PROFESSIONAL INFORMATION

WARNING: THROMBOTIC MICROANGIOPATHY and THROMBOEMBOLISM

Cases of thrombotic microangiopathy and thrombotic events were reported when on average a cumulative amount of >100 U/kg/24 hours of activated prothrombin complex concentrate was administered for 24 hours or more to patients receiving Hemlibra prophylaxis. Monitor for the development of thrombotic microangiopathy and thrombotic events if activated prothrombin complex concentrate (aPCC) is administered. Discontinue aPCC and suspend dosing of Hemlibra if symptoms occur.

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

Hemlibra® 30 mg/1 mL solution for injection

Hemlibra® 60 mg/0,4 mL solution for injection

Hemlibra® 105 mg/0,7 mL solution for injection

Hemlibra® 150 mg/1 mL solution for injection

Sugar free.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Hemlibra contains emicizumab as the active substance.

Hemlibra 30 mg/1 mL solution for injection: Each vial of 1 mL contains 30 mg of emicizumab at a concentration of 30 mg/mL.

Hemlibra 60 mg/0,4 mL solution for injection: Each vial of 0,4 mL contains 60 mg of emicizumab at a concentration of 150 mg/mL.

Hemlibra 105 mg/0,7 mL solution for injection: Each vial of 0,7 mL contains 105 mg of emicizumab at a concentration of 150 mg/mL.

Hemlibra 150 mg/1 mL solution for injection: Each vial of 1 mL contains 150 mg of emicizumab at a concentration of 150 mg/mL.

For the full list of excipients, see section 6.1.

Hemlibra is a humanised monoclonal modified immunoglobulin G4 (IgG4) antibody produced using recombinant DNA technology in mammalian Chinese Hamster Ovary (CHO) cells.

3 PHARMACEUTICAL FORM

Hemlibra is a colourless to slightly yellow solution.

Hemlibra solution for injection vials are for single-use only.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hemlibra is indicated for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in adults and children with haemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors.

There are limited data in infants less than 1 year of age.

4.2 Posology and method of administration

General

Treatment should be initiated under the supervision of a medical practitioner experienced in the treatment of haemophilia and/or bleeding disorders.

Posology

Treatment with bypassing agents should be discontinued 24 hours before starting Hemlibra therapy (see section 4.4). Factor VIII (FVIII) prophylaxis may be continued for the first 7 days of Hemlibra treatment.

Recommended dosage (all patients)

The recommended loading dose is 3 mg/kg administered as a subcutaneous injection once weekly for the first 4 weeks, followed by a maintenance dose from week 5 of either:

- 1,5 mg/kg once weekly, or
- 3 mg/kg every two weeks, or
- 6 mg/kg every four weeks

The maintenance dose regimen should be selected based on the medical practitioner and patient/caregiver dosing regimen preference to support adherence.

Method of administration

Hemlibra solution is a sterile, preservative-free, and ready to use solution for subcutaneous injection that does not need to be diluted.

Hemlibra solution should be inspected visually to ensure there is no particulate matter or discolouration prior to administration.

Hemlibra is for subcutaneous use only. Hemlibra should be administered using appropriate aseptic technique (see section 6.6).

The injection should be restricted to the recommended injection sites: the abdomen, the upper outer arms and the thighs (see section 5.1). No data are available on injection at other sites of the body.

Administration of Hemlibra subcutaneous injection in the upper outer arm should be performed by a trained caregiver or healthcare professional.

Alternating the site of injection may help prevent or reduce injection site reactions (see section 4.8). Hemlibra subcutaneous injection should not be administered into areas where the skin is red, bruised, tender or hard, or areas where there are moles or scars.

During treatment with Hemlibra, other medicinal products for subcutaneous administration should, preferably, be injected at different anatomical sites.

A 1 mL syringe should be used for an injection up to 1 mL of Hemlibra solution. Administer doses of Hemlibra greater than 1 mL and up to 2 mL with a 2 mL or 3 mL syringe.

Recommended criteria for syringes, needles and vial adaptor are defined to ensure correct and safe administration of Hemlibra. These criteria are based on handling considerations (e.g. dosing accuracy, subcutaneous injection), Hemlibra characteristics (e.g. viscosity), and compatibility between Hemlibra and device materials.

Administration by the patient and/or caregiver:

Hemlibra is intended for use under the guidance of a healthcare professional. After proper training in subcutaneous injection technique, a patient may self-inject Hemlibra, or the patient's caregiver may administer Hemlibra, if their medical practitioner determines that it is appropriate, see Patient Instructions for Use below.

The medical practitioner and the caregiver should determine the appropriateness of the child self-injecting Hemlibra. However, self-administration is not recommended for children below 7 years of age.

Duration of treatment

Hemlibra is intended for long-term prophylactic treatment.

Dosage adjustments during treatment

No dosage adjustments of Hemlibra are recommended.

Delayed or missed doses

If a patient misses a scheduled weekly subcutaneous injection of Hemlibra, the patient should be instructed to take the missed dose as soon as possible, approximately 24 hours before the next scheduled dose. The patient should then administer the next dose on the usual scheduled dosing day. The patient should not take two doses on the same day to make up for a missed dose.

Patient: Instructions for Use.

Hemlibra Injection - Single-Dose Vial(s)

Using either the TRANSFER NEEDLE WITH FILTER, TRANSFER NEEDLE, VIAL ADAPTOR or VIAL ADAPTOR WITH FILTER option

You must read, understand and follow the Instructions for Use before injecting Hemlibra. Your healthcare professional should show you how to prepare, measure, and inject Hemlibra properly before you use it for the first time. Ask your healthcare professional if you have any questions.

Important Information:

Do not use these instructions when using a Vial Adapter to withdraw Hemlibra from the vial. These instructions are for use with the Transfer Needle only.

- **Do not** inject yourself or someone else unless you have been shown how to by your healthcare professional.
- Make sure the name Hemlibra appears on the box and vial label.
- Before opening the vial, read the vial label to make sure you have the correct medicine strength(s) needed to give the dose prescribed by your healthcare professional. Depending on your dose, you may need to use more than 1 vial to give yourself the correct dose.
- Check the expiry date on the box and vial label. **Do not** use if the expiry date has passed.
- **Only use the vial once.** After you inject your dose, dispose of (throw away) any unused Hemlibra left in the vial. Do not save unused medicine in the vial for later use.
- **Only use the syringes, transfer needles with filter or transfer needles or vial adaptors and vial adaptors with filter, and injection needles that your healthcare professional prescribes**.
- **Use the syringes, transfer needles with filter or transfer needles or vial adaptors or vial adaptors with filter and injection needles only once. Dispose of (throw away) any used caps, vials, syringes and needles.**

- If your prescribed dose is more than 2 mL, you will need to have more than one subcutaneous injection of Hemlibra; contact your healthcare professional for the appropriate injection instructions.

You must inject Hemlibra only under the skin.

