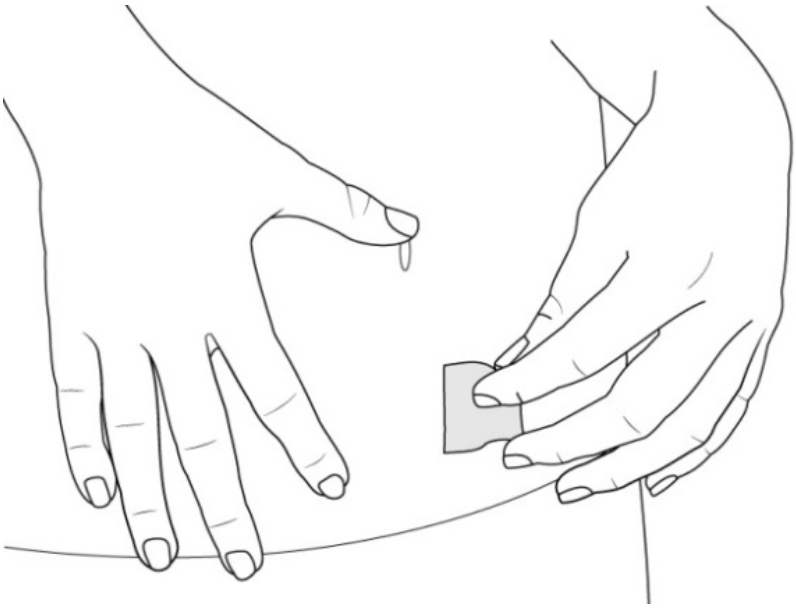


Figure F

Injecting the Medicine with the Prefilled Pen

Complete the Injection without stopping. Read all steps first before beginning.

Do not remove the Clear Cap until you are ready to inject.

Step 7. Remove Clear Prefilled Pen Cap and Dispose of the Cap

- Hold the prefilled pen with one hand and **pull the Clear Prefilled Pen Cap straight off** with the other hand.
- **Do not** twist the Clear Cap, (see **Figure G**). If you cannot remove the Clear Cap, ask a caregiver for help or contact your healthcare provider.
- The Clear Cap has a metal part inside, this is normal.
- **Do not** put the Clear Cap back on after it has been removed, because this could start the injection and cause injury.
- Dispose of the Clear Cap in a sharps container.

Important:

- **Do not touch the gray needle shield of the prefilled pen to avoid injury.**
- **Do not** put the prefilled pen down after removing the Clear Cap.

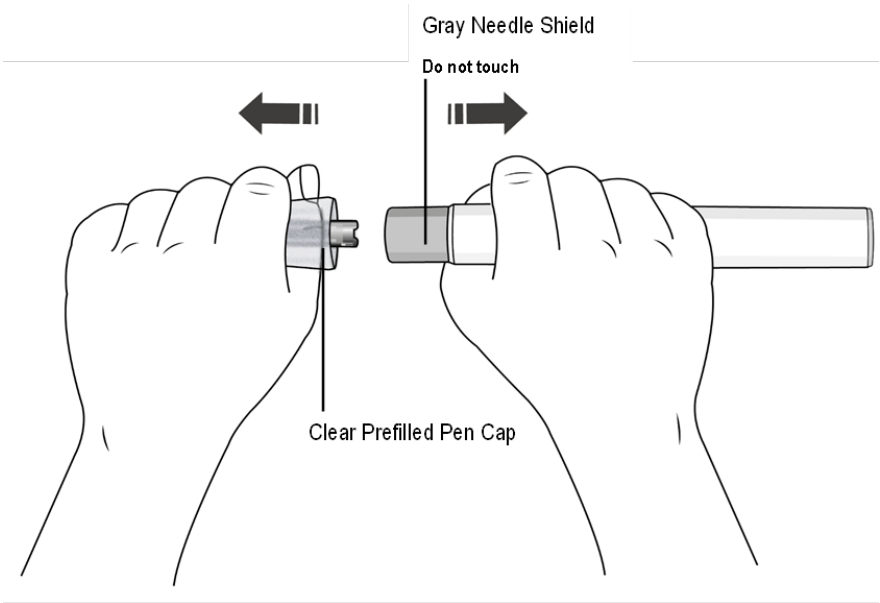


Figure G

Step 8. Pinch the Skin and place the Prefilled Pen on the injection site

Immediately after removing the clear prefilled pen cap, complete the following steps without stopping:

- **Gently pinch** the area of cleaned skin around the injection site and hold the area firmly until the injection is complete (see **Figure H**).
- Place the prefilled pen at a 90˚ angle on the cleaned injection site (see **Figure H**).
- **Make sure you can see the viewing window.**

