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

ANDEMBRY 200 mg solution for injection in pre-filled syringe
ANDEMBRY 200 mg solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ANDEMBRY 200 mg solution for injection in pre-filled syringe

Each pre-filled syringe contains 200 mg of garadacimab* in 1.2 mL solution.

ANDEMBRY 200 mg solution for injection in pre-filled pen

Each pre-filled pen contains 200 mg of garadacimab* in 1.2 mL solution.

*Garadacimab is a fully human IgG4 monoclonal antibody produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

Excipients with known effect

Each pre-filled syringe/pen contains 19.3 mg of proline and 0.24 mg of polysorbate 80.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

The solution is a slightly opalescent to clear, brownish-yellow to yellow liquid.

The solution has a pH of approximately 6.1 and an osmolality of approximately 470 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Posology

The recommended dose of ANDEMBRY, in adults and children 12 years of age and above, 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.

Consideration should be given to discontinuing treatment in patients with normal C1-INH HAE (nC1-INH) who have shown insufficient reduction in attacks after 3 months of treatment (see section 4.4 and 5.1).

ANDEMBRY is not intended for the treatment of acute HAE attacks (see section 4.4).

Missed doses

If a dose of ANDEMBRY is missed, the patient should be instructed to administer the dose as soon as possible.

Special populations

Elderly

No dose adjustment is required for patients above 65 years of age (see section 5.2).

Renal and hepatic impairment

No dose adjustment is required in patients with renal or hepatic impairment (see section 5.2).

Paediatric population

The safety and efficacy of garadacimab in children less than 12 years have not been established. No data are available.

Method of administration

ANDEMBRY is intended for subcutaneous use only.

Each ANDEMBRY unit (pre-filled syringe or pre-filled pen) is intended for single use only (see section 6.6).

The injection should be restricted to the following injection sites: the abdomen, the thighs and the upper outer arms (see section 5.2). 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.

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 reactions

Hypersensitivity reactions have not been observed but may theoretically occur. In case of severe hypersensitivity reactions, administration of garadacimab should be discontinued, and appropriate treatment instituted.

General

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

There are limited data available on the use of garadacimab in HAE patients with nC1-INH (see section 5.1).

Some subcategories of nC1-INH HAE 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 and to discontinue the treatment if clinical response is not observed (see sections 4.2 and 5.1).

Interference with coagulation test

ANDEMBRY can prolong activated partial thromboplastin time (aPTT) due to an interaction of garadacimab with the aPTT assay. The extent of aPTT prolongation could be variable depending on drug exposure as well as additional parameters, such as natural variation in FXII levels, and other coagulation factors. 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 ANDEMBRY can prolong aPTT in this assay.

Excipients

This medicinal product contains 19.3 mg of proline in each pre-filled syringe/pen which is equivalent to 16.1 mg/mL. Proline may be harmful for patients with hyperprolinaemia, a rare genetic disorder in which proline builds up in the body.

This medicinal product contains 0.24 mg of polysorbate 80 in each pre-filled syringe/pen which is equivalent to 0.2 mg/mL. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No dedicated drug-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. The use of analgesic, antibacterial, antihistamine, anti-inflammatory and anti-rheumatic medications had no effect on the PK of garadacimab. 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of garadacimab in pregnant women. Monoclonal antibodies such as garadacimab are transported across the placenta mainly during the third trimester of pregnancy; therefore, potential effects on a fetus are likely to be greater during the third trimester of pregnancy. A pre- and postnatal development study conducted in pregnant rabbits revealed no evidence of harm to the developing fetus. (see section 5.3). As a precautionary measure, it is preferable to avoid the use of garadacimab during pregnancy.

Breast-feeding

It is unknown whether garadacimab 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. Consequently, transfer of IgG antibodies to the newborns through milk may happen during the first few days. In this short period, a risk to the breast-fed child cannot be excluded. Afterwards, garadacimab could be used during breast-feeding if clinically needed.

Fertility

Effect on fertility has not been evaluated in humans. Garadacimab had no effect on male or female fertility in rabbits (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most commonly observed adverse reactions associated with ANDEMBRY were injection site reactions (ISR) including injection site erythema, injection site bruising, injection site pruritus and injection site urticaria, headache and abdominal pain.

Tabulated list of adverse reactions

Table 1 summarises adverse reactions observed in the *VANGUARD pivotal trial*, which included 39 subjects with HAE who received at least 1 dose of ANDEMBRY.

The frequency of adverse reactions listed in Table 1 is defined using 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).

Table 1: Adverse drug reactions (ADRs) obtained from clinical studies with ANDEMBRY

System organ class	Adverse drug reaction	Frequency
General disorders and administration site conditions	Injection site reactions*	Common
Nervous system disorders	Headache	Common
Gastrointestinal disorders	Abdominal pain	Common

*Injection site reactions include, erythema, bruising, pruritus, and injection site urticaria

Paediatric population

The safety of ANDEMBRY was evaluated in a subgroup of 11 subjects aged 12 to < 18 years old. No difference from the overall safety profile was seen between adults and children.

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 national reporting system listed in Appendix V.

4.9 Overdose

There is no available information to identify potential signs and symptoms of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in hereditary angioedema, ATC code: B06AC07

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 inhibits its catalytic activity. The inhibition of FXIIa, the first factor activated in the contact system, prevents HAE attacks by blocking the activation of prekallikrein to kallikrein and the generation of bradykinin, which is associated with inflammation and swelling in HAE attacks.

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

Clinical efficacy and safety

VANGUARD pivotal study

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

The study contained 64 patients aged 12 years and older including 58 adult and 6 pediatric patients who experienced at least 2 attacks during the up to 2-month run-in period. Patients were randomised 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 treatment 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 prophylactic HAE treatments. During the study run-in period, attack rates of ≥ 3 attacks/month were observed in 59.4% of patients overall. Mean baseline number of attacks per month was 3.07 in the ANDEMBRY group compared to 2.52 in the placebo group.

The primary efficacy endpoint was the time-normalised number of HAE attacks from day 1 through the end of the 6-month treatment period. The key secondary endpoints were: the percent reduction in the mean time-normalised number of HAE attacks, the number of subjects who were attack free from day 1 through the end of the first 3-months the percent of subjects with good or excellent responses to the SGART from day 1 through the end of the 6-month treatment period.

Table 2: Results of key primary and secondary efficacy measures (ITT analysis set)

	ANDEMBRY 200 mg (N = 39)	**Placebo (N = 25)**

Number of evaluable patients, n	39	24[a]
Primary endpoint		
Total number of HAE attacks from Day 1 to 182	63	264
Time-normalised number of HAE attacks from Day 1 to 182		
Mean (95% CI)	0.27 (0.05, 0.49)	2.01 (1.44, 2.57)
P-value*	< 0.001	
Adjusted LS mean[b] (95% CI)	0.22 (0.11, 0.47)	2.07 (1.49, 2.87)
Secondary endpoints		
Percent reduction in time-normalised number of HAE attacks relative to placebo[c]		
Mean (95% CI)	86.51 (57.84, 95.68)	
P-value*	< 0.001	
Percent (number) of subjects who were attack free from day 1 through the end of month 3	71.79 (28)	8.33 (2)
P-value*	< 0.001	
Percent (number) of subjects with good or excellent response to SGART at day 182	82 (31)	33 (8)
P-value*	< 0.001	

HAE – hereditary angioedema; ITT – intent to treat; N – number of patients in the ITT analysis set; LS – least squares; CI – confidence interval; SGART – Subjects Global Assessment of Response to Therapy

[a] One patient had a treatment period of less than 30 Days and was therefore not included in the analysis

[b] After adjusting for baseline attack rate

[c] Median percent reduction for this endpoint was 100

***** A hierarchical testing procedure controls for the overall alpha level of 5% (2-sided)

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 exploratory endpoint of Angioedema Quality of Life Questionnaire (AE-QoL) total and domain (functioning, fatigue/mood, fear/shame, and nutrition) scores, compared to the placebo at day 182 **(Table 3)** showed improvement in the ANDEMBRY treated patients. A reduction of six points in the AE-QoL has been defined as the minimal clinically important difference (MCID). Changes from baseline greater than the MCID were observed in 88% of patients treated with ANDEMBRY.

Table 3: AE-QoL total score and domains change from baseline to day 182 (ITT analysis set)[a]

AE-QoL total score and domains change from baseline to day 182[b], mean (SD)	**ANDEMBRY 200 mg (N=39)**	**Placebo (N=25)**
Patients Included in the Analysis, n	33	20
Total Score	-26.5 (17.9)	-2.2 (19.1)

Functioning	-35.8 (23.2)	1.9 (29.6)
Fatigue/Mood	-21.1 (22.9)	-5.8 (27.1)
Fears/Shame	-28.0 (24.1)	-2.5 (18.6)
Nutrition:	-16.7 (23.3)	-0.6 (16.5)

ITT = intention-to-treat; N = number of patients in the ITT Analysis Set; SD = standard deviation.
[a] Angioedema Quality of Life is only answered by patients of age ≥ 18 years.
[b] A lower AE-QoL score represents greater improvement

The efficacy profile in pediatric patients 12 years of age and older (n=6) was consistent with that of the overall population.

VANGUARD Open Label Extension Study

Patients who completed VANGUARD (n=57) in addition to patients from a phase 2 study (n=35) rolled over into the VANGUARD open-label extension study which also enrolled 69 new patients. From the start of treatment through 16.7 months (median duration of exposure 9.49 months) 96/161 (59.6%) patients remained attack-free. The safety and efficacy profile in adolescent patients ages 12 years and older (n=10) was consistent with that of the overall population.

Normal C1-INH HAE population

Normal C1-INH HAE includes patients with known or unknown mutations. The safety and efficacy of garadacimab was evaluated in 6 patients with known mutations: HAE-FXII (n=3) or HAE-PLG (plasminogen) (n=3) in the phase 2 study 2001.

Among the three genetically confirmed HAE-FXII patients enrolled, one withdrew during the second month of the treatment period due to lack of efficacy after showing a reduction in overall attack rate from 4.35 to 3.51 attacks per month and a reduction in severe attacks from 1.09 to 0.58 attacks per month. The remaining two patients completed the initial 12-week treatment period, with one demonstrating a reduction in attack rate from 3.24 to 0.36 attacks per month and the other becoming attack-free from an initial attack rate of 3.20 attacks per month. Both patients continued garadacimab for the duration of the second treatment period of 20 and 17 months, after which both patients rolled over into the phase 3 extension study and received garadacimab for an additional 18 months and remained attack free.

Additionally, the 3 patients with HAE-PLG completed the initial 12-week treatment period and did not continue into the treatment extension period. One patient reported a decrease in their monthly overall attack rate to 1.75 and a severe attack rate to 0.35 during the treatment period, compared to 3.20 and 1.60, respectively, during the run-in period. The remaining two patients reported an increase in their monthly attack rates to 6.8 and 3.17 during the treatment period compared to 2.28 and 1.45 during the run-in period respectively. None of the reported attacks was classified as severe attack.

Overall, the safety profile of garadacimab in patients with nC1-INH was similar to that observed in patients with HAE-C1-INH.

Immunogenicity

Treatment with ANDEMBRY has been associated with development of low-titer treatment emergent anti-drug antibodies (ADA) in 2.9% (5/172) of treated subjects. Due to the low titer of ADA registered in these subjects, neutralizing antibodies could not be detected. However, although the clinical relevance of ADA could not be fully established, available data indicate that there was no apparent impact of the presence of ADA on safety or efficacy.

Paediatric population

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

5.2 Pharmacokinetic properties

In the *VANGUARD pivotal trial*, patients treated with 200 mg garadacimab subcutaneous once monthly presented mean (SD) area under the curve over the dosing interval at steady-state ($AUC_{tau,ss}$), maximum concentration at steady-state ($C_{max,ss}$), and minimum concentration at steady-state ($C_{min,ss}$) of 10300 (3380) mcg·h/mL, 21.2 (6.58) mcg/mL, and 9.30 (3.73) mcg/mL, respectively. Steady-state exposure of garadacimab was achieved after the initial subcutaneous administration of loading dose of 400 mg (2 doses of 200 mg).

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.

Biotransformation

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

Special populations

No dedicated studies have been conducted to evaluate the pharmacokinetics of garadacimab in special patient populations including gender, age, pregnant women.

In a population pharmacokinetic analysis, after correcting for body weight (43.3 to 153 kg), no influence of gender, age (12 to 73 years), race, or ethnicity was apparent on clearance or volume of distribution of garadacimab.

Although body weight was identified as an important covariate describing the variability of clearance and volume of distribution, the difference was not clinically relevant and no dose adjustments are recommended.

Renal and hepatic impairment

Dedicated studies on subjects with renal or hepatic impairment were not conducted.