Storing Hemlibra vials:

- Keep the vial in the refrigerator (2°C to 8°C). **Do not** freeze.
- Keep the vial in the original box to protect the medicine from light.
- Once removed from the refrigerator, the unopened vial can be kept at room temperature (below 30°C) for up to 7 days. After storage at room temperature unopened vials may be returned to the refrigerator. The total amount of time outside cold storage and at room temperature should not exceed 7 days.
- Discard vials that have been kept at room temperature for more than 7 days or have been in temperatures above 30°C.
- Keep the vials, out of the sight and reach of children.
- Take the vial out of the refrigerator 15 minutes before use and allow it to reach room temperature (below 30°C) before preparing an injection.
- **Do not** shake the vial.

Storing needles and syringes:

- Keep the transfer needle (with or without filter),injection needle and syringe dry.
- Keep the transfer needle (with or without filter), injection needle and syringe out of the sight and reach of children.

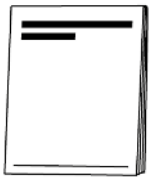
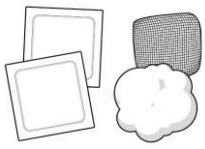
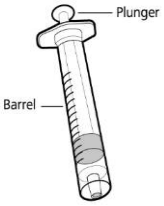
Inspecting the medicine and your supplies

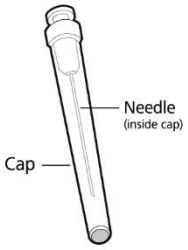
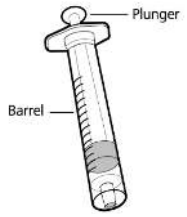
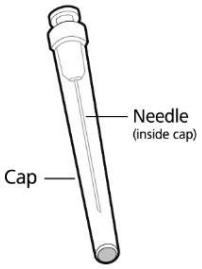
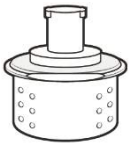
- Collect all supplies listed below to prepare and give your injection.
- Check the expiry date on the box, on the vial label and on the supplies listed below. Do not use if the expiry date has passed.

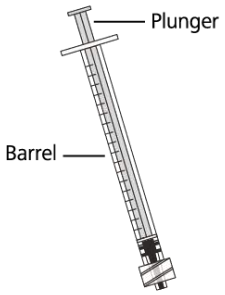
Do not use the vial if:

- the medicine is cloudy, hazy or coloured.
- the medicine contains particles.
- the cap covering the stopper is missing.

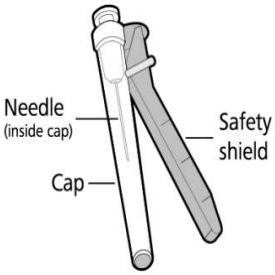
- Inspect the supplies for damage. Do not use if they appear damaged or if they have been dropped.
- Place the supplies on a clean, well-lit flat work surface.

INCLUDED IN THE BOX: 	• Vial containing the medicine
	• Hemlibra instructions for Use
NOT INCLUDED IN THE BOX:	
	• **Alcohol wipes** **Note**: If you need to use more than 1 vial to inject your prescribed dose, you must use a new alcohol wipe for each vial. • **Gauze** • **Cotton Ball**
EITHER 	• **Syringe (For use with transfer needle with filter)** **Note:** For injection amount up to 1 mL use a **1 mL syringe.** For injection amount between 1mL and 2 mL use a **2 mL or 3 mL syringe.** **Note: Do not** use 2 or 3 mL syringe for doses up to 1 mL

	• **18G Transfer needle with 5 micrometre filter** **Note:** If you need to use more than 1 vial to inject your prescribed dose, you must use a new transfer needle with filter for each vial. **Do not** use the transfer needle with filter to inject the medicine.
OR	
	• **Syringe (For use with transfer needle)** **Note:** For injection amount up to 1 mL use a 1 mL syringe. For injection amount between 1mL and 2 mL use a 2 or 3 mL syringe.
	• **18G Transfer Needle** **Note:** If you need to use more than 1 vial to inject your prescribed dose, you must use a new transfer needle for each vial. Do not use the transfer needle to inject medicine.
OR	
	• **Vial adaptor** (To be added on top of vial). **Note:** Used for withdrawing medicine from the vial to the syringe. If you need to use more than 1 vial to inject your prescribed dose, you must use a new vial adaptor for each vial. ⚠ **Do not insert injection needle into vial adaptor.**
OR	
	• **Vial adaptor with filter** (To be added on top of vial). **Note:** Used for withdrawing medicine from the vial to the syringe. If you need to use more than 1 vial to inject your prescribed dose, you must use a new vial



FOR ALL OPTIONS



adaptor for each vial.

⚠ Do not insert injection needle into vial adaptor.

- **Syringe with Low Dead Space (LDS) Plunger**

  Important:

  ○ For injection amount up to 1 mL use a **1 mL LDS syringe**.

  ○ For injection amount over 1 mL use **3 mL LDS syringe**.

  Note: Do not use 3 mL LDS syringe for doses up to 1 mL.

- **Injection Needle with safety shield** (Used to inject medicine)

Transfer needle with filter and transfer needle: Do not use the injection needle to withdraw medicine from vial.

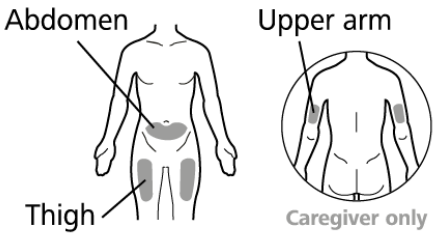
Vial adaptor and vial adaptor with filter: Do not insert the injection needle into the vial adaptor or use the injection needle to withdraw medicine from the vial.

Sharps disposal container

Get Ready:

- Before use, allow the vial(s) to warm up to room temperature for about 15 minutes on a clean flat surface away from direct sunlight.
- **Do not** try to warm the vial by any other way.
- **Wash your hands** well with soap and water.

Selecting and preparing an injection site:



- Clean the chosen injection site area using an alcohol wipe.
- Let the skin dry for about 10 seconds.
- **Do not** touch, fan or blow on the cleaned area before your injection.

For your injection you can use your:

- Thigh (front and middle).
- Stomach area (abdomen), except for 5 cm around the navel (belly button).
- Outer area of the upper arm (only if a caregiver is giving the injection).
- You should use a different injection site each time you give an injection, at least 2,5 cm away from the area you used for any previous injection.
- **Do not** inject into areas that could be irritated by a belt or waistband. Do not inject into moles, scars, bruises, or areas where the skin is tender, red, hard or the skin is broken.

Preparing the syringe for the injection

- **Do not** touch exposed needles or place them on a surface once the cap has been removed.
- Once the syringe has been filled with the medicine, it must be used immediately.
- Once the injection needle cap has been removed, the medicine in the syringe must be injected under the skin within 5 minutes. **Do not** use the syringe if the needle touches any surface.

Important information after the injection

- If you see drops of blood at the injection site, you can press a sterile cotton ball or gauze over the injection site for at least 10 seconds, until bleeding has stopped.

- If you have bruising (small area of bleeding under the skin), an ice pack can also be applied with gentle pressure to the site. If bleeding does not stop, please contact your healthcare professional.
- **Do not** rub the injection site after injection.