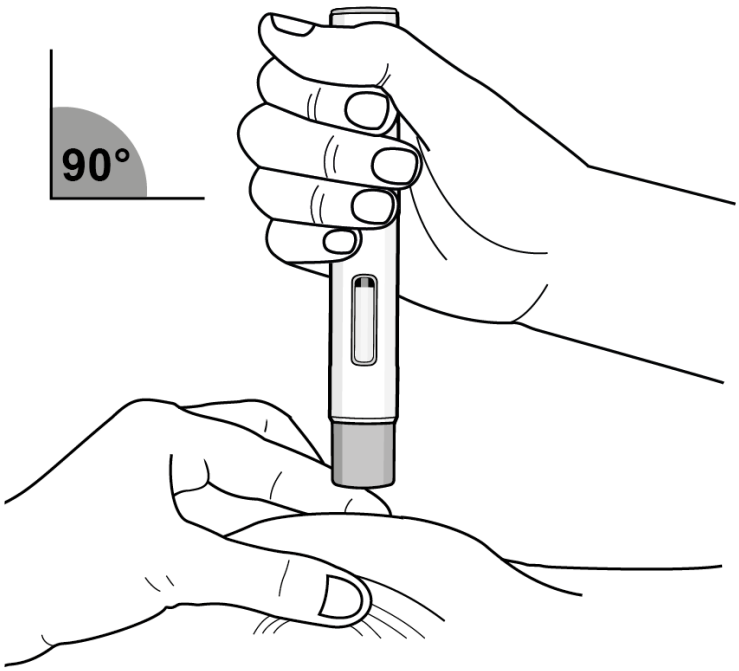


Figure H

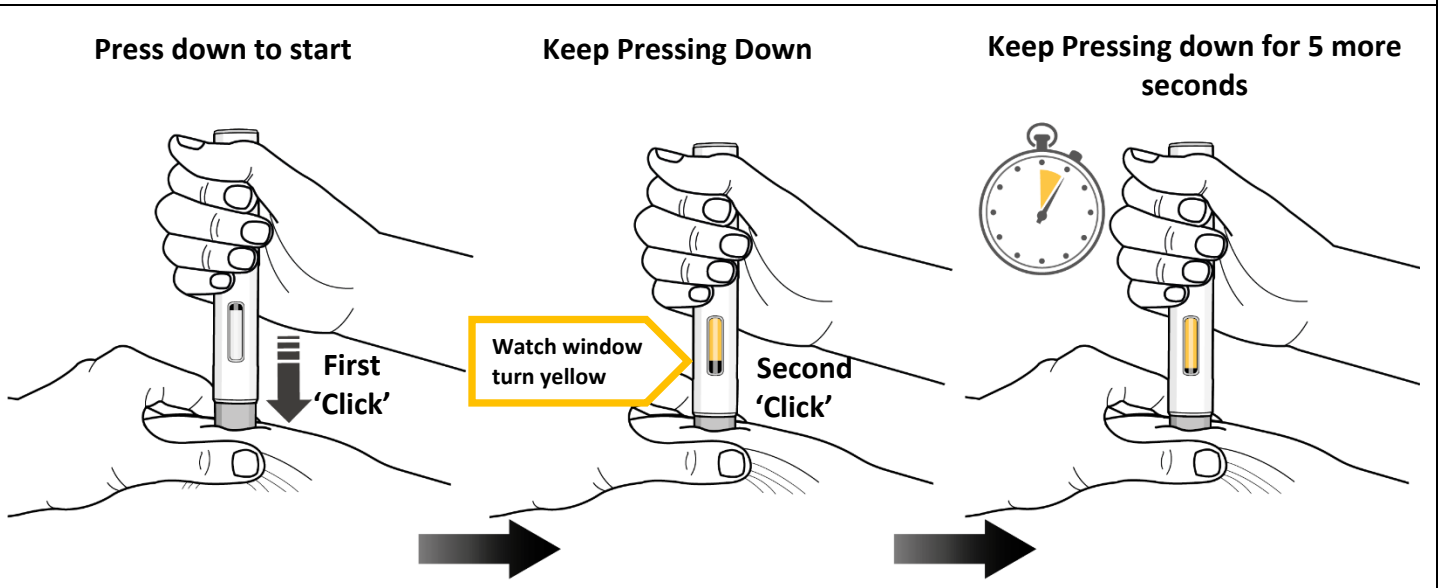
Step 9. Inject Medicine (see **Figure I**)

You Must Read all of Step 9 before injecting.
The injection may take up to 15 seconds.

To ensure you receive a full dose you must keep the prefilled pen firmly pressed against your pinched skin until:

- **The yellow plunger has stopped moving and filled the viewing window**, and
- **5 seconds has passed after the 2nd "Click."**

Press the gray needle shield down firmly against the pinched skin to start the injection and keep pressing down until all the steps below are complete.