As IgG monoclonal antibodies are mainly eliminated via intracellular catabolism, renal impairment or hepatic impairment is not expected to influence clearance of garadacimab.
Based on population pharmacokinetic analysis, hepatic impairment had no effect on the pharmacokinetics of garadacimab.

In a population pharmacokinetic analysis, renal impairment (estimated glomerular filtration rate: ≥90 mL/min [normal, N=149], 60 to <90 mL/min [mild, N=22], and 30 to <60 mL/min [moderate, N=1]) had no effect on the pharmacokinetics of garadacimab.

5.3 Preclinical safety data

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

Reproductive toxicity

Male and female fertility were unaffected based upon no observed adverse findings on mating, fecundity, fertility indices, on maternal reproductive parameters, embryo survival or sperm assessment in sexually mature rabbits that received garadacimab intravenously once every three days resulting in approximately 83- and 103-fold the exposure (based on AUC) in females and males, respectively, at the recommended human dose of 200 mg subcutaneously once monthly.

In a pre- and post-natal development study, pregnant rabbits were administered garadacimab subcutaneously once every five days from implantation through weaning. There was no maternal and off-spring, through six months of age, garadacimab-related toxicity in rabbits receiving subcutaneous garadacimab resulting in approximately 53-fold the clinical exposure (based on AUC) at the recommended human dose of 200 mg subcutaneously once monthly.

Garadacimab crossed the placenta in rabbits. With subcutaneous administration of garadacimab corresponding to approximately 53-fold the clinical exposure (based on AUC) at the recommended human dose of 200 mg subcutaneously once monthly, at gestation day 29, fetal plasma concentrations were 40.8% of maternal concentrations.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Arginine monohydrochloride
Proline
Polysorbate 80 (E 433)
Water for injections

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

ANDEMBRY may be stored at room temperature (up to 25 °C) for a single period of up to 2 months, but not beyond the expiry date.

6.4 Special precautions for storage

Store in a refrigerator (2 ºC – 8 ºC).

Do not freeze.

Keep the pre-filled syringe or pre-filled pen in the outer carton in order to protect from light.

Do not return ANDEMBRY to refrigerated storage after storage at room temperature.

6.5 Nature and contents of container

ANDEMBRY 200 mg solution for injection in pre-filled syringe

1.2 mL of solution in a pre-filled glass syringe (type I glass) with a bromobutyl stopper, 27G x 1/2 5B special thin-walled (STW) staked needle, and is assembled with an extended finger flange and needle safety device.

ANDEMBRY is available as unit packs containing 1 assembled pre-filled syringe and in multipacks containing 3 (3 packs of 1) assembled pre-filled syringes.

ANDEMBRY 200 mg solution for injection in pre-filled pen

1.2 mL of solution in a pre-filled glass syringe (type I glass) with a bromobutyl stopper, 27G x 1/2 5B special thin-walled (STW) staked needle. Each pre-filled syringe is assembled with a pen.

ANDEMBRY is available as unit packs containing 1 assembled pre-filled pen and in multipacks containing 3 (3 packs of 1) assembled pre-filled pens.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Before use, ANDEMBRY should be visually inspected for appearance by gentle inversion. The solution should be slightly opalescent to clear, brownish-yellow to yellow. Solutions that are discoloured or contain particles should not be used.

Do not shake.

Administration steps

ANDEMBRY 200 mg solution for injection in pre-filled syringe

After removing the pre-filled syringe with needle safety device from the refrigerator, wait 30 minutes before injecting to allow the solution to reach room temperature. Inject ANDEMBRY subcutaneously into the abdomen, thigh or upper arm. Rotation of the injection site is recommended (see section 4.2).

Each pre-filled syringe with needle safety device is for single use only. Discard the pre-filled syringe with needle safety device after injection is completed in a sharps container or closed puncture resistant container.

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

ANDEMBRY 200 mg solution for injection in pre-filled pen

After removing the pre-filled pen from the refrigerator, wait 30 minutes before injecting to allow the solution to reach room temperature. Inject ANDEMBRY subcutaneously into the abdomen, thigh or upper arm. Rotation of the injection site is recommended (see section 4.2).

Injection with the pre-filled pen may take up to 15 seconds.

Listen for the first ‘click’ (this signals the start of injection, and the yellow plunger will start to move across the window). Keep pressing and watch the yellow plunger move down to fill the window. A second ‘click’ will be heard and the viewing window will be completely yellow. Wait an extra 5 seconds to make sure the full dose was received.

Each pre-filled pen is for single use only. Discard the pre-filled pen after injection is completed in a sharps container or closed puncture resistant container.

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

7. MARKETING AUTHORISATION HOLDER

CSL Behring GmbH
Emil-von-Behring-Strasse 76
D-35041 Marburg
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1885/001
EU/1/24/1885/002
EU/1/24/1885/003
EU/1/24/1885/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

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

Name and address of the manufacturer of the biological active substance

CSL Behring (Australia) Pty Ltd
189-209 Camp Road
Broadmeadows, Victoria 3047
Australia

Name and address of the manufacturer responsible for batch release

CSL Behring GmbH
Emil-von-Behring-Strasse 76
35041 Marburg
Germany

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 (PSURs)**

The requirements for submission of PSURs 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 (MAH) shall submit the first PSUR 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 marketing authorisation holder (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 - UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

ANDEMBRY 200 mg solution for injection in pre-filled syringe
garadacimab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 200 mg garadacimab in 1.2 mL solution.

3. LIST OF EXCIPIENTS

histidine, arginine monohydrochloride, proline, polysorbate 80, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake.
For single use only.
Read the package leaflet before use.
Subcutaneous use.

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.
Can be stored at room temperature (up to 25 °C) for a single period of up to 2 months.
Date removed from refrigerator: _____

Do not re-refrigerate after it has reached room temperature.
Keep the pre-filled syringe 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

CSL Behring GmbH
Emil-von-Behring-Strasse 76
35041 Marburg
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1885/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ANDEMBRY 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – MULTIPACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

ANDEMBRY 200 mg solution for injection in pre-filled syringe
garadacimab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 200 mg garadacimab in 1.2 mL solution

3. LIST OF EXCIPIENTS

histidine, arginine monohydrochloride, proline, polysorbate 80, water for injections. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

3 (3 packs of 1) pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake.
For single use only.
Read the package leaflet before use.
Subcutaneous use.

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.
Can be stored at room temperature (up to 25 °C) for a single period of up to 2 months.

Date removed from refrigerator: _____

Do not re-refrigerate after it has reached room temperature.
Keep the pre-filled syringe 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

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Emil-von-Behring-Strasse 76
35041 Marburg
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1885/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

N/A

16. INFORMATION IN BRAILLE

ANDEMBRY 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON - MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

ANDEMBRY 200 mg solution for injection in pre-filled syringe
garadacimab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 200 mg garadacimab in 1.2 mL solution.

3. LIST OF EXCIPIENTS

histidine, arginine monohydrochloride, proline, polysorbate 80, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled syringe

Component of a multipack, cannot be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake.
For single use only.
Read the package leaflet before use.
Subcutaneous use.

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.

Can be stored at room temperature (up to 25 °C) for a single period of up to 2 months.

Date removed from refrigerator: _____

Do not re-refrigerate after it has reached room temperature.
Keep the pre-filled syringe 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

CSL Behring GmbH
Emil-von-Behring-Strasse 76
35041 Marburg
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1885/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ANDEMBRY 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL – PRE-FILLED SYRINGE

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

ANDEMBRY 200 mg
solution for injection
garadacimab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1.2 mL

6. OTHER

CSL Behring GmbH

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

ANDEMBRY 200 mg solution for injection in pre-filled pen
garadacimab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 200 mg garadacimab in 1.2 mL solution.

3. LIST OF EXCIPIENTS

histidine, arginine monohydrochloride, proline, polysorbate 80, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled pen

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake.
For single use only.
Read the package leaflet before use.
Subcutaneous use.

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 pen in the outer carton in order to protect from light
Can be stored at room temperature (up to 25 °C) for a single period of up to 2 months.

Date removed from refrigerator: _____

Do not re-refrigerate after it has reached room temperature.

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

CSL Behring GmbH
Emil-von-Behring-Strasse 76
35041 Marburg
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1885/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ANDEMBRY 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – MULTIPACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

ANDEMBRY 200 mg solution for injection in pre-filled pen
garadacimab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 200 mg garadacimab in 1.2 mL solution.

3. LIST OF EXCIPIENTS

histidine, arginine monohydrochloride, proline, polysorbate 80, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

3 (3 packs of 1) pre-filled pen

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake.
For single use only.
Read the package leaflet before use.
Subcutaneous use.

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 pen in the outer carton in order to protect from light
Can be stored at room temperature (up to 25 °C) for a single period of up to 2 months.

Date removed from refrigerator: _____

Do not re-refrigerate after it has reached room temperature.

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

CSL Behring GmbH
Emil-von-Behring-Strasse 76
35041 Marburg
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1885/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ANDEMBRY 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON - MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

ANDEMBRY 200 mg solution for injection in pre-filled pen
garadacimab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 200 mg garadacimab in 1.2 mL solution.

3. LIST OF EXCIPIENTS

histidine, arginine monohydrochloride, proline, polysorbate 80, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled pen

Component of a multipack, cannot be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake.
For single use only.
Read the package leaflet before use.
Subcutaneous use.

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 pen in the outer carton in order to protect from light.
Can be stored at room temperature (up to 25 °C) for a single period of up to 2 months.

Date removed from refrigerator: _____

Do not re-refrigerate after it has reached room temperature.

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

CSL Behring GmbH
Emil-von-Behring-Strasse 76
35041 Marburg
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1885/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ANDEMBRY 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL – PRE-FILLED PEN

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

ANDEMBRY 200 mg
solution for injection
garadacimab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1.2 mL

6. OTHER

Read the package leaflet before use

CSL Behring GmbH
Emil-von-Behring-Strasse 76
35041 Marburg
Germany

B. PACKAGE LEAFLET

Package leaflet: Information for the user

ANDEMBRY 200 mg solution for injection in pre-filled syringe
garadacimab

▼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 ANDEMBRY is and what it is used for

ANDEMBRY contains the active substance garadacimab.

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

HAE is a condition that causes recurrent episodes of rapid swelling, known as HAE attacks, in different parts of the body, including the

- hands and feet;
- face, eyelids, lips or tongue
- voice-box (larynx) and throat, which may make breathing difficult;
- genitals;
- stomach and gut

HAE attacks may be painful and disabling. Attacks that affect your throat or larynx may be dangerous or even life threatening.

HAE often runs in families, but some people may not have a family history. Three types of HAE are known, based on the type of genetic defect and its effect on a protein that circulates in your blood, named C1 esterase inhibitor (C1-INH). A person can have low levels of C1-INH in the body (type I HAE), poorly functioning C1-INH (type II HAE), or HAE with normal functioning C1-INH (type III HAE). The last type is extremely rare. All three types produce the same clinical symptoms of localized swelling.

C1-INH regulates a process in the body that controls the production of an inflammatory substance called bradykinin. Overproduction of bradykinin causes swelling and inflammation in people with HAE.

The active substance in ANDEMBRY, garadacimab, blocks the activation of a protein known as factor XIIa (FXIIa), which is involved in stimulating bradykinin production. By blocking FXIIa activity, garadacimab reduces the level of bradykinin, thereby preventing HAE attacks. Some subcategories of normal C1-INH HAE may not respond to treatment with garadacimab. Talk to your doctor if you have any concerns about your medicine.

2. What you need to know before you use ANDEMBRY

Do not use ANDEMBRY

- if you are allegic to garadacimab or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

- Talk to your doctor, pharmacist or nurse before using ANDEMBRY.
- If you have a severe allergic reaction to ANDEMBRY with symptoms such as hives, tight chest, difficulty breathing, wheezing, hypotension or anaphylaxis, tell your doctor, pharmacist or nurse **immediately**.
- Treat a hereditary angioedema attack with your regular rescue medicine without taking additional doses of ANDEMBRY.

Keeping a record

It is strongly recommended that every time you have a dose of ANDEMBRY, you write down the name and batch number of the medicine. This is so that you keep a record of the batches used.

Laboratory tests

Tell your doctor if you are using ANDEMBRY before you have laboratory tests to measure how well your blood is clotting. This is because ANDEMBRY may interfere with some laboratory tests, leading to inaccurate results.

Children and adolescents

ANDEMBRY is not recommended for use in children under 12 years of age. This is because it has not been studied in this age group.

Other medicines and ANDEMBRY

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

ANDEMBRY is not known to affect other medicines or be affected by other medicines.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before starting ANDEMBRY. There is limited information on the safety of ANDEMBRY use during pregnancy and breast-feeding. As a precaution, it is preferable to avoid the use of ANDEMBRY during pregnancy. Your doctor will discuss with you the risks and benefits of taking this medicine.