Disposing of the medicine and supplies:

Important: Always keep the sharps disposal container out of reach of children.

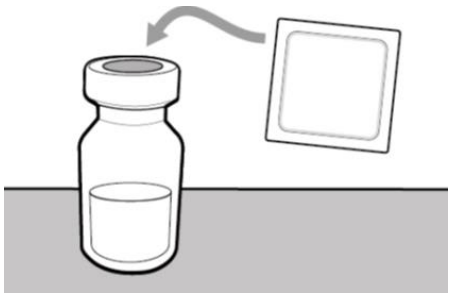
- Throw away any used vial(s), needles or vial adaptors, vial/injection needle caps and used syringes in a sharps or puncture-proof container.
- Put your used needles or vial adaptors and syringes in a sharps disposal container straight away after use. **Do not** dispose of (throw away) any loose needles and syringes in your household waste.
- 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 and stable during use.
    - leak-resistant.
    - properly labelled 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 (throw away) your sharps disposal container.

Do not dispose of (throw away) any used sharps disposal container in your household waste unless your local guidelines permit this. Do not recycle your used sharps disposal container.

1. PREPARATION FOR USE USING THE TRANSFER NEEDLE WITH FILTER OPTION

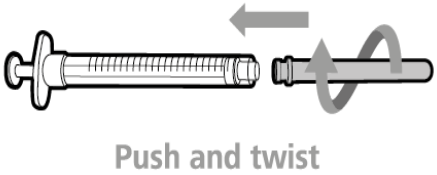
Step 1. Remove vial cap and clean top

- Take the cap off the vial(s).
- Throw away the vial cap(s) into the sharps disposal container.

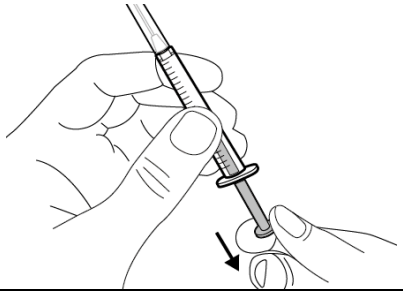


- Clean the top of the vial(s) stopper with an alcohol wipe.

Step 2. Attach transfer needle with filter to syringe

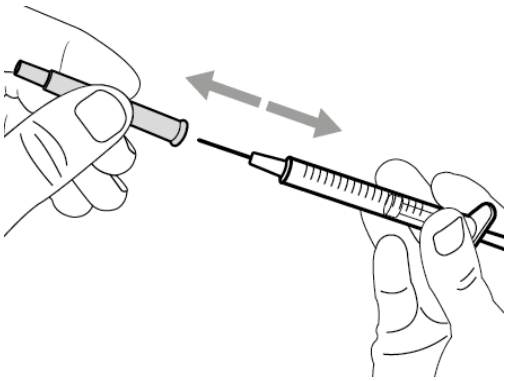


- **Push and twist the transfer needle with filter clockwise** on to the syringe until it is fully attached.



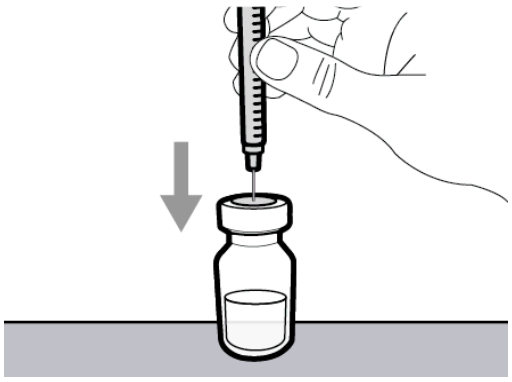
- Slowly pull back on the plunger and draw air into the syringe that is the same amount as your prescribed dose.

Step 3. Uncap transfer needle with filter

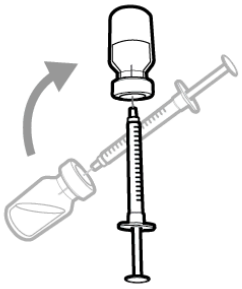


- Hold the syringe by the barrel with the transfer needle with filter pointing up.
- Carefully pull the transfer needle with filter cap straight off and away from your body. **Do not throw the cap away. Place the transfer needle with filter cap down on a clean flat surface.** You will need to recap the transfer needle with filter after transferring the medicine.
- **Do not touch** the needle tip or place it on a surface after the needle cap has been removed.

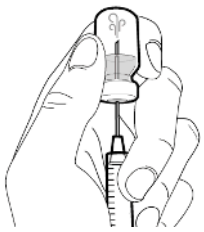
Step 4. Inject air into vial



- Keep the vial on the flat working surface and insert the transfer needle with filter and syringe straight down into the centre of the vial stopper.

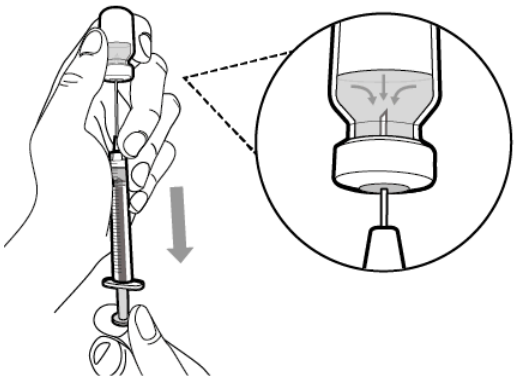


- Keep the needle in the vial and turn the vial upside down.



- With the needle pointing upwards, push on the plunger to inject the air from the syringe **above the medicine.**
- Keep your finger pressed down on the syringe plunger.
- **Do not** inject air into the medicine as this could create air bubbles or foam in the medicine.

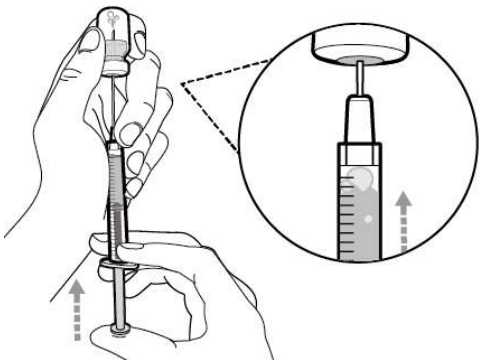
Step 5. Transfer medicine to syringe

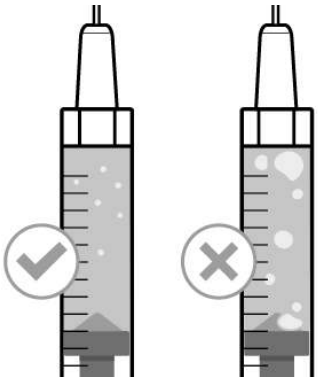


- Slide the tip of the needle down so that it is **within the medicine.**
- With the syringe pointing upwards, slowly pull back the plunger to prevent air bubbles/foam.
  Fill the syringe with more than the amount of medicine needed for your prescribed dose.
- **Hold the plunger firmly** to ensure it does not pull back in.
- Be careful not to pull the plunger out of the syringe.