Press down to start the injection and listen for a **First 'Click**'. • The First "Click" means the injection has started. • The yellow plunger will start moving in the viewing window. **Keep pressing** the prefilled pen down.	**Keep pressing** the prefilled pen down and **watch the viewing window.** • The window will turn yellow and • You will hear a **Second 'Click'.** **Keep pressing** the prefilled pen down.	**Keep pressing** the prefilled pen **down** for **5 more seconds to make sure you get the full dose.**

Figure I

- **Do not** remove the prefilled pen until the yellow plunger has stopped moving and completely filled the viewing window, and 5 seconds has passed after the Second "Click"
- **Do not remove, tilt, or rotate the prefilled pen during the injection.**

Step 10. Release the Pinch and Remove the Prefilled Pen

- Release the pinch and remove the prefilled pen at a 90° angle from the skin (see **Figure J**).
- As the prefilled pen is lifted from the skin, the gray needle shield returns to the original (before use) position, and will lock into place, covering the needle.

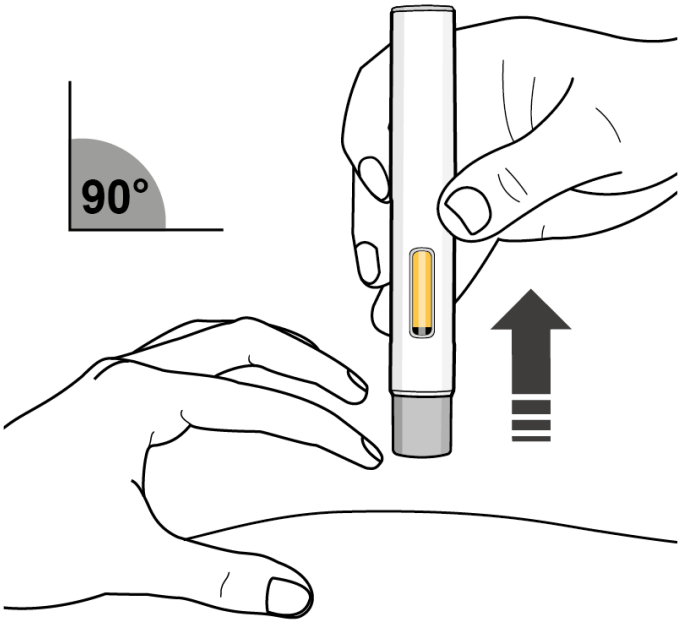


Figure J

Important: If you think that you have not received the full dose contact your healthcare provider right away.

- If there is a little bleeding at the injection site, you can press a cotton ball or gauze over the injection site.
- **Do not** rub the injection site.
- If needed, you may cover the injection site with a small adhesive bandage.

Disposal

Step 11. Disposing of the Prefilled Pen

- **Do not** try to reuse the prefilled pen.
- After injecting your dose, put the prefilled pen into a sharps container or closed puncture-resistant container (see **Figure K**).

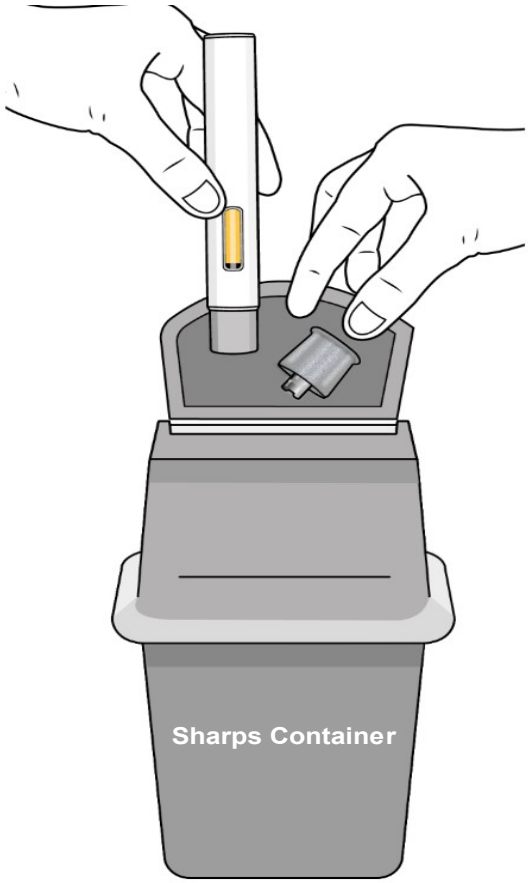


Figure K

- If you do not have a sharps container, you may use a household container that is:
  - Made of heavy-duty plastic
  - Can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
  - Upright stable during use
  - Leak-resistant
  - Properly labeled to warn of hazardous waste inside the container
- When your sharps container is almost full, you will need to follow your local guidelines for the right way to dispose of your sharps container. There may be local laws about how you should throw away used needles and syringes.
- **Do not** dispose of your used sharps container in your household trash unless your local guidelines permit this.
- **Do not** recycle your used sharps container.

Step 12. Keep Track of Your Treatment

- If required by your physician, record your injection in a diary to help keep track of your medicine.

Instructions for Use: step by step guide for Prefilled Syringe with Needle Safety Device

Preparing for an Injection

Step 1. Let the Prefilled Syringe Reach Room Temperature

- Remove the prefilled syringe from the carton box and place it on a **clean flat surface**.
- **Do not** remove the prefilled syringe from the carton box by holding onto the needle cap or plunger.
- **Do not** move or pull on the plunger.
- Wait **30 minutes** for the medicine to reach room temperature if it has been stored in the refrigerator (see **Figure A**).
- Injecting the medicine cold could cause you some discomfort.
- **Do not** try to speed up the warming process in any way. **Do not** microwave the prefilled syringe, run hot water over it, or leave it in direct sunlight.