Driving and using machines

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

ANDEMBRY contains proline

This medicine contains 19.3 mg of proline in each pre-filled syringe which is equivalent to 16.1 mg/mL. Proline may be harmful for patients with hyperprolinaemia, a rare genetic disorder in which proline builds up in the body. If you (or your child) have hyperprolinaemia, do not use this medicine unless your doctor has recommended it.

ANDEMBRY contains polysorbate 80

This medicine contains 0.24 mg of polysorbate 80 in each pre-filled syringe which is equivalent to 0.2 mg/mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use ANDEMBRY

ANDEMBRY is provided in single-use pre-filled syringes with a needle safety device. Your treatment will be started under the supervision of and managed by a healthcare provider.

Always use this medicine exactly as described in this leaflet or as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure or have any further questions on the use of this medicine.

How much ANDEMBRY to use

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.

How to inject ANDEMBRY

You can self-inject ANDEMBRY or a caregiver can inject it. In both cases, you or your caregiver must carefully read and follow the instructions in section 7, "Instructions for Use".

- ANDEMBRY is for injection under the skin ('subcutaneous injection') in the tummy (abdomen), thigh or upper arm.
- A doctor, pharmacists or nurse should show you how to inject ANDEMBRY properly before you use it for the first time. Do not self-inject or allow a caregiver to inject you until you have been trained to inject the medicine.
- Use each pre-filled syringe only once.
- If the pre-filled syringe with needle safety device does not perform as intended, tell your doctor, pharmacist or nurse as soon as possible.
- Rotation of the injection site is recommended.

If you take more ANDEMBRY than you should

Tell your doctor, pharmacist or nurse if you take too much ANDEMBRY.

If you forget to use ANDEMBRY

If you miss a dose of ANDEMBRY, inject your dose as soon as possible. If you are not sure when to inject ANDEMBRY after a missed dose, ask your doctor, pharmacist or nurse.

If you stop using ANDEMBRY

It is important that you keep injecting ANDEMBRY as instructed by your doctor even if you feel better.
If you have any further questions about 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.
Tell your doctor, pharmacist or nurse if you notice any of the following side effects.

Common (may affect up to 1 in 10 people)

- Injection site reactions including redness, bruising, itchiness, and urticaria
- Headache
- Abdominal pain

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 national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store ANDEMBRY

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 outer carton and label 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 in order to protect from light.

The pre-filled syringe may be stored at room temperature (up to 25 °C) for a single period of up to 2 months, but not beyond the expiry date.

Do not return ANDEMBRY to refrigerated storage after storage at room temperature.

Do not use this medicine if you notice signs of deterioration such as particles or changed colour of the solution.

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 ANDEMBRY contains

- The active substance is garadacimab. Each pre-filled syringe contains 200 mg of garadacimab in 1.2 ml solution.

- The other ingredients are histidine, arginine monohydrochloride, proline, polysorbate 80 and water for injections – see section 2 “ANDEMBRY contains proline and polysorbate 80”.

What ANDEMBRY looks like and contents of the pack

ANDEMBRY is presented as a slightly opalescent to clear, brownish-yellow to yellow solution for injection in a pre-filled syringe.

ANDEMBRY is available as a single pack containing one pre-filled syringe and in multipacks of 3 cartons, each containing 1 pre-filled syringe.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
CSL Behring GmbH
Emil-von-Behring-Strasse 76
D-35041 Marburg
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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CSL Behring NV
Tél/Tel: +32 15 28 89 20

България
МагнаФарм България ЕАД
Тел: +359 2 810 3949

Česká republika
CSL Behring s.r.o.
Tel: +420 702 137 233

Danmark
CSL Behring AB
Tlf: +46 8 544 966 70

Deutschland
CSL Behring GmbH
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CentralPharma Communications OÜ
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España
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Hrvatska

Lietuva
CentralPharma Communications UAB
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Tel.: +48 22 213 22 65

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Sverige
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This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

7. Instructions for Use

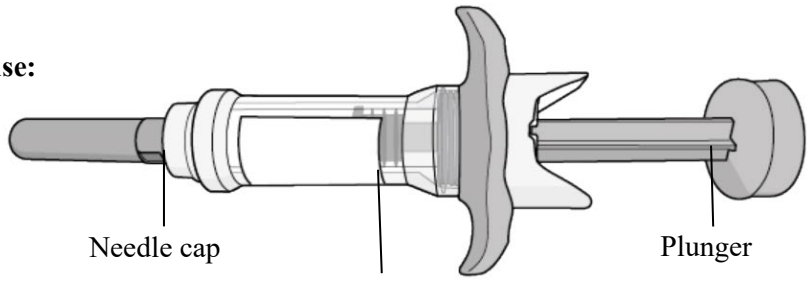
ANDEMBRY solution for injection in pre-filled syringe
Subcutaneous use

Important:

This pre-filled syringe works differently than other injection devices. Read the Instructions for Use carefully before using it, and each time you get a new pre-filled syringe. There may be new information. This information does not replace talking to your healthcare provider about your medical condition or treatment. In adolescent patients, ANDEMBRY should be given under the supervision of an adult.
Make sure you have been trained by your healthcare provider before you use this pre-filled syringe for the first time.

Parts of the pre-filled syringe (see **Figure A):**

Before use:



After use:

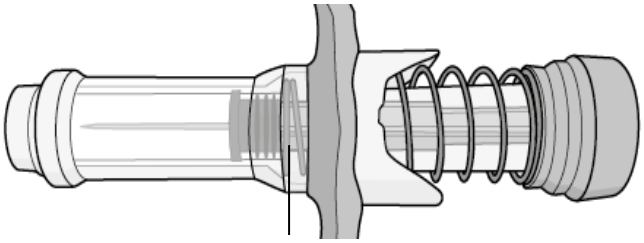


Figure A

Read the following safety information:

- Keep the pre-filled syringe in its original carton box until use, to protect it from light.
- **Do not** remove the needle cap until you are ready to inject the medicine.
- **Do not** recap the pre-filled syringe.
- **Do not** reuse the same pre-filled syringe. The pre-filled syringe contains 1 dose and is for single-use only.
- The pre-filled syringe is for subcutaneous (under the skin) injection only.
- **Do not** use the pre-filled syringe if it looks damaged, has cracks, is leaking medicine, or has been dropped. In these cases throw away the pre-filled syringe and use a new one.
- **Do not** inject the pre-filled syringe through clothing.
- **Keep ANDEMBRY out of reach of children.**

How should I store ANDEMBRY?

- Store in a refrigerator, between 2˚C to 8˚C, in its original carton until use, to protect it from light.
- **Do not** freeze. If the pre-filled syringe has been frozen, **do not** use the pre-filled syringe even if it is thawed.
- The refrigerated pre-filled syringe may be used until the expiry date printed on the label.
- Take the pre-filled syringe out of the refrigerator 30 minutes before use, allowing it to reach room temperature.

Alternative storage (room temperature):

- If needed, for example when traveling, the pre-filled syringe may be stored at room temperature (up to 25˚C) for a single period of up to 2 months, but not beyond the expiry date.
- If you decide to store the pre-filled syringe at room temperature:
    - In the space provided on the carton box, write the date that you first removed the pre-filled syringe from the refrigerator to help you keep track of how long it has been stored at room temperature.
    - **do not** put the pre-filled syringe back in the refrigerator after it has reached room temperature.
    - throw away the pre-filled syringe if it has been stored at room temperature for longer than 2 months.

Supplies needed for the pre-filled syringe injection (see **Figure B):**
Included in the carton box:

- 1 pre-filled syringe

Required but not included:

- Alcohol pad
- Cotton ball or gauze pad
- Sharps container or puncture-resistant container for disposal (see **Step 12. Disposing of the Syringe**)

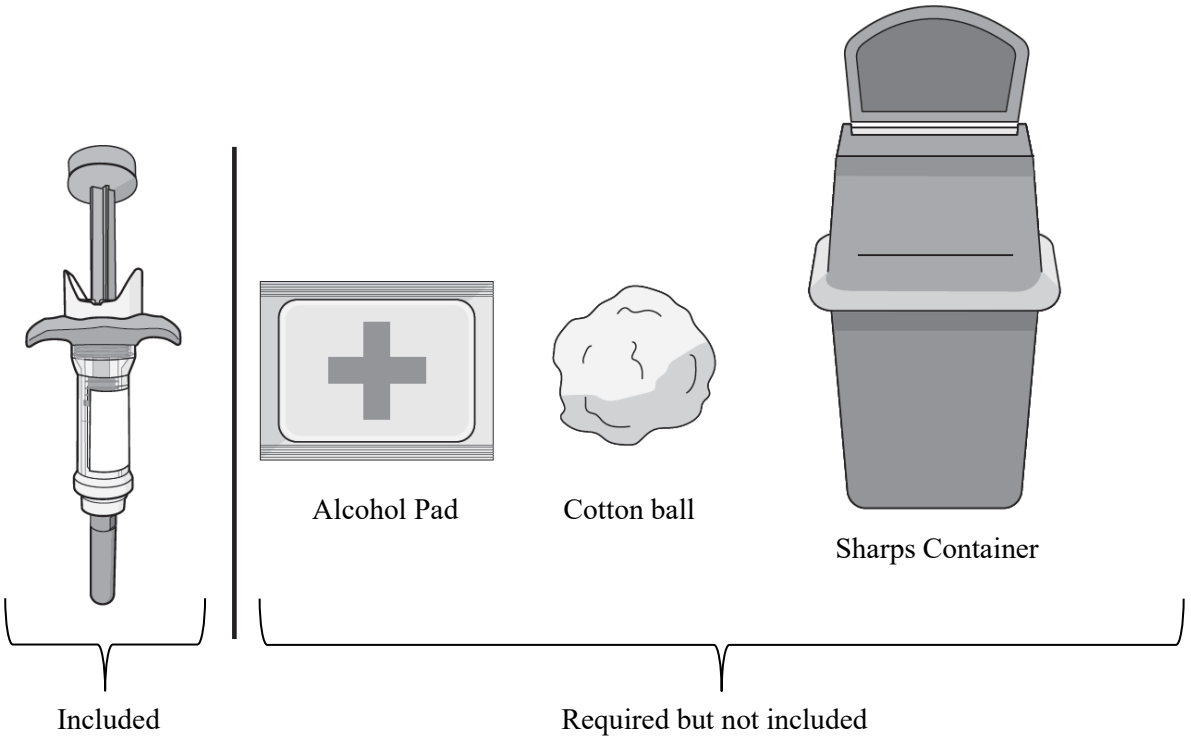


Figure B

Preparing for an Injection

Step 1. Let the pre-filled syringe reach room temperature

- Remove the pre-filled syringe from the carton box and place it on a **clean flat surface**.
- **Do not** remove the pre-filled 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 C**).
- 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 pre-filled syringe, run hot water over it, or leave it in direct sunlight.

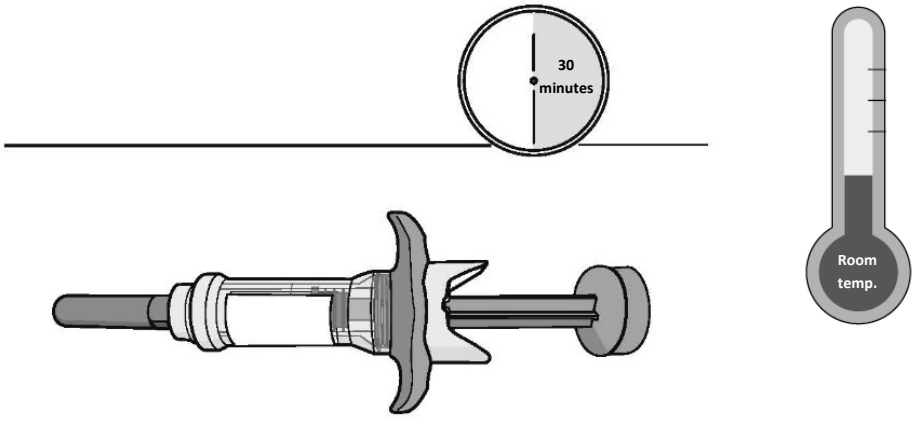


Figure C

Step 2. Check the expiry date

- Check the expiry date on the pre-filled syringe (see **Figure D**).
- **Do not use** the pre-filled syringe if the expiry date has passed.
- **Do not use** the pre-filled syringe if it has been stored at room temperature for longer than 2 months.
- If the expiry date has passed or the syringe has been stored at room temperature for longer than 2 months, then safely dispose of the pre-filled syringe and take a new one (see **Step 12. Disposing of the syringe**).