Important: If your prescribed dose is more than the amount of medicine in the vial, **withdraw all of the medicine** and go to the "**Combining Vials**" section now.

Step 6. Remove air bubbles





- Keep the needle in the vial and check the syringe for larger air bubbles. Large air bubble can reduce the dose you receive.
- **Remove the larger air bubbles** by gently **tapping** the syringe barrel with your fingers until the air bubbles rise to the top of the syringe. Move the tip of the needle **above the medicine** and slowly push the plunger up to push the air bubbles out of the syringe.
- If the amount of medicine in the syringe is now at or below your prescribed dose, move the tip of the needle to **within the medicine** and slowly **pull** back the plunger until you have **more** than the amount of medicine needed for your **prescribed dose.**
- Be careful not to pull the plunger out of the syringe.
- Repeat the steps above until you have

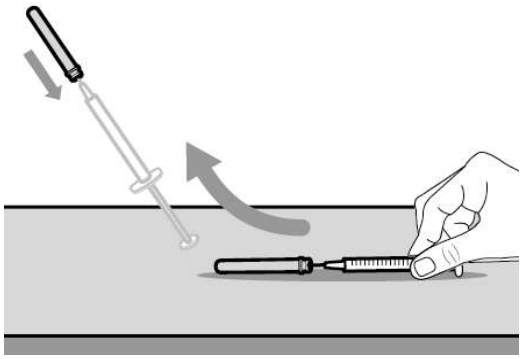
removed the larger air bubbles.

Note: Ensure you have enough medicine in the syringe to complete your dose before moving onto the next step. If you cannot remove all medicine, turn the vial upright to reach the remaining amount.

⚠ **Do not** use the transfer needle with filter to inject medicine as this may cause pain and bleeding.

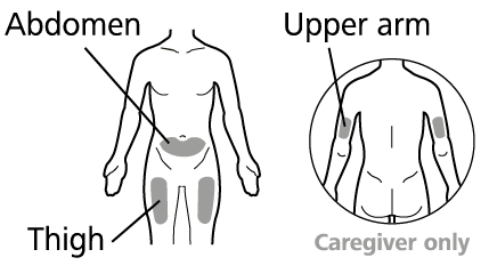
2. INJECTION

Step 7. Recap transfer needle with filter



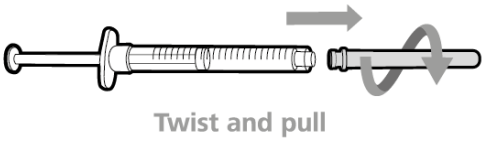
- Remove the syringe and transfer needle with filter from the vial.
- **Using one hand**, **slide** the transfer needle with filter into the cap and **scoop upwards** to cover the needle.
- Once the needle is covered, push the transfer needle with filter cap towards the syringe to fully attach it with **one hand** to prevent accidentally injuring yourself with the needle.

Step 8. Clean injection site



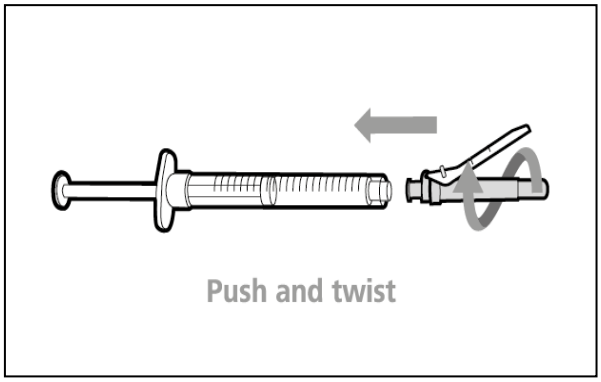
- Select and **clean** your injection site with an alcohol wipe.

Step 9. Remove the used transfer needle With filter from the syringe



- Remove the transfer needle with filter from the syringe by twisting anticlockwise and gently pulling.
- Throw away the used transfer needle with filter into a sharps disposal container.

Step 10. Attach injection needle to syringe

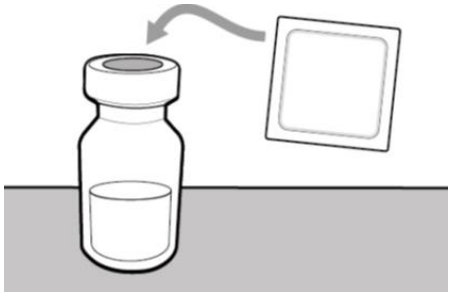


- Push and twist the injection needle clockwise onto the syringe until it is fully attached.

1. PREPARATION FOR USE USING THE TRANSFER NEEDLE OPTION

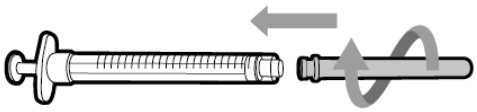
Step 1. Remove vial cap and clean top

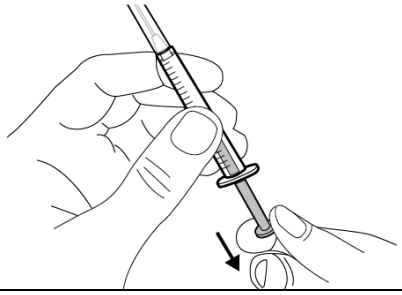
- Take the cap off the vial(s).



- Clean the top of the vial(s) stopper with an alcohol wipe.
- Dispose of (throw away) the vial cap(s) into the sharps disposal container.

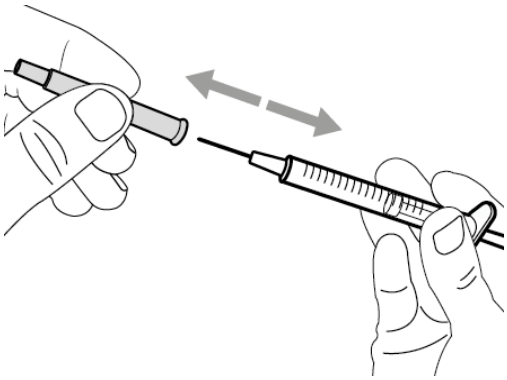
Step 2. Attach transfer needle to syringe





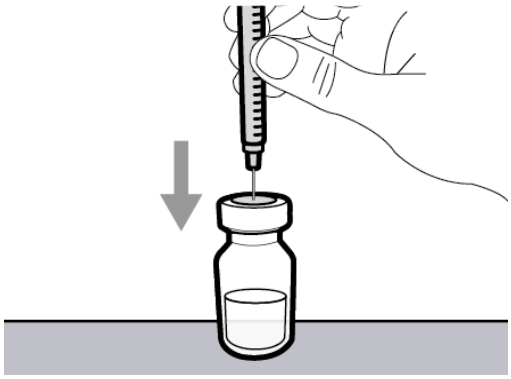
- **Push and twist the transfer needle clockwise** on to the syringe until it is fully attached.
- Slowly pull back on the plunger and draw air into the syringe that is the same amount for your prescribed dose.