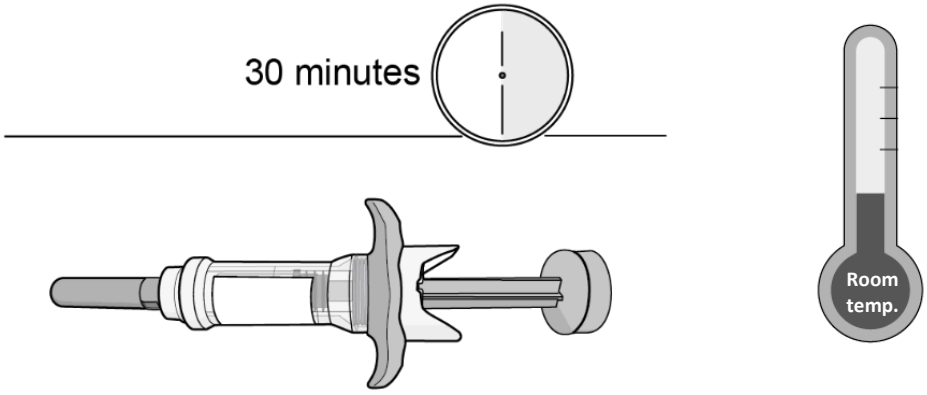


Figure A

Step 2. Check the Expiration

- Check the expiration date on the prefilled syringe (see **Figure B**).
- **Do not use** the prefilled syringe if the expiration date has passed.
- **Do not use** the prefilled syringe if stored at room temperature for longer than 2 months**.**
- If the expiration date has passed or if stored at room temperature for longer than 2 months, then safely dispose of the prefilled syringe and get a new one (see **Step 12. Disposing of the Syringe**).

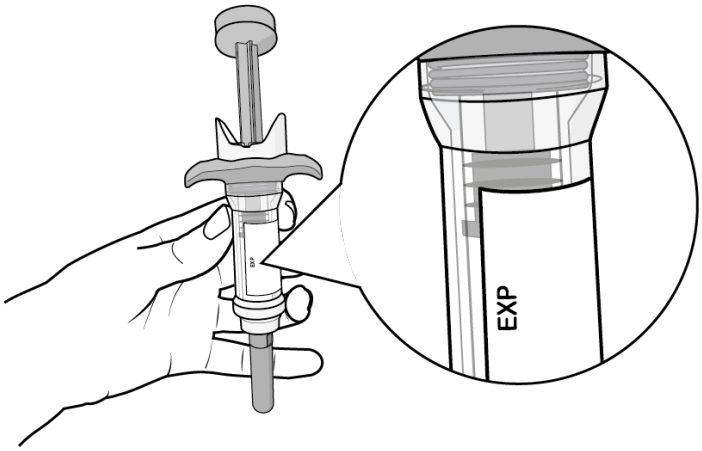


Figure B

Step 3. Inspect the Prefilled Syringe

- Inspect the medicine through the clear window of the prefilled syringe (see **Figure C** and **Figure D**).
- Peel back the label to inspect the medicine if you cannot see enough of the medicine through the clear window of the prefilled syringe (see **Figure D**).
- It is normal to see air bubbles. **Do not** try to remove the air bubbles**.**
- The medicine should be slightly opalescent to clear, brownish-yellow to yellow liquid.
- If the medicine is discoloured or contains particles (see **Figure C**), then **do not use.** Safely dispose of the prefilled syringe and get a new one (see **Step 12. Disposing of the Syringe**).
- Check the prefilled syringe. If it looks damaged, has cracks or is leaking medicine, or has been dropped, then safely dispose of the prefilled syringe and get a new one.