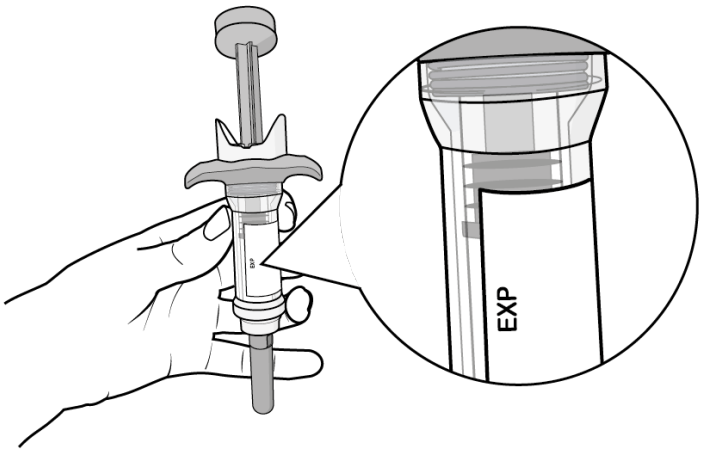


Figure D

Step 3. Inspect the pre-filled syringe

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

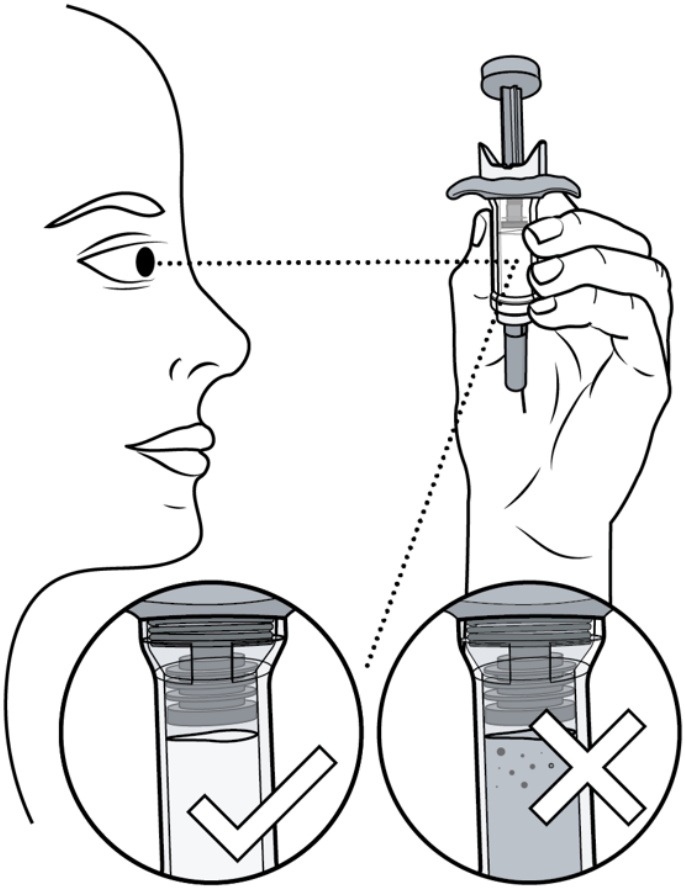


Figure E

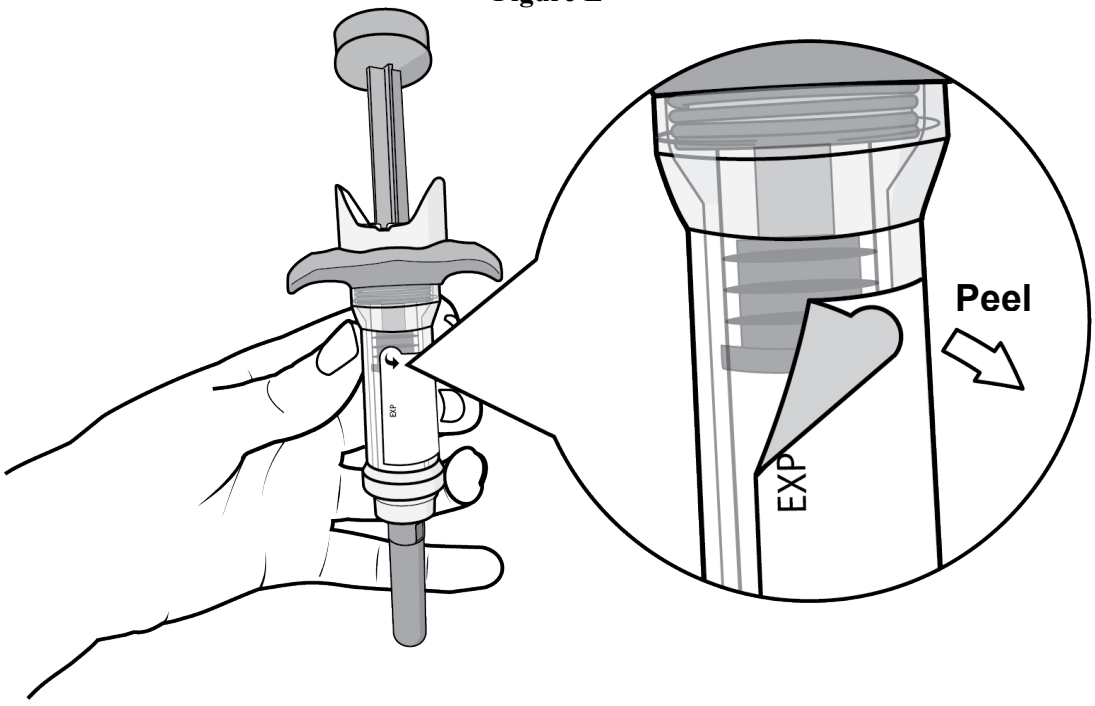


Figure F

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 G**).

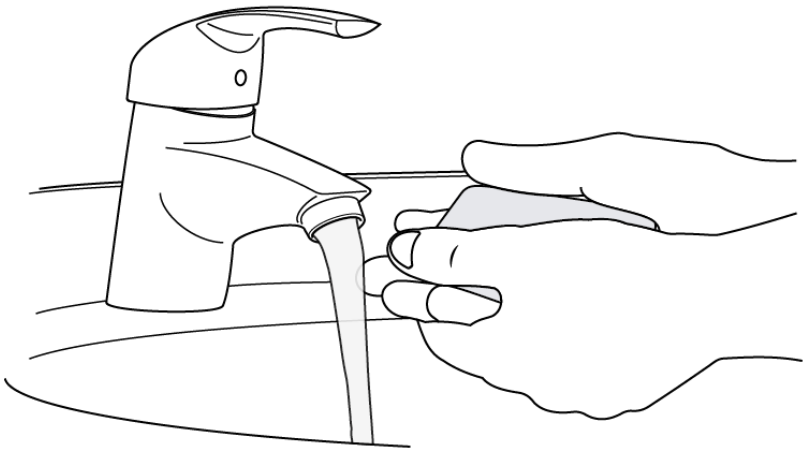


Figure G

Step 5. Select the injection site

- Inject into the thigh or belly (abdomen) area, but stay 2 cm away from the belly button (navel) (see **Figure H**).
- If somebody else (like a caregiver) gives you the injection, you can also use the upper arm.
- Rotate your injection sites. **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 into areas where the skin is tender, red, hard, or injured.

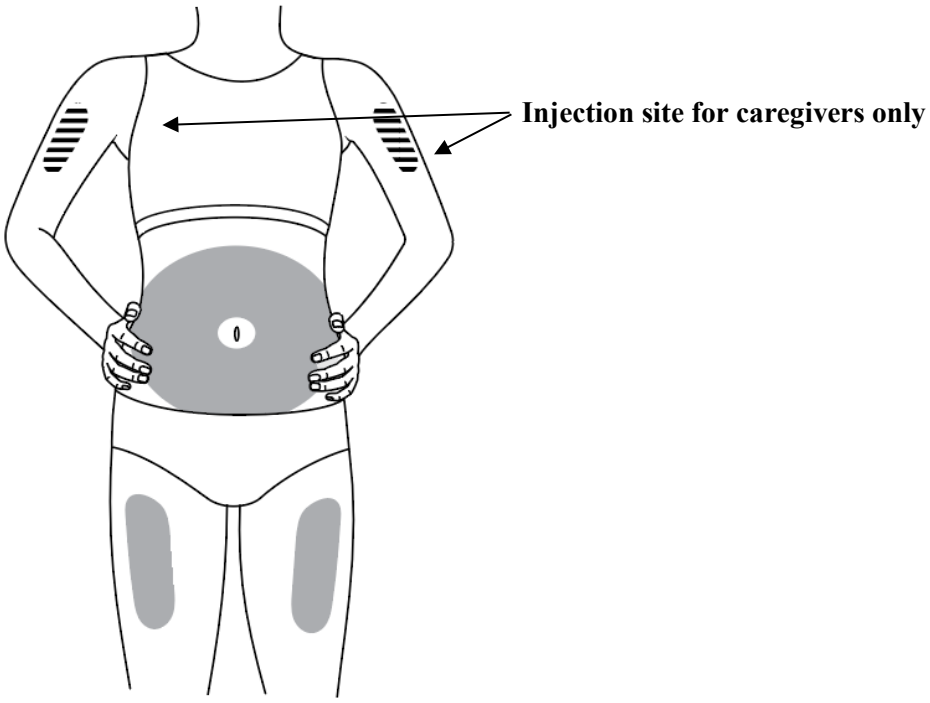


Figure H

Step 6. Prepare the injection site

- Clean the injection site with an alcohol pad in a circular motion (see **Figure I**).
- 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.

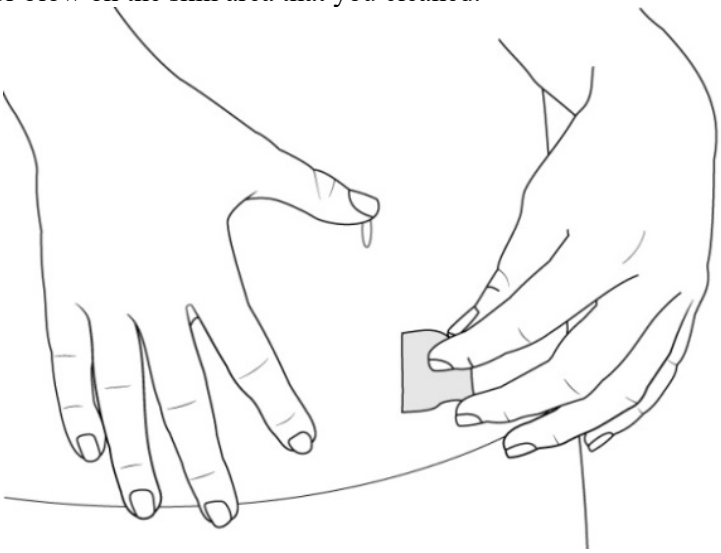


Figure I

<u>Injecting the medicine with the pre-filled syringe</u>

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 pre-filled syringe by the body, with the needle facing away from you.
- **Pull the needle cap straight off** with one hand while holding the pre-filled syringe with the other hand (see **Figure J**). 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 pre-filled syringe.
- Dispose of the needle cap in a sharps container or puncture resistant 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.