Step 3. Uncap transfer needle

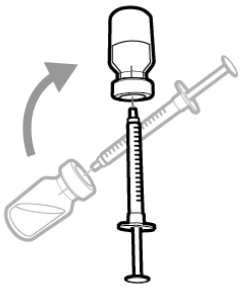


- Hold the syringe by the barrel with the transfer needle pointing up.
- Carefully pull the transfer needle cap straight off and away from your body. **Do not throw the cap away. Place the transfer needle cap down on a flat surface.** You will need to recap the transfer needle after transferring the medicine.
- **Do not touch** the needle tip or place it on a surface after the needle cap has been removed.

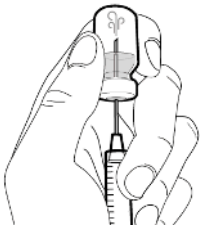
Step 4. Inject air into vial



- Keep the vial on the flat working surface and insert the transfer needle and syringe straight down into the centre of the vial stopper.

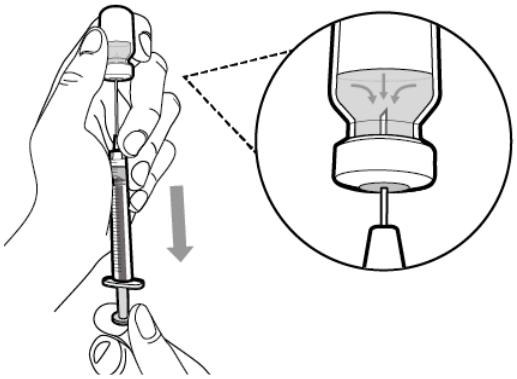


- Keep the needle in the vial and turn the vial upside down.



- With the needle pointing upwards, push on the plunger to inject the air from the syringe **above the medicine**.
- Keep your finger pressed down on the syringe plunger.
- **Do not** inject air into the medicine as this could create air bubbles in the medicine.

Step 5. Transfer medicine to syringe

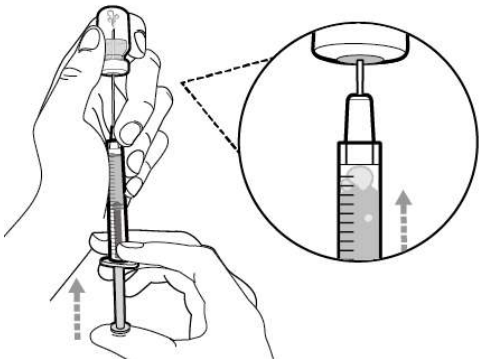


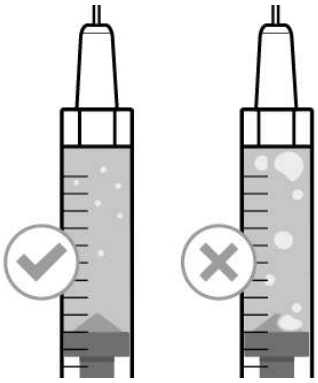
- Slide the tip of the needle down so that it is within the medicine.
- Slowly pull back the plunger to fill the syringe with more than the amount of medicine needed for your prescribed dose.
- Be careful not to pull the plunger out

of the syringe.

Important: If your prescribed dose is more than the amount of medicine in the vial, **withdraw all of the medicine** and go to the **Combining Vials** section now.

Step 6. Remove air bubbles





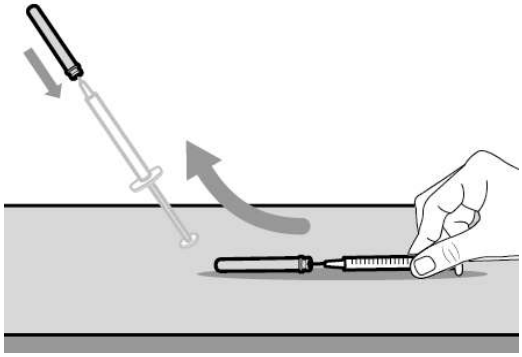
- Keep the needle in the vial and check the syringe for larger air bubbles. Too large an air bubble can reduce the dose you receive.
- **Remove the larger air bubbles** by gently tapping the syringe barrel with your fingers until the air bubbles rise to the top of the syringe. Move the tip of the needle **above the medicine** and slowly push the plunger up to push the air bubbles out of the syringe
- If the amount of medicine in the syringe is now at or below your prescribed dose, move the tip of the needle to **within the medicine** and slowly **pull** back the plunger until you have **more** than the amount of medicine needed for your **prescribed dose**.
- Be careful not to pull the plunger out of the syringe
- Repeat the steps above until you have removed the larger air bubbles.

Note: Ensure you have enough medicine in the syringe to complete your dose before moving onto the next step. If you cannot remove all of the medicine, turn the vial upright to reach the remaining amount.

Do not use the transfer needle to inject medicine as this may cause harm such as pain and bleeding.

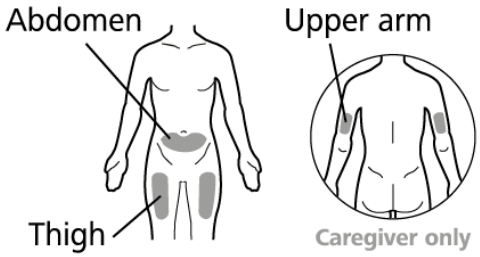
2. INJECTION

Step 7. Recap transfer needle



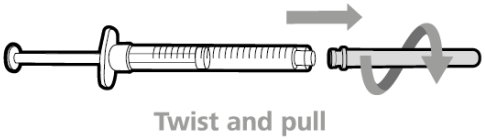
- Remove the syringe and transfer needle from the vial.
- **Using one hand, slide** the transfer needle into the cap and **scoop upwards** to cover the needle.
- Once the needle is covered, push the transfer needle cap towards the syringe to fully attach it with **one hand** to prevent accidentally hurting yourself with the needle

Step 8. Clean injection site



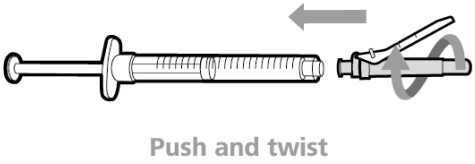
- Select and clean your injection site with an alcohol wipe.

Step 9. Remove transfer needle



- Remove the transfer needle from the syringe by twisting anticlockwise and gently pulling.
- Dispose of (throw away) the used transfer needle into a sharps disposal container.

Step 10. Attach injection needle to syringe

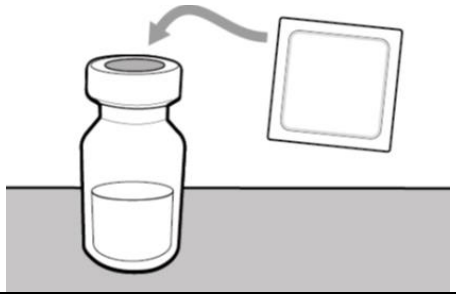


- Push and twist the injection needle clockwise onto the syringe until it is fully attached.