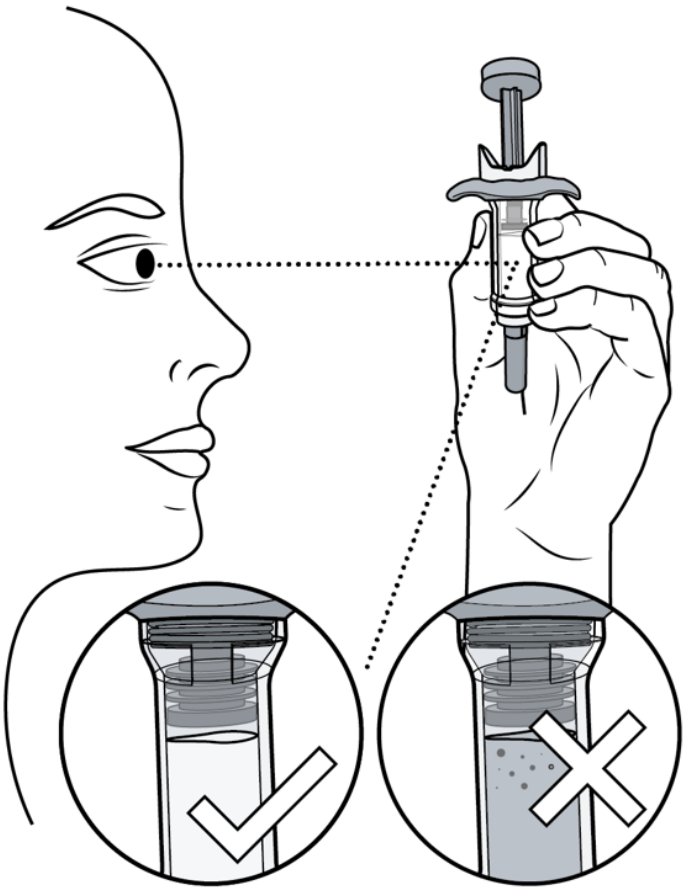


Figure C

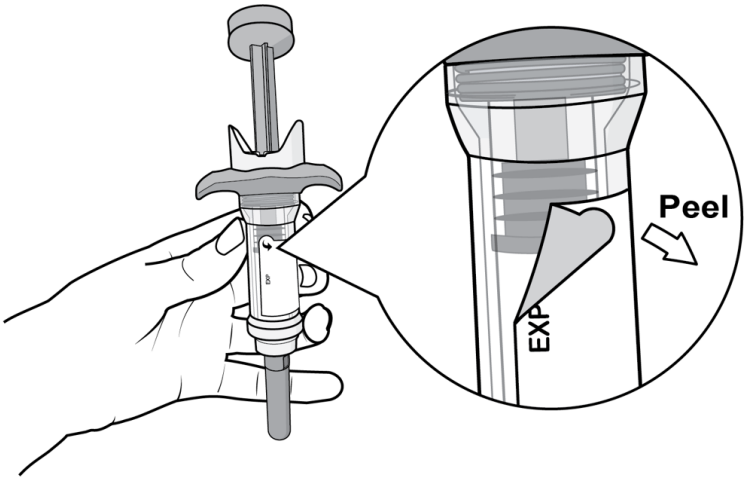


Figure D

Choose and Prepare an Injection Site

Step 4. Clean Your Hands

- Wash your hands well with soap and water or use hand sanitizer (see **Figure E**).

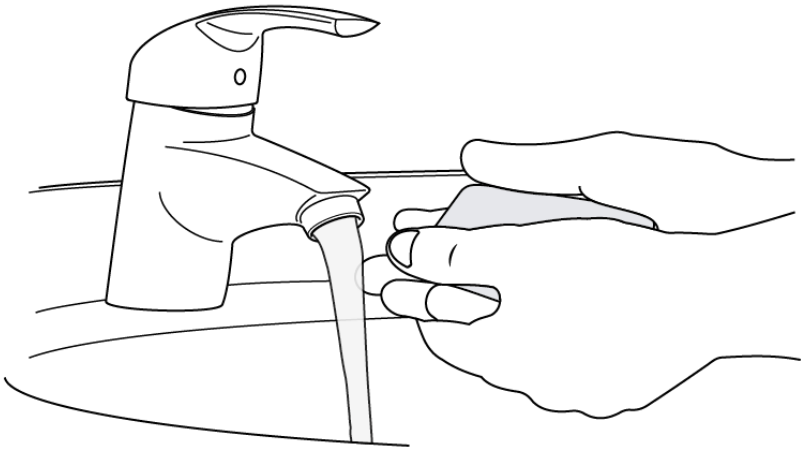


Figure E

Step 5. Select the Injection Site

- Inject into the thigh or belly (abdomen) area, but stay 1 inch (2 cm) away from the belly button (navel) (see **Figure F**).
- If somebody else (like a caregiver) gives you the injection, you can also use the upper arm.
- Change (rotate) your injection sites with each injection. **Do not Inject** in the same injection site multiple times if you see that the skin is damaged.
- Do not inject into the belly button, moles, scars or bruises or stretch marks, or into areas where the skin is tender, red, hard, or injured.

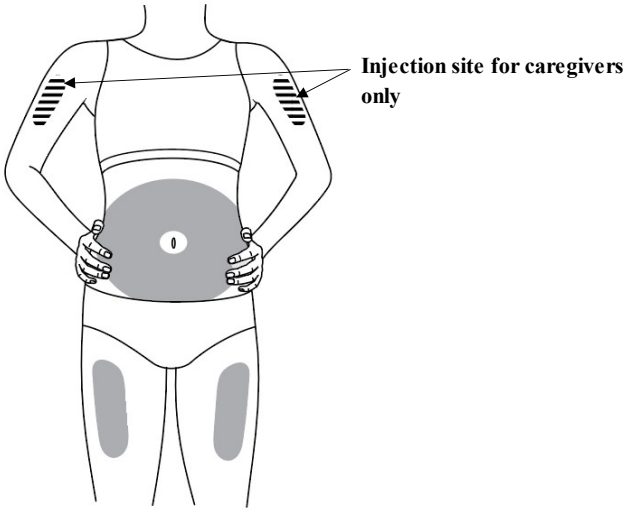


Figure F

Step 6. Prepare the Injection Site

- Clean the injection site with an alcohol pad in a circular motion (see **Figure G**).
- Allow the injection site to air dry.
- **Do not** touch the cleaned injection site before giving the injection.
- **Do not** fan or blow on the skin area that you cleaned.