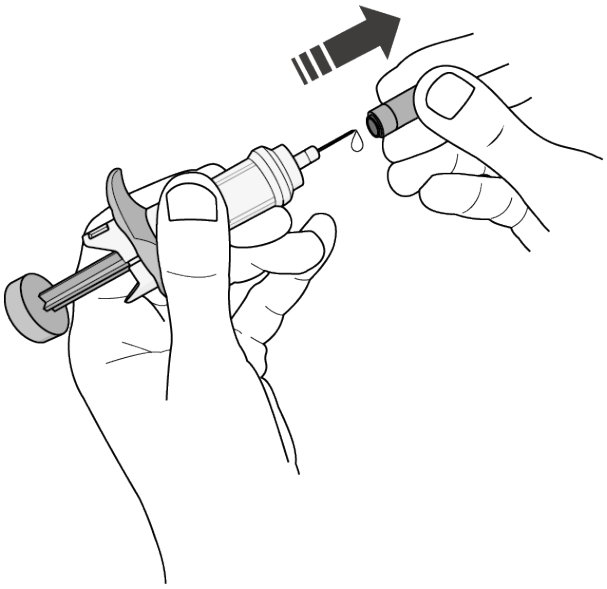


Figure J

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 K**).
- Fully insert the needle at an angle between 45˚ and 90˚. **Do not** change the angle during the injection. (see **Figure K**: images show an example of injection at a 90˚ angle).
- **Do not hold or push on the plunger while inserting the needle into the skin.**

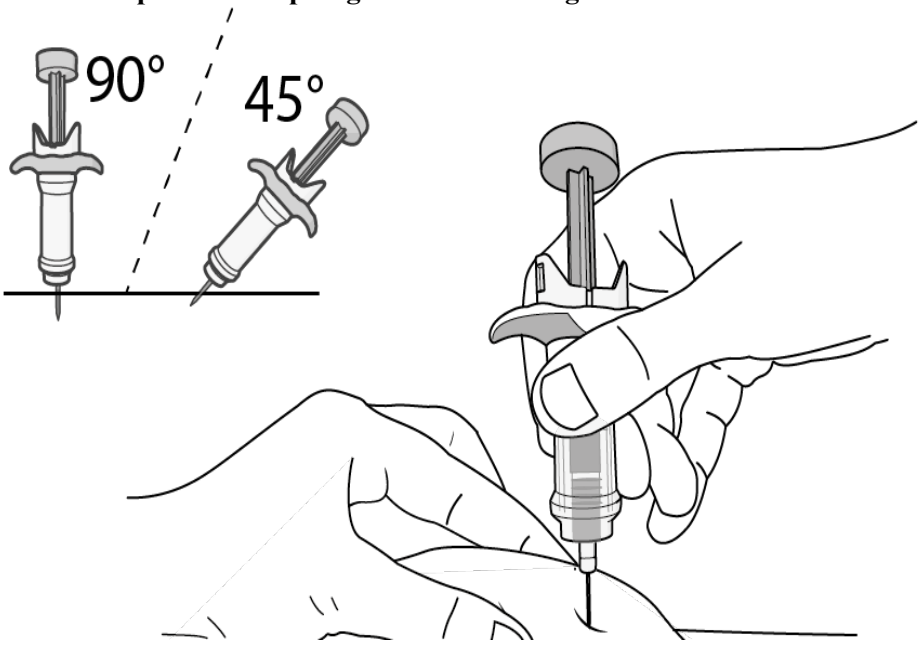


Figure K

Step 9. Inject medicine

- Hold the pre-filled syringe in place and inject all of the medicine by firmly **pushing the plunger all the way down** (see **Figure L**).
- Press the plunger all the way down until it stops to get the full dose. Push firmly on the plunger until the end of the injection (See **Figure M**).

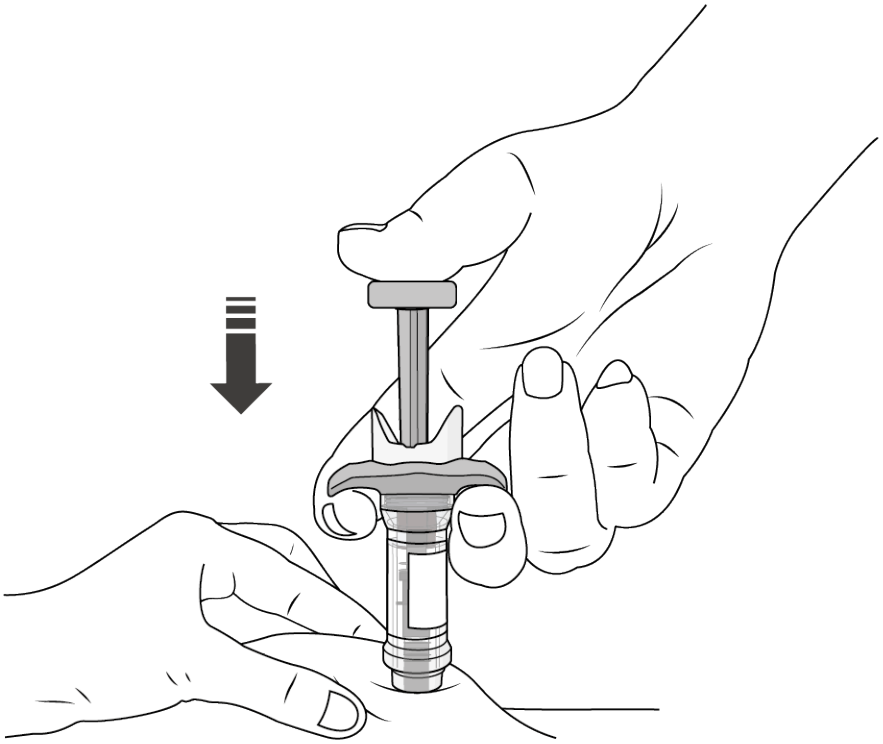


Figure L

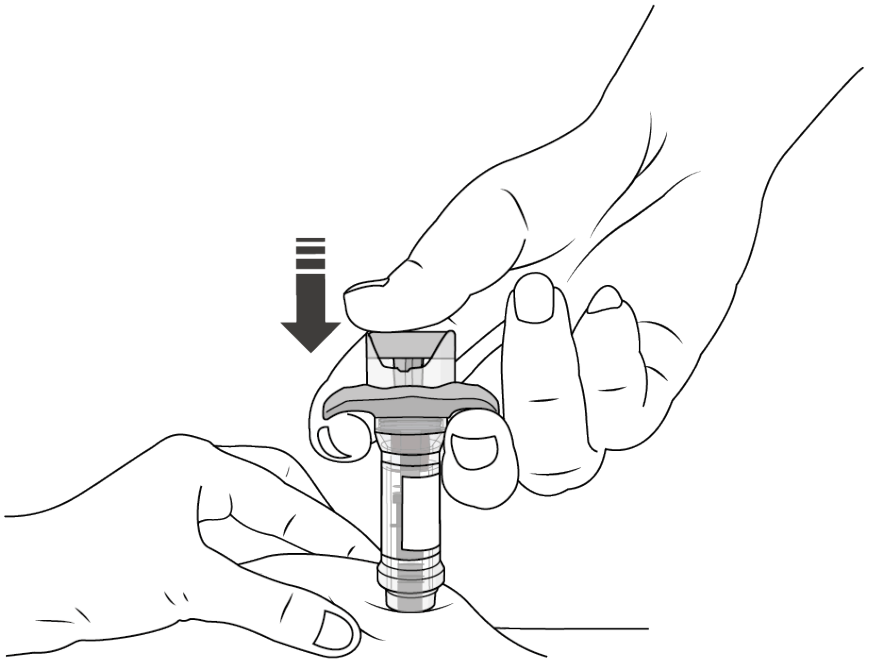


Figure M

Step 10. Release plunger

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

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

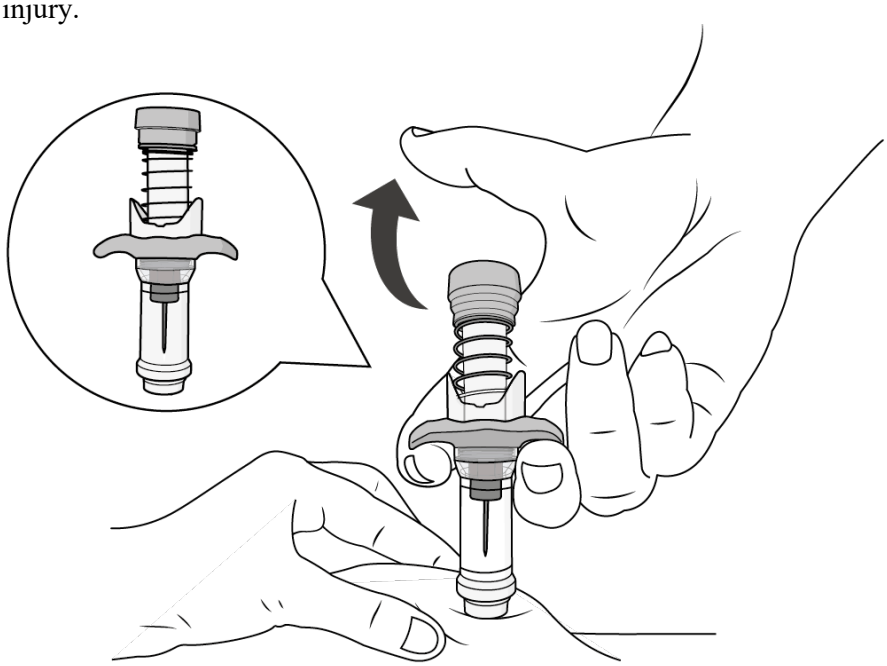


Figure N

Step 11. Release the pinch and remove the pre-filled syringe

- Release the pinch around the skin and remove the pre-filled syringe from the injection site (see **Figure O**).

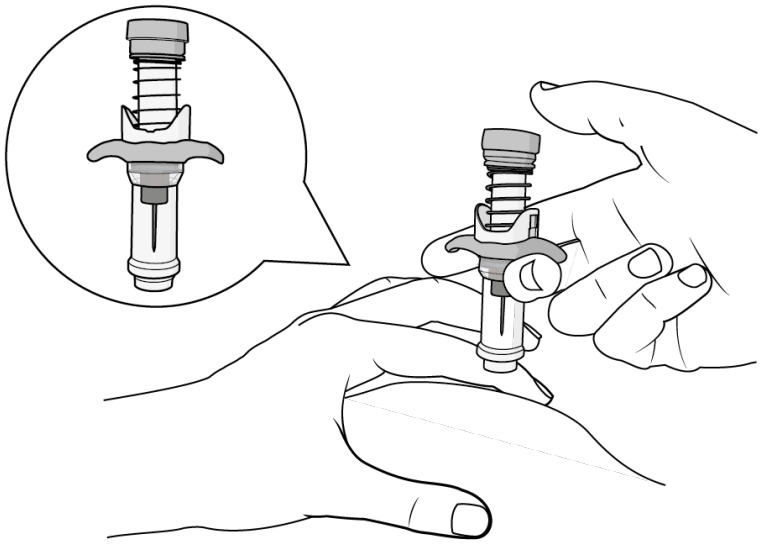


Figure O

- 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 pre-filled syringe.
- After injecting the dose, put the syringe into a sharps disposal container or closed puncture-resistant container (see **Figure P).**

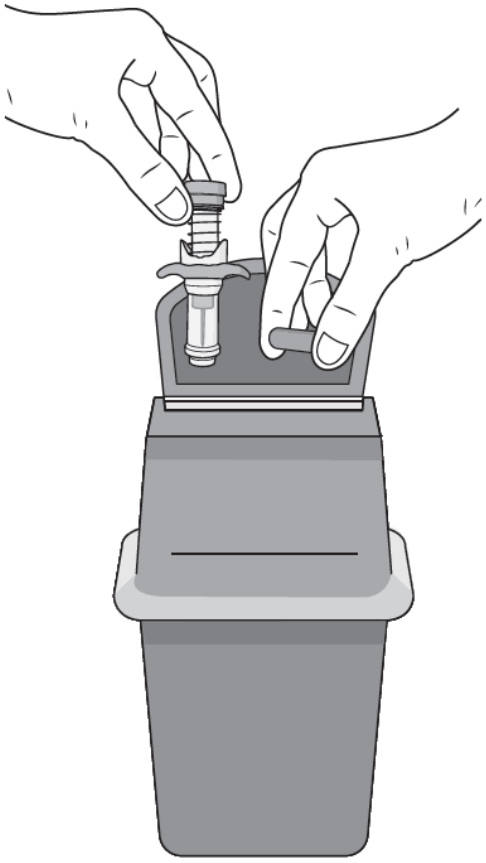


Figure P

- If you do not have a sharps disposal container or closed puncture-resistant container, you may use a household container that is:
    - Made of heavy-duty plastic
    - Can be closed with a tight-fitting, puncture-resistant lid, to keep sharps safely inside
    - 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. Ask your pharmacist / healthcare provider for more information on how to dispose of your sharps container.
- **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.

Package leaflet: Information for the user
ANDEMBRY 200 mg solution for injection in pre-filled pen
garadacimab

▼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 ANDEMBRY is and what it is used for

ANDEMBRY contains the active substance garadacimab.

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

HAE is a condition that causes recurrent episodes of swelling, known as HAE attacks, in different parts of the body, including the:

- hands and feet;
- face, eyelids, lips or tongue;
- voice-box (larynx) and throat, which may make breathing difficult;
- genitals;
- stomach and gut.

HAE attacks may be painful and disabling. Attacks that affect your throat or larynx may be dangerous or even life threatening.

HAE is a condition that often runs in families, but some people may not have a family history. Three types of HAE are known, based on the type of genetic defect and its effect on a protein that circulates in your blood, named C1 esterase inhibitor (C1-INH). A person can have low levels of C1-INH in the body (type I HAE), poorly functioning C1-INH (type II HAE), or HAE with normal functioning C1-INH (type III HAE). The last type is extremely rare. All three types produce the same clinical symptoms of localized swelling.

C1-INH regulates a process in the body that controls the production of an inflammatory substance called bradykinin. Overproduction of bradykinin causes swelling and inflammation in people with HAE.