1. PREPARATION FOR USE USING THE VIAL ADAPTOR OPTION

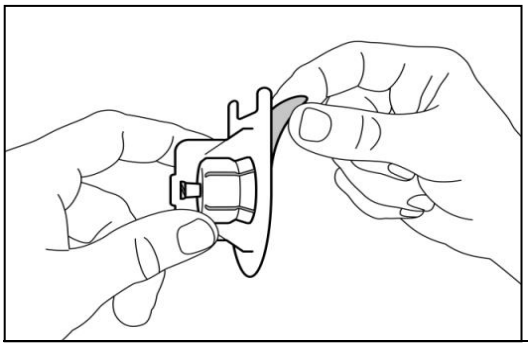
Step 1. Remove vial cap and clean top

- Take the cap off the vial(s).
- Throw away the vial cap(s) into the sharps disposal container.



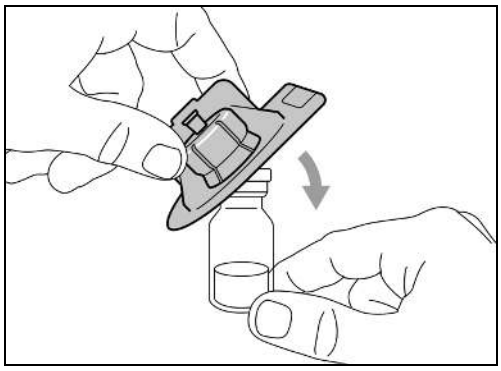
- Clean the top of the vial(s) stopper with an alcohol wipe.

Step 2. Insert vial adaptor onto vial

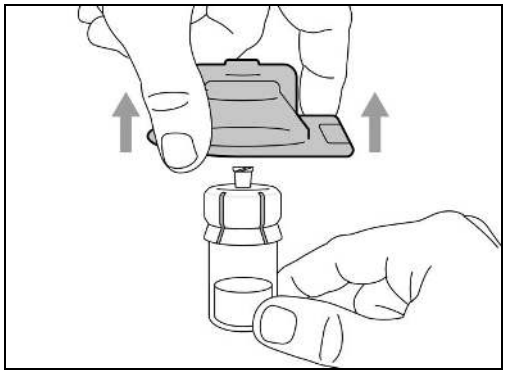


- Peel off back to open the blister pack.

⚠ **Do not remove the vial adaptor from the clear plastic blister pack.**

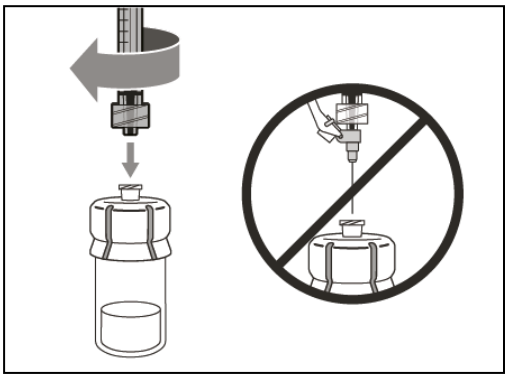


- Firmly press down the plastic blister pack with the vial adaptor onto the new vial at an angle, until you hear a **"click**".



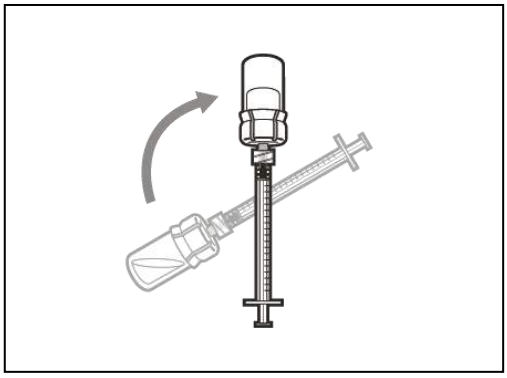
- Remove and throw away the plastic blister pack.
- **Do not** touch the tip of vial adaptor.

Step 3. Connect syringe to vial adaptor



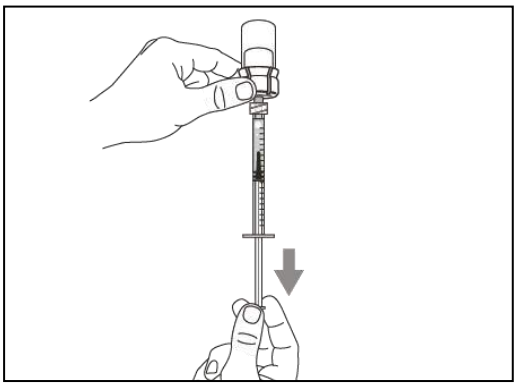
- **Remove syringe cap** (if required).
- **Push and twist the syringe clockwise** on to the vial adaptor until it is fully attached.

Step 4. Transfer medicine to syringe



- Keep the vial adaptor attached to the syringe and turn the vial upside down.

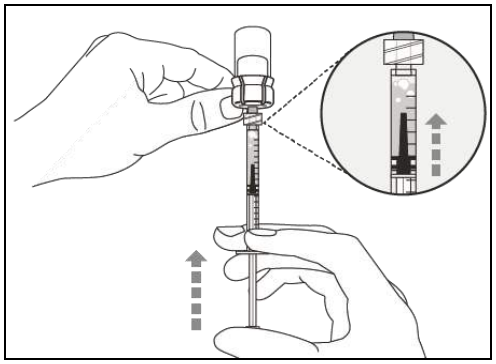
Step 5



- With the syringe pointing upwards, slowly pull back the plunger to **fill the syringe with** more than the amount **of medicine** needed for your prescribed dose.
- **Hold plunger firmly** to ensure it does not pull back in.
- Be careful not to pull the plunger out of the syringe.

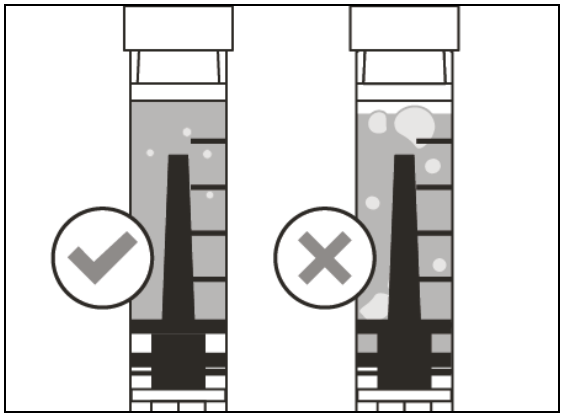
Important: If your prescribed dose is more than the amount of Hemlibra in the vial, **withdraw all medicine** and go to the **"Combining Vials" section** now

Step 6. Remove air bubbles



- Keep the vial attached to the syringe and **check the syringe for larger air bubbles**. Large air bubbles can reduce the dose you receive.