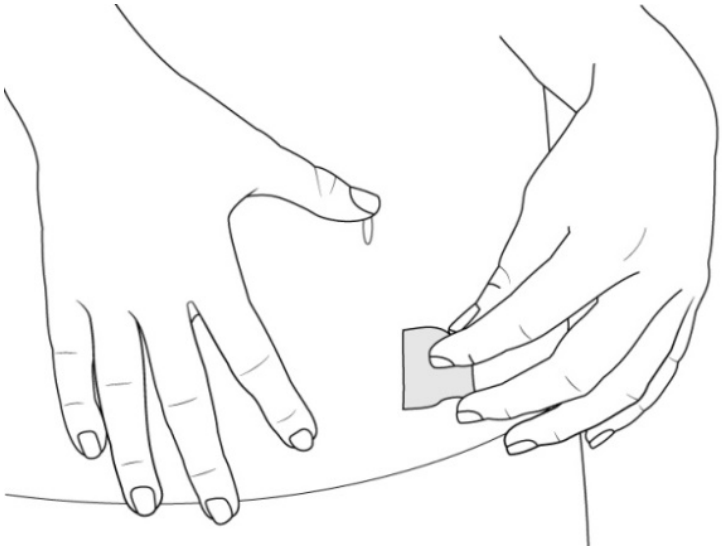


Figure G

Injecting the Medicine with the Prefilled Syringe

Complete the Injection without stopping. Read all steps first before beginning.

Step 7. Remove Needle Cap and Dispose of the Cap

- **Do not** remove the needle cap until you are ready to inject.
- Hold the prefilled syringe by the body, with the needle facing away from you.
- **Pull the needle cap straight off** with one hand while holding the prefilled syringe with the other hand (see **Figure H**). If you cannot remove the cap, you should ask a caregiver for help or contact your healthcare provider.
- **Do not touch or hold the plunger during needle cap removal.**
- **Do not** re-cap the prefilled syringe.
- Dispose of the needle cap in a sharps container.
- You may see a drop of liquid at the end of the needle. This is normal.
- **The needle should be kept sterile after removing the needle cap. Do not** touch the needle or let it touch any surfaces after removing the needle cap.

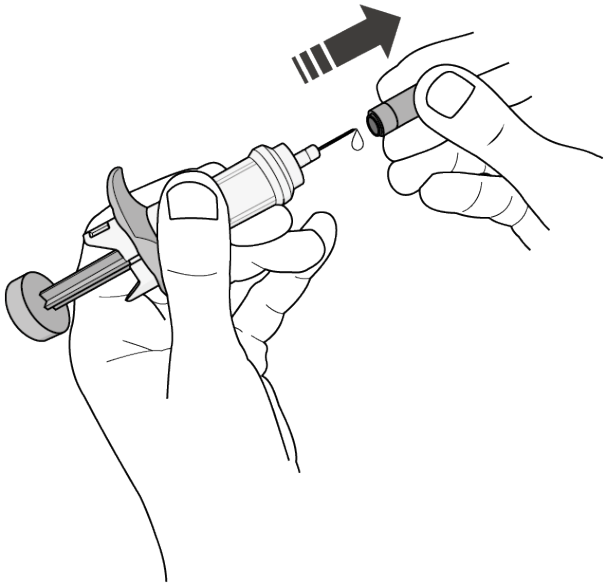


Figure H

Step 8. Pinch the skin and Insert the Needle

Immediately after removing the needle cap, complete the following steps without stopping:

- Gently pinch the area of cleaned skin around the injection site and hold that area firmly until the injection is complete (see **Figure I**).
- Fully insert the needle at an angle between 45˚ and 90˚. **Do not** change the angle during the injection. (see **Figure I**: images show an example of injection at 90˚ angle).
- **Do not hold or push on the plunger while inserting the needle into the skin.**