The active substance in ANDEMBRY, garadacimab, blocks the activation of a protein known as factor XIIa (FXIIa), which is involved in stimulating bradykinin production. By blocking FXIIa activity, garadacimab reduces the level of bradykinin, thereby preventing HAE attacks. Some subcategories of normal C1-INH HAE may not respond to treatment with garadacimab. Talk to your doctor if you have any concerns about your medicine.

2. What you need to know before you use ANDEMBRY

Do not use ANDEMBRY

If you are allegic to garadacimab or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

- Talk to your doctor, pharmacist or nurse before using ANDEMBRY.
- If you have a severe allergic reaction to ANDEMBRY with symptoms such as hives, tight chest, difficulty breathing, wheezing, hypotension or anaphylaxis, tell your doctor, pharmacist or nurse **immediately**.
- Treat a hereditary angioedema attack with your regular rescue medicine without taking additional doses of ANDEMBRY.

Keeping a record

It is strongly recommended that every time you have a dose of ANDEMBRY, you write down the name and batch number of the medicine. This is so that you keep a record of the batches used.

Laboratory tests

Tell your doctor if you are using ANDEMBRY before you have laboratory tests to measure how well your blood is clotting. This is because ANDEMBRY may interfere with some laboratory tests, leading to inaccurate results.

Children and adolescents

ANDEMBRY is not recommended for use in children under 12 years of age. This is because it has not been studied in this age group.

Other medicines and ANDEMBRY

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.
ANDEMBRY is not known to affect other medicines or be affected by other medicines.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before starting ANDEMBRY. There is limited information on the safety of ANDEMBRY use during pregnancy and breast-feeding. As a precaution, it is preferable to avoid the use of ANDEMBRY during pregnancy.Your doctor will discuss with you the risks and benefits of taking this medicine.

Driving and using machines

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

ANDEMBRY contains proline

This medicine contains 19.3 mg of proline in each pre-filled pen which is equivalent to 16.1 mg/mL. Proline may be harmful for patients with hyperprolinaemia, a rare genetic disorder in which proline builds up in the body. If you (or your child) have hyperprolinaemia, do not use this medicine unless your doctor has recommended it.

ANDEMBRY contains polysorbate 80

This medicine contains 0.24 mg of polysorbate 80 in each pre-filled pen which is equivalent to 0.2 mg/mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use ANDEMBRY

ANDEMBRY is provided in a single-use pre-filled pen. Your treatment will be started and managed under the supervision of a healthcare provider.

Always use this medicine exactly as described in this leaflet or as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure or have any further questions on the use of this medicine.

How much ANDEMBRY to use

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 every month.

How to inject ANDEMBRY

You can self inject ANDEMBRY or a caregiver can inject it for you. In both cases, you or your caregiver must carefully read and follow the instructions in section 7, "Instructions for Use".

- ANDEMBRY is for injection under the skin ('subcutaneous injection') in the tummy (abdomen), thigh or upper arm.
- A doctor, pharmacists or nurse should show you how to inject ANDEMBRY properly before you use it for the first time. Do not self-inject or allow a caregiver to inject youuntil you have been trained to inject the medicine.
- Use each pre-filled pen only once.
- If the pre-filled pen does not perform as intended, tell your doctor, pharmacist or nurse as soon as possible.
- Rotation of the injection site is recommended.

If you take more ANDEMBRY than you should

Tell your doctor, pharmacist or nurse if you take too much ANDEMBRY.

If you forget to use ANDEMBRY

If you miss a dose of ANDEMBRY, inject your dose as soon as possible. If you are not sure when to inject ANDEMBRY after a missed dose, ask your doctor, pharmacist or nurse.

If you stop using ANDEMBRY

It is important that you keep injecting ANDEMBRY as instructed by your doctor even if you feel better.
If you have any further questions about 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.

Tell your doctor, pharmacist or nurse if you notice any of the following side effects.

Common (may affect up to 1 in 10 people)
- Injection site reactions including redness, bruising, itchiness, and urticaria
- Headache
- Abdominal pain

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 national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store ANDEMBRY

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 outer carton and label 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 pen in the outer carton in order to protect from light.

The pre-filled pen may be stored at room temperature (up to 25 °C) for a single period of up to 2 months, but not beyond the expiry date.

Do not return ANDEMBRY to refrigerated storage after storage at room temperature.

Do not use this medicine if you notice signs of deterioration such as particles or changed color of the solution.

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 ANDEMBRY contains

- The active substance is garadacimab. Each pre-filled pen contains 200 mg of garadacimab in 1.2 ml solution.
- The other ingredients are histidine, arginine monohydrochloride, proline, polysorbate 80 and water for injections – see section 2 “ANDEMBRY contains proline and polysorbate 80”.

What ANDEMBRY looks like and contents of the pack

ANDEMBRY is presented as a slightly opalescent to clear, brownish-yellow to yellow solution for injection in a pre-filled pen.

ANDEMBRY is available as a single pack containing one 1.2 ml pre-filled pen and in multipacks of 3 cartons, each containing 1 pre-filled pen.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

CSL Behring GmbH
Emil-von-Behring-Strasse 76
D-35041 Marburg
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

7. Instructions for Use

ANDEMBRY solution for injection in pre-filled pen subcutaneous use

Important:

This pre-filled pen works differently than other injection devices. Read the Instructions for Use carefully before using it, and each time you get a new pre-filled pen. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

In adolescent patients ANDEMBRY should be given under the supervision of an adult.
Make sure you have been trained by your healthcare provider before you use this pre-filled pen for the first time.

Parts of the pre-filled pen (see **Figure A**):

Continue to next sections to prepare and perform the injection.

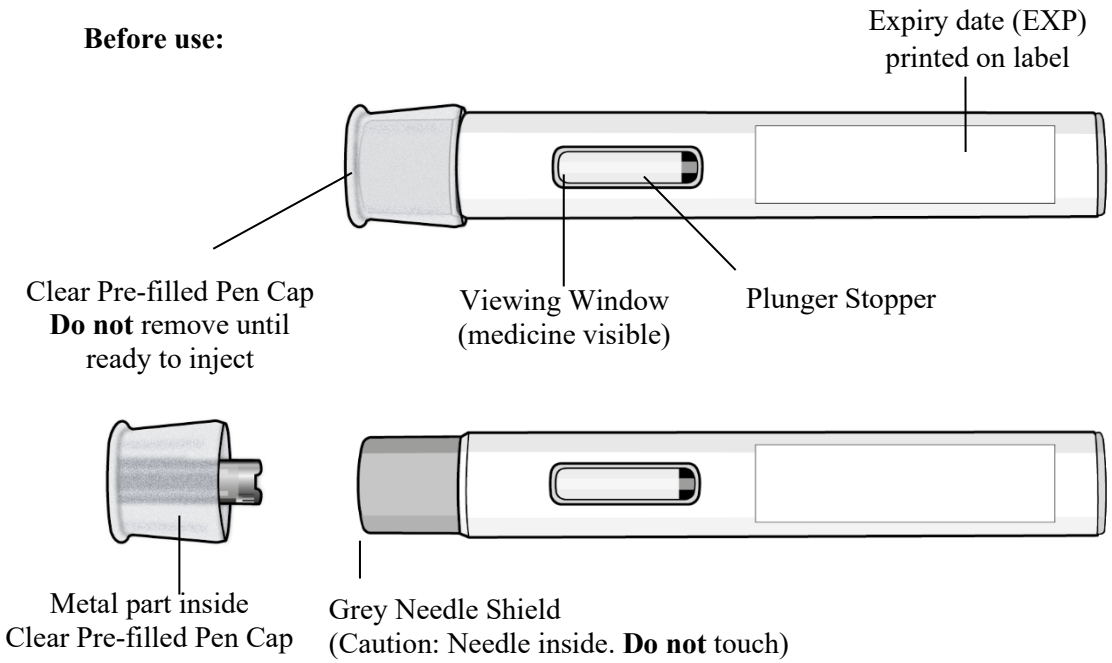


Figure A

Read the following safety information:

- Keep the pre-filled pen in its original carton box until use, to protect it from light.
- **Do not** remove the clear pre-filled pen cap until you are ready to inject.
- **Do not** put the clear pre-filled pen cap back on the pre-filled pen after it has been removed because this could start the injection and cause injury.

- The pre-filled pen contains 1 dose and is for single-use only. **Do not** try to reuse the same pre-filled pen.
- **Do not** use the pre-filled pen if the expiry date has passed.
- The pre-filled pen is for subcutaneous (under the skin) injection only.
- **Do not** use the pre-filled pen if it looks damaged, has cracks, is leaking medicine, or has been dropped. In these cases, throw away the pre-filled pen as described in **Step 11** and use a new one.
- **Do not** inject through clothing.
- **Do not** touch or try to remove the grey needle shield at any time.
- **Keep ANDEMBRY out of reach of children.**

Contact your healthcare provider if you have any questions.

How should I store ANDEMBRY?
- Store ANDEMBRY pre-filled pen in a refrigerator, between 2 ˚C to 8 ˚C in its original carton until use, to protect it from light.
- Do not freeze. If the pre-filled pen has been frozen, **do not** use the pre-filled pen even if it is thawed.
- Take the pre-filled pen out of the refrigerator 30 minutes before use, allowing it to reach room temperature.

Alternative storage (room temperature)
- If needed, for example when traveling, the pre-filled pen may be stored at room temperature (up to 25˚C) for a single period of up to 2 months, but not beyond the expiry date.
- If you decide to store the pre-filled pen at room temperature:
    - In the space provided on the carton box, write the date you first removed the pre-filled pen from the refrigerator to help you keep track of how long it has been stored at room temperature.
    - **do not** put the pre-filled pen back in the refrigerator after it has reached room temperature.
    - throw away the pre-filled pen if it has been stored at room temperature for longer than 2 months (see **Step 11. Disposing of the pre-filled pen**).

Supplies needed for your pre-filled pen injection (see **Figure B)**:
Included in the carton box:
- 1 Single-dose pre-filled pen

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 **Step 11. Disposing of the pre-filled pen**)

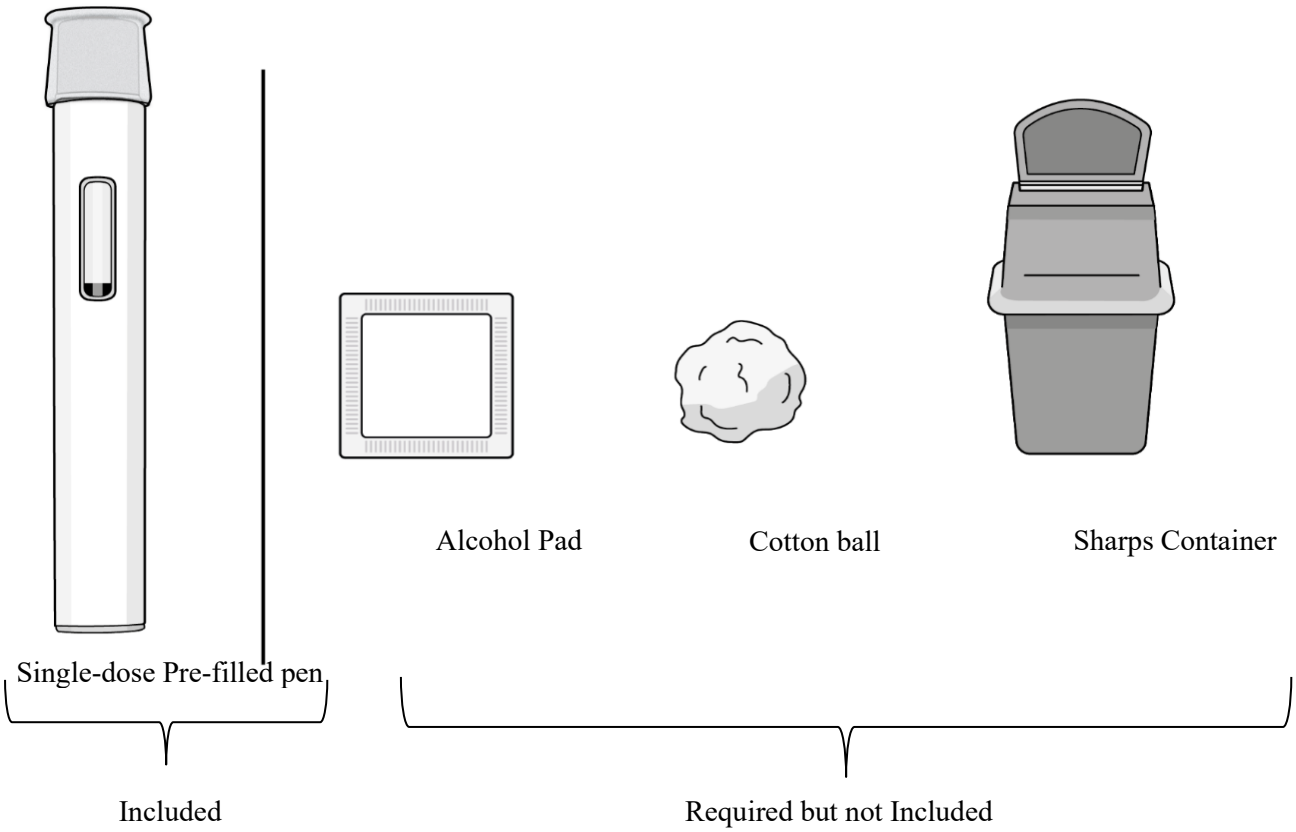


Figure B

Preparing for an Injection

Do not remove the clear pre-filled pen cap until immediately before the injection.