Step 7

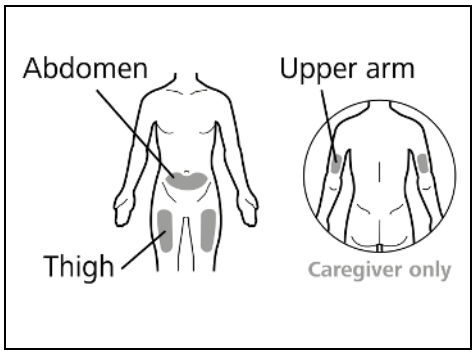


- **Remove the larger air bubbles** by gently **tapping** the syringe barrel with your finger until the air bubbles rise to the top of the syringe. **Slowly push the plunger** to push the large air bubbles out of the syringe.
- If the amount of medicine in the syringe is now at or below your prescribed dose, slowly pull back the plunger until you have **more** than the amount of medicine needed for your **prescribed dose**.
- Be careful not to pull the plunger out of the syringe.
- Repeat the steps above until you have removed the large air bubbles.

Note: Ensure you have enough medicine in the syringe to complete your dose before moving on to the next step.

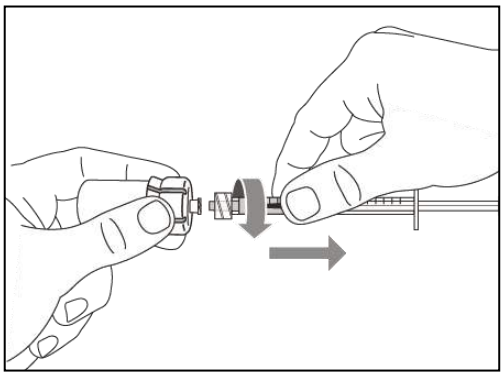
2. INJECTION

Step 8. Clean injection site



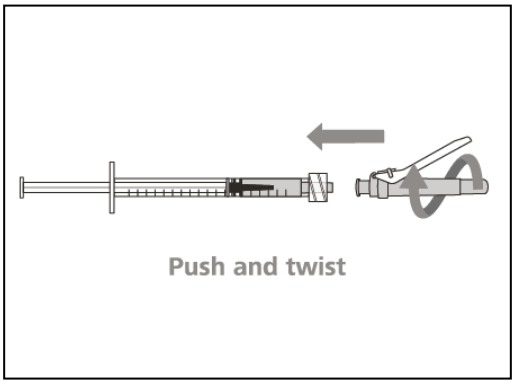
- Select and **clean** your injection site with an alcohol wipe.

Step 9. Remove syringe from vial adaptor



- Remove the syringe from the vial adaptor by twisting anticlockwise and gently pulling.
- Throw away the used vial/vial adaptor into a sharps disposal container.

Step 10. Attach injection needle to syringe

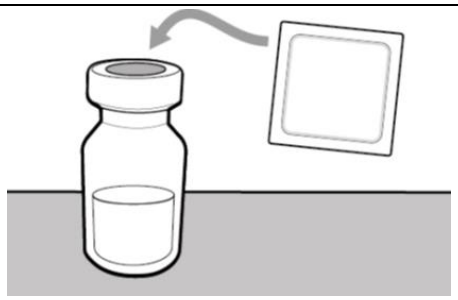


- Push and twist the injection needle clockwise onto the syringe until it is fully attached.
- **Do not** insert the injection needle into vial adaptor or use the injection needle to withdraw medicine from vial.

1. PREPARATION FOR USE USING THE VIAL ADAPTOR WITH FILTER OPTION

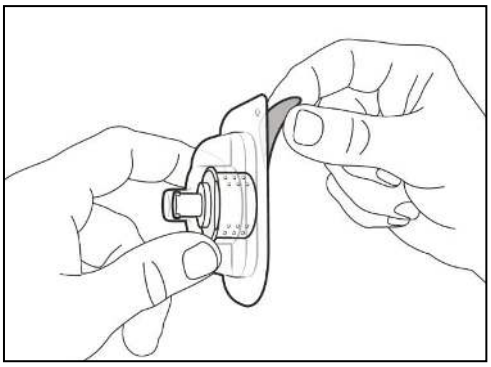
Step 1. Remove vial cap and clean top

- Take the cap off the vial(s).
- Throw away the vial cap(s) into the sharps disposal container.



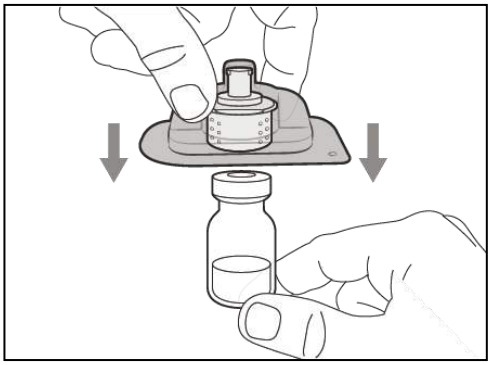
- Clean the top of the vial(s) stopper with an alcohol wipe.

Step 2. Insert vial adaptor with filter onto vial

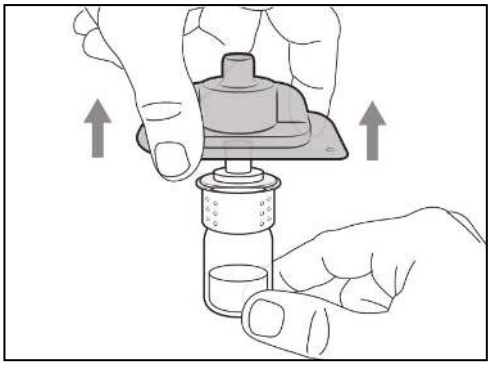


- Peel off back to open the blister pack.

⚠ **Do not remove the vial adaptor with filter from the clear plastic blister pack.**



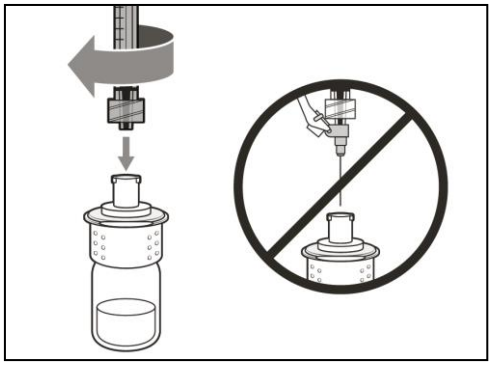
- Firmly press down the plastic blister pack with the vial adaptor with filter onto the new vial at an angle, until you hear a **"click**".



- Remove and throw away the plastic blister pack.
- **Do not** touch the tip of vial adaptor with filter.

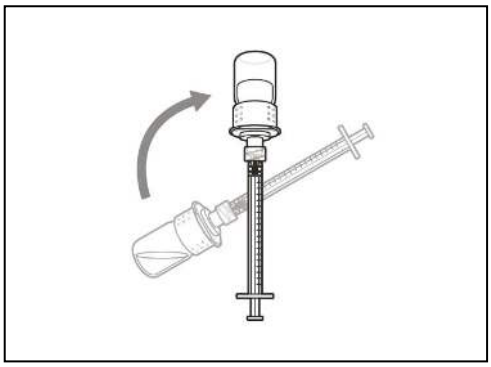
Step 3. Connect syringe to vial adaptor with filter

- **Remove syringe cap** (if required).