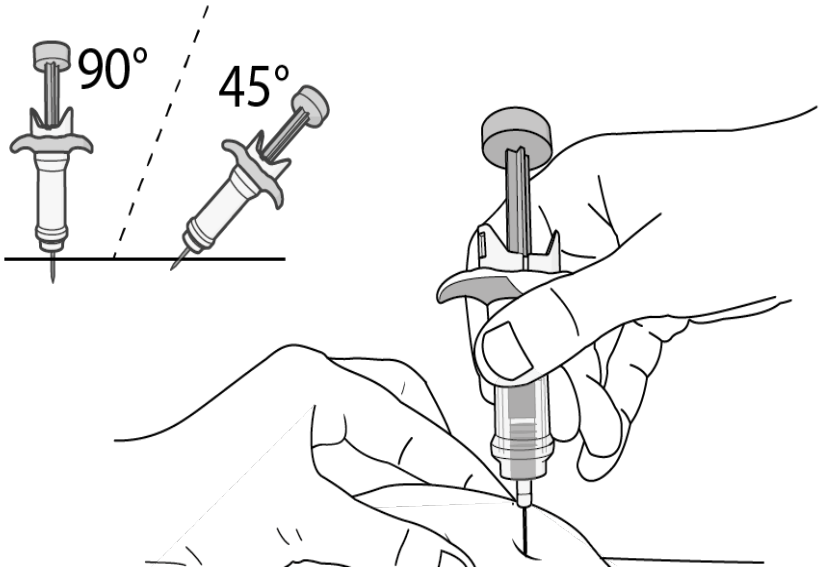


Figure I

Step 9. Inject Medicine

- Hold the prefilled syringe in place and inject all of the medicine by firmly **pushing the plunger all the way down** (see **Figure J**).
- Press the plunger all the way down until it stops to get the full dose. Pushing firmly on the plunger until the end of the injection (See **Figure K**).

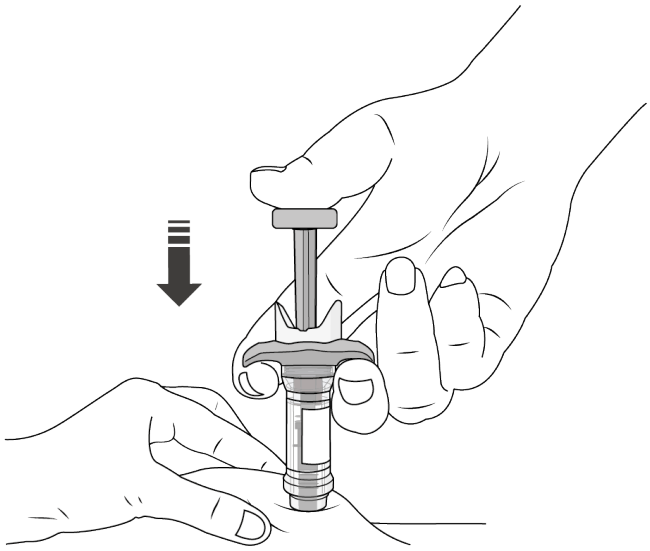


Figure J

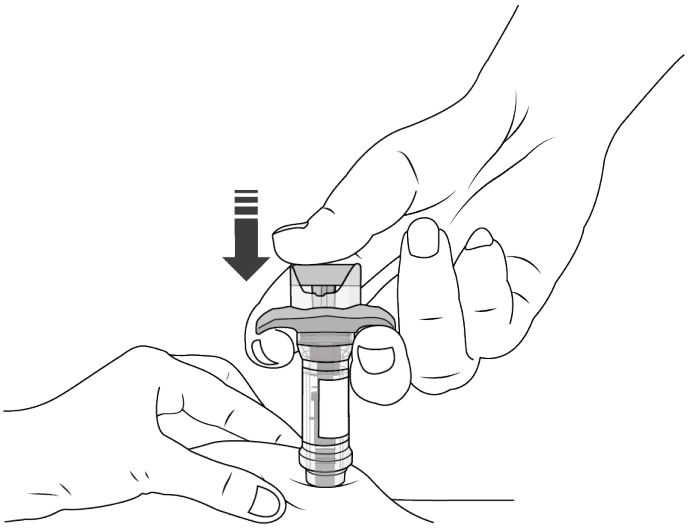


Figure K

Step 10. Release plunger

- After the plunger has been fully pushed down and the full dose injected, slowly remove the thumb from the plunger before removing the syringe from the skin (see **Figure L**). This will make the needle retract inside the syringe.

Caution: Do not remove the syringe from the skin before removing the thumb, as this could result in a needle stick injury.

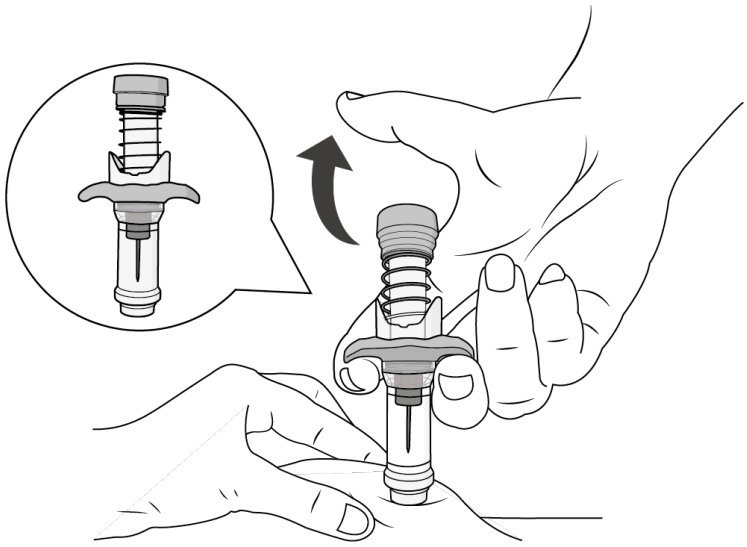


Figure L

Step 11. Release the Pinch and Remove the Prefilled Syringe

- Release the pinch and remove the prefilled syringe from the injection site (see **Figure M**).