Step 1. Let the pre-filled pen reach room temperature

- Remove the pre-filled 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 C**).
- 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.

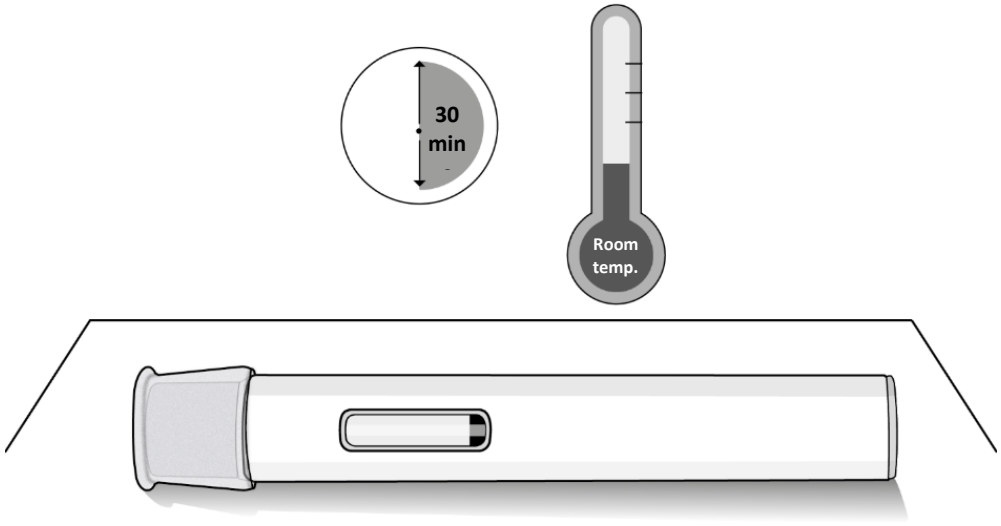


Figure C

Step 2. Check the expiry date

- Check the expiry date on the pre-filled pen label (see **Figure D**).
- **Do not use** the pre-filled pen if the expiry date has passed.
- **Do not use** the pre-filled pen if it has been stored at room temperature for longer than 2 months.
- If the expiry date has passed or if stored at room temperature for longer than 2 months, then safely dispose of the pre-filled pen and take a new one (see **Step 11. Disposing of the pre-filled pen**).

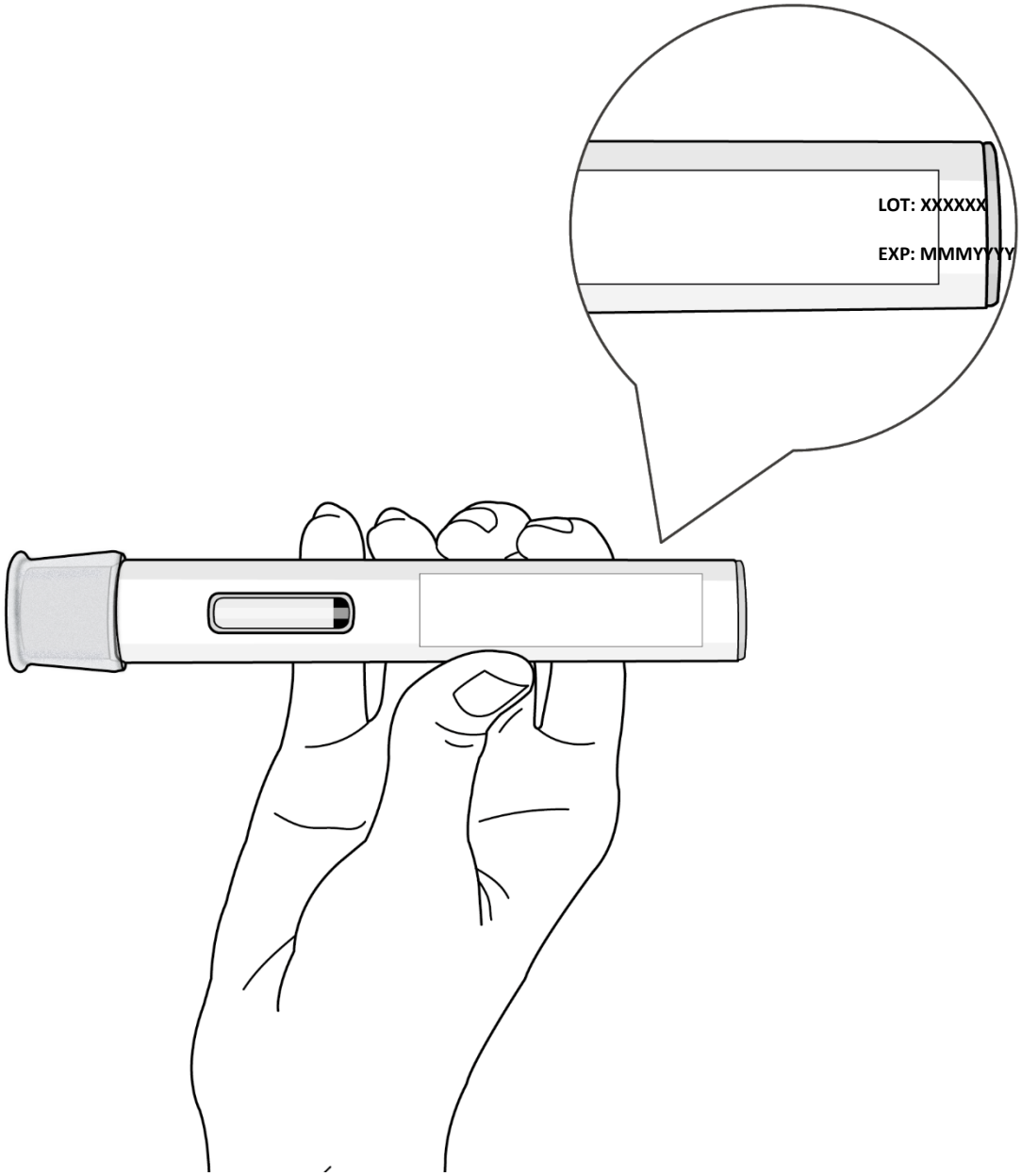


Figure D

Step 3. Inspect the pre-filled pen and the medicine

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

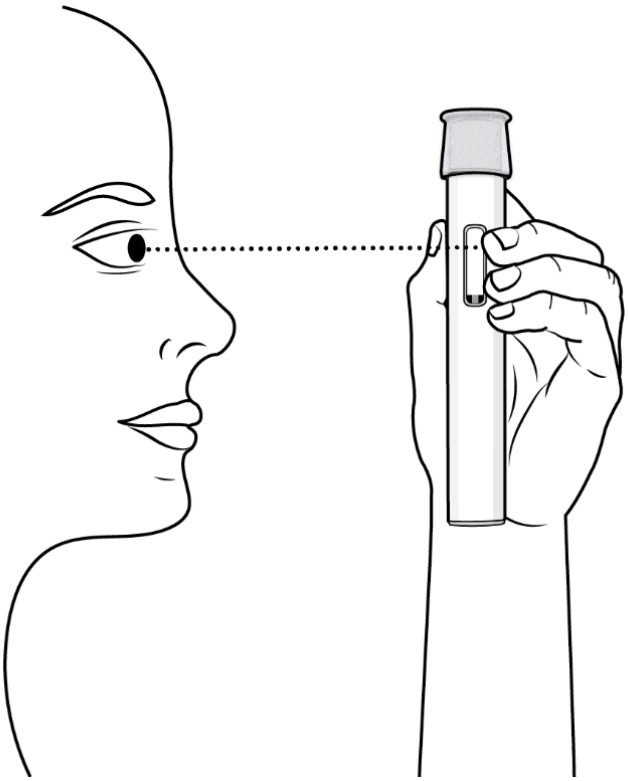


Figure E

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 F**).

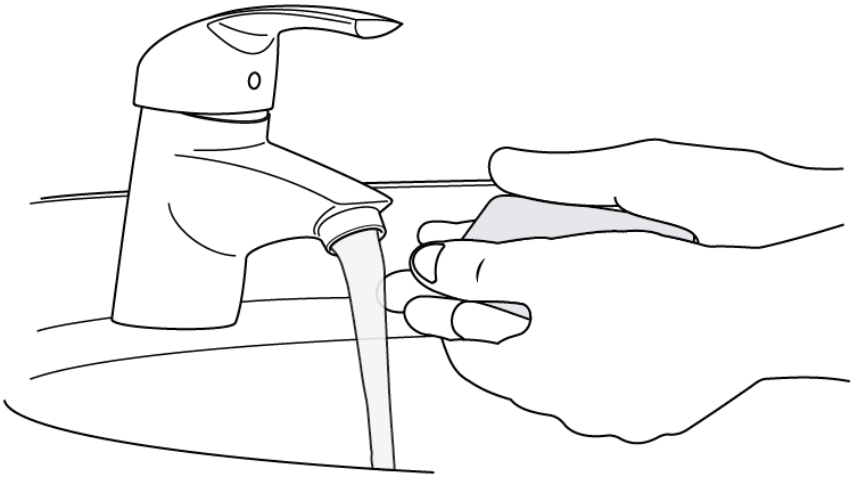


Figure F

Step 5. Select the injection site

- Inject into the **thigh or belly (abdomen) area**, but stay 2 cm away from the belly button (navel) (see **Figure G**)
- 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 site with each injection. **Do not inject** in the same place multiple times if the skin is damaged.
- **Do not** inject into the belly button, moles, scars or bruises, or into areas where the skin is tender, red, hard, or injured.

Self-injection sites

Caregiver Injection sites

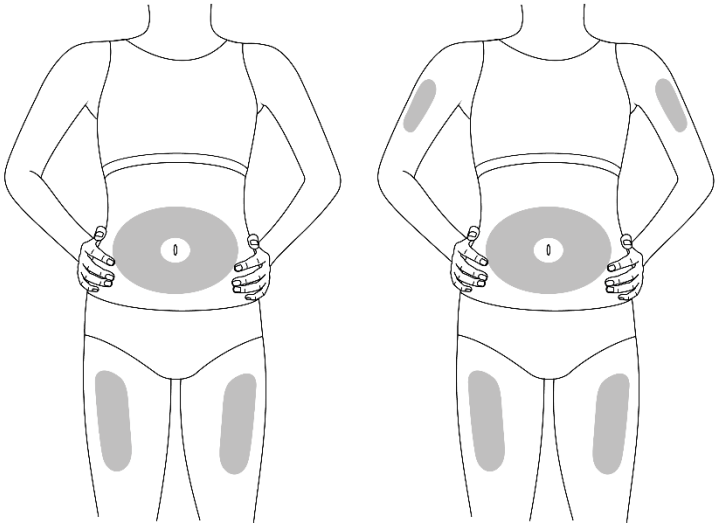


Figure G

Step 6. Prepare the injection site

- Clean the injection site with an alcohol pad (see **Figure H**).
- 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.

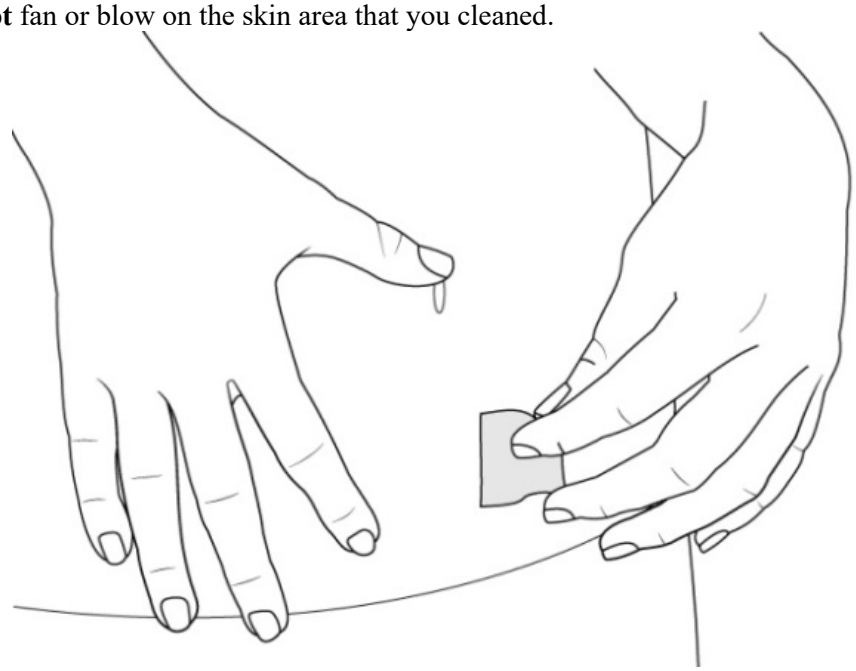


Figure H

<u>Injecting the Medicine with the Pre-filled pen</u>

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 pre-filled pen cap and dispose of the cap

- Hold the pre-filled pen with one hand and **pull the clear pre-filled pen cap straight off** with the other hand.
- **Do not** twist the Clear Cap, (see **Figure I**). 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 or closed puncture-resistant container.