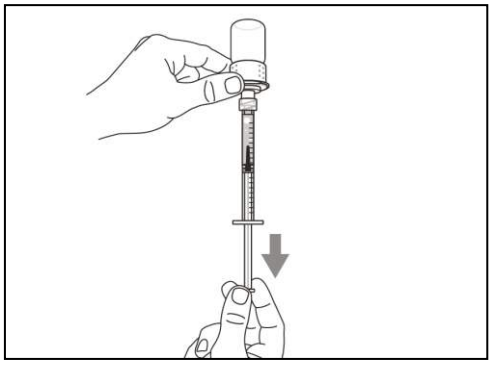
- **Push and twist the syringe clockwise** on to the vial adaptor with filter until it is fully attached.

Step 4. Transfer medicine to syringe



- Keep the vial adaptor with filter attached to the syringe and turn the vial upside down.

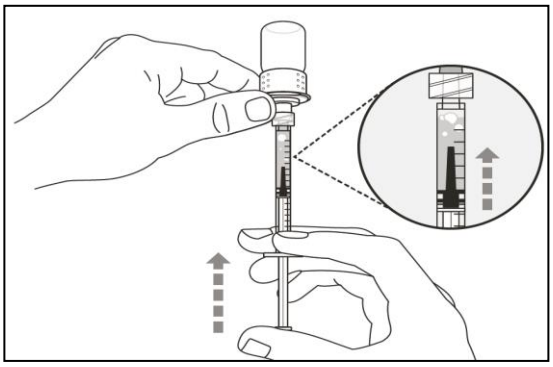
Step 5



- With the syringe pointing upwards, slowly pull back the plunger to **fill the syringe with** more than the amount **of medicine** needed for your prescribed dose.
- **Hold plunger firmly** to ensure it does not pull back in.
- Be careful not to pull the plunger out of the syringe.

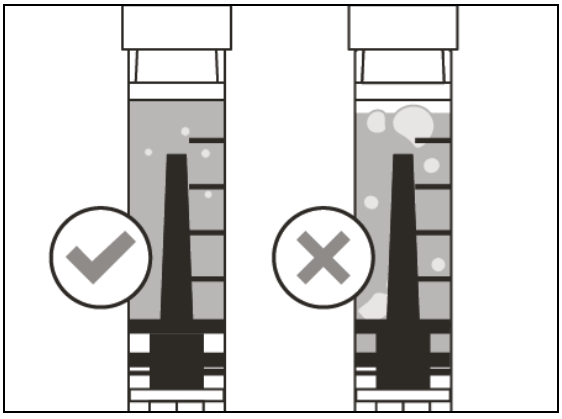
Important: If your prescribed dose is more than the amount of Hemlibra in the vial, **withdraw all medicine** and go to the **"Combining Vials" section** now

Step 6. Remove air bubbles



- Keep the vial attached to the syringe and **check the syringe for larger air bubbles**. Large air bubbles can reduce the dose you receive.

Step 7

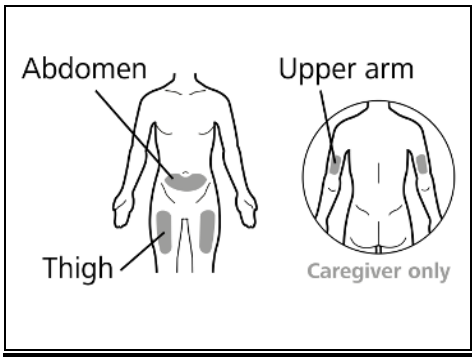


- **Remove the larger air bubbles** by gently **tapping** the syringe barrel with your finger until the air bubbles rise to the top of the syringe. **Slowly push the plunger** to push the large air bubbles out of the syringe.
- If the amount of medicine in the syringe is now at or below your prescribed dose, slowly pull back the plunger until you have **more** than the amount of medicine needed for your **prescribed dose**.
- Be careful not to pull the plunger out of the syringe.
- Repeat the steps above until you have removed the large air bubbles.

Note: Ensure you have enough medicine in the syringe to complete your dose before moving on to the next step.

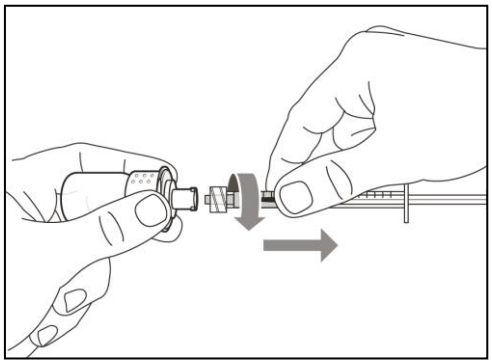
2. INJECTION

Step 8. Clean injection site



- Select and **clean** your injection site with an alcohol wipe.

Step 9. Remove syringe from vial adaptor with filter

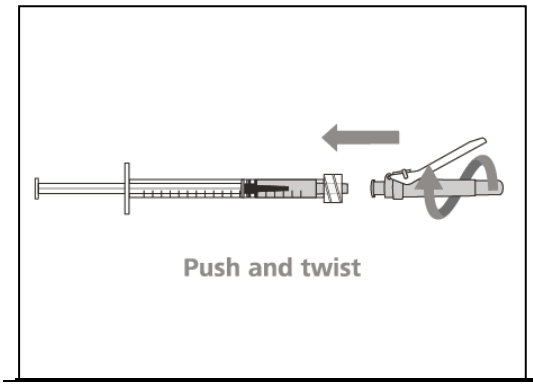


- Remove the syringe from the vial adaptor with filter by twisting anticlockwise and gently pulling.
- Throw away the used vial/vial adaptor with filter into a sharps disposal container.

Step 10. Attach injection needle to syringe

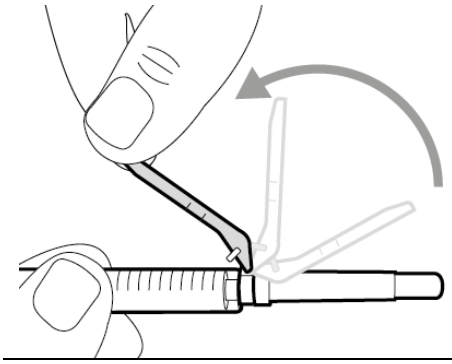
- Push and twist the injection needle clockwise onto the syringe until it is fully attached.
- **Do not** insert the injection needle into vial adaptor with filter or use the

injection needle to withdraw medicine from vial.



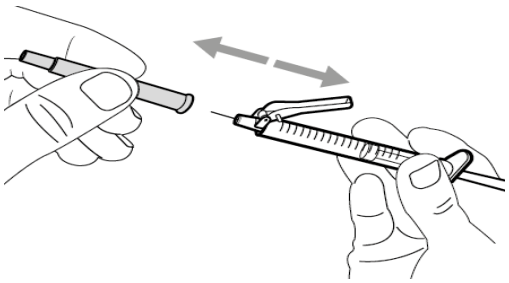
Follow the instructions below for the TRANSFER NEEDLE WITH FILTER, TRANSFER NEEDLE, VIAL ADAPTOR and VIAL ADAPTOR WITH FILTER options

Step 11. Move safety shield