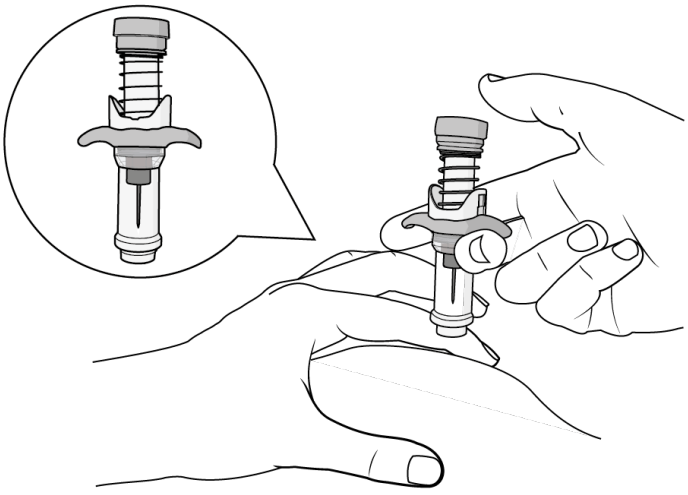


Figure M

- If there is a little bleeding at the injection site, you can press a cotton ball or gauze over the injection site.
- Do not rub the injection site.
- If needed, you may cover the injection site with a small adhesive bandage.

Disposal

Step 12. Disposing of the Syringe

- **Do not** reuse the prefilled syringe.
- After injecting the dose, put the syringe into a sharps disposal container or closed puncture-resistant container (see **Figure N**).

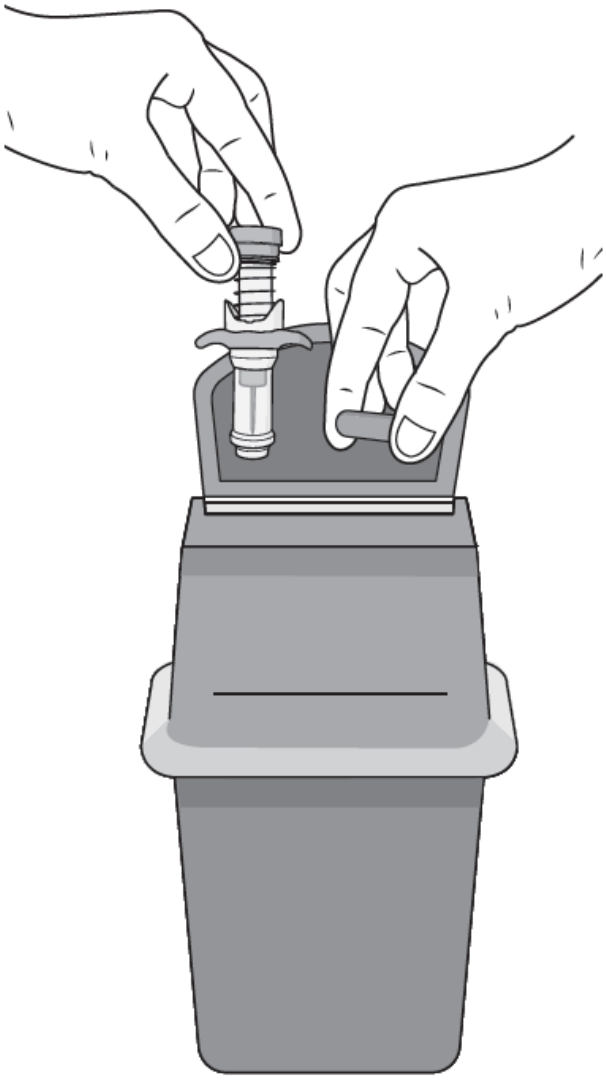


Figure N

- If you do not have a sharps disposal container, you may use a household container that is:
  - Made of heavy-duty plastic
  - Can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
  - Upright stable during use
  - Leak-resistant
  - Properly labeled to warn of hazardous waste inside the container
- When your sharps disposal container is almost full, you will need to follow your local guidelines for the right way to dispose of your sharps disposal container. There may be local laws about how you should throw away used needles and syringes.
- **Do not** dispose of your used sharps disposal container in your household trash unless your local guidelines permit this.
- **Do not** recycle your used sharps disposal container.

Step 13. Keep Track of Treatment

- If required by your physician, record your injection in a diary to help keep track of your medicine.

If you want more information about ANDEMBRY:

- 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: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website https://www.cslbehring.ca/ , or by calling 1-866-773-7721 .

This leaflet was prepared by CSL Behring Canada Inc.

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