Important:

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

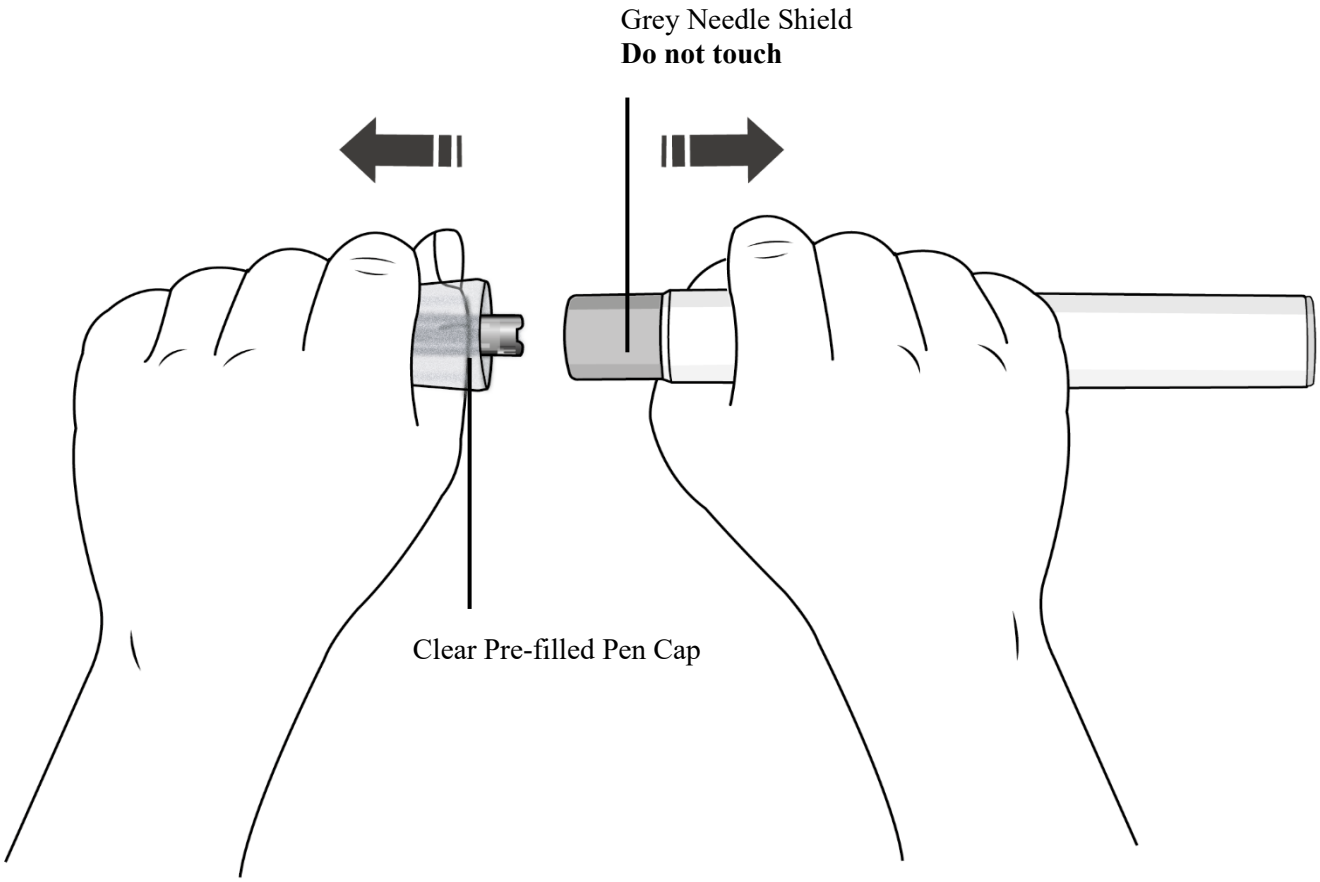


Figure I

Step 8. Pinch the skin and place the pre-filled pen on the injection site
Immediately after removing the clear pre-filled 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 J**).
- Place the pre-filled pen at a 90˚ angle on the cleaned injection site (see **Figure J**).
- **Make sure you can see the viewing window.**

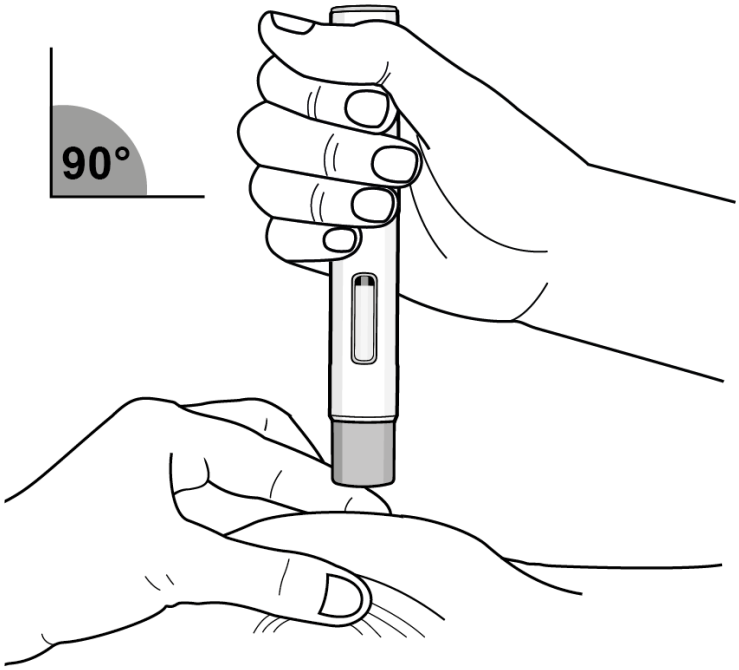


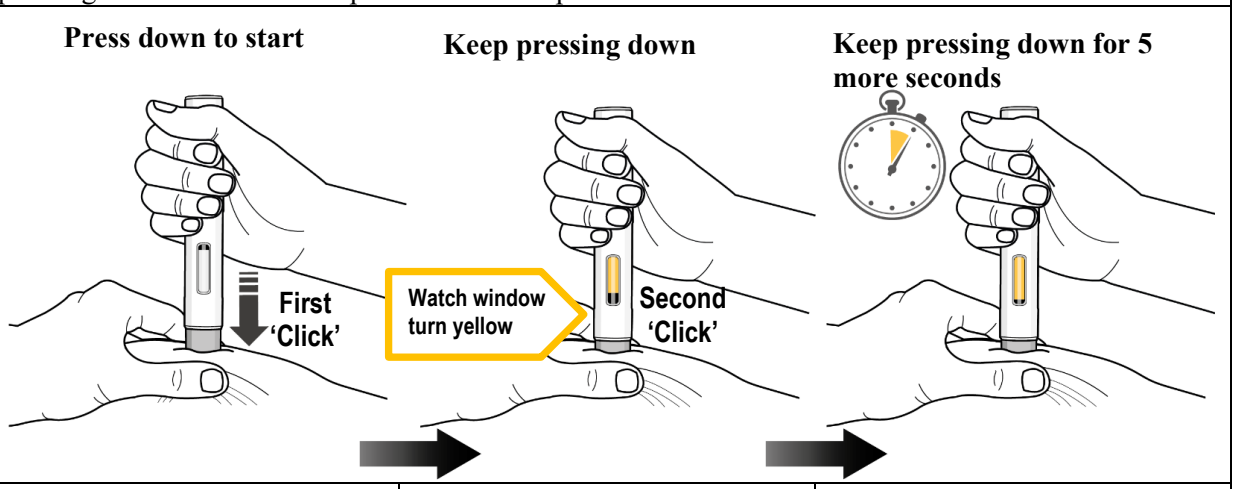
Figure J

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

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 pre-filled 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 grey 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 pre-filled pen down.	**Keep pressing** the pre-filled pen down and **watch the viewing window.** • The window will turn yellow and • You will hear a **Second 'click'.** **Keep pressing** the pre-filled pen down.	**Keep pressing** the pre-filled pen **down** for **5 more seconds to make sure you get the full dose.**

Figure K

- **Do not** remove the pre-filled 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 pre-filled pen during the injection.**

Step 10. Release the pinch and remove the pre-filled pen

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

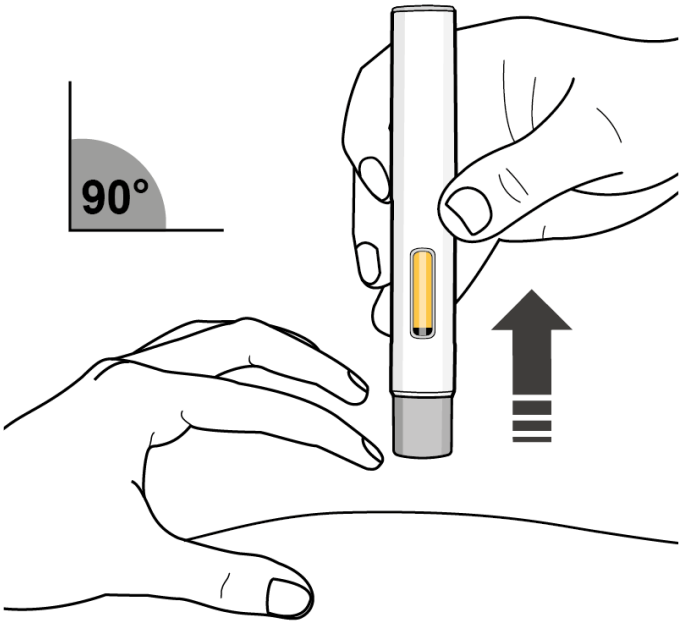


Figure L

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 pre-filled pen

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

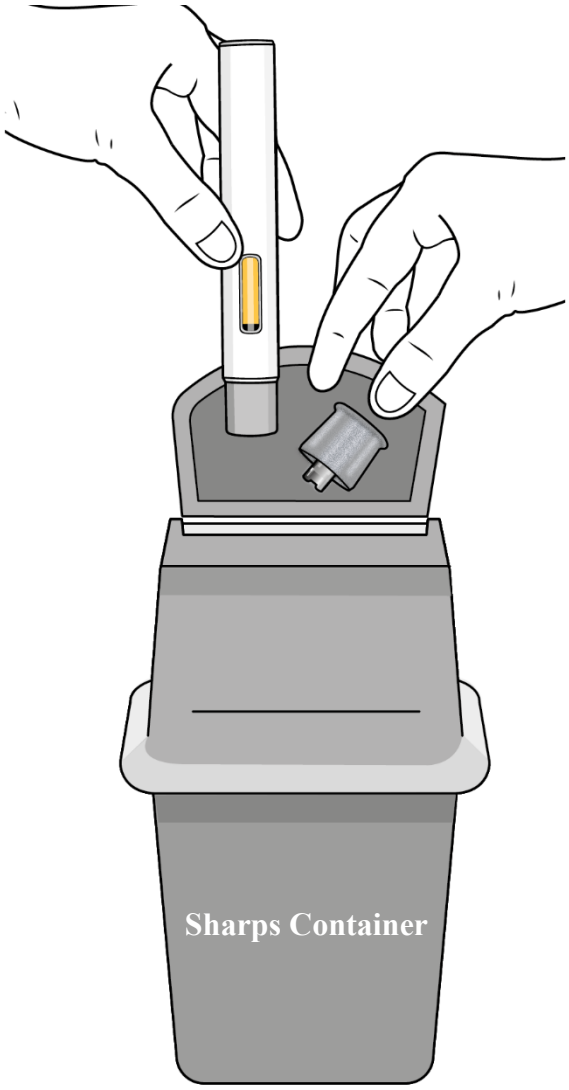


Figure M

- If you do not have a sharps container or closed puncture resistant 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. Ask your pharmacist / healthcare provider for more information on how to dispose of your sharps container.
- **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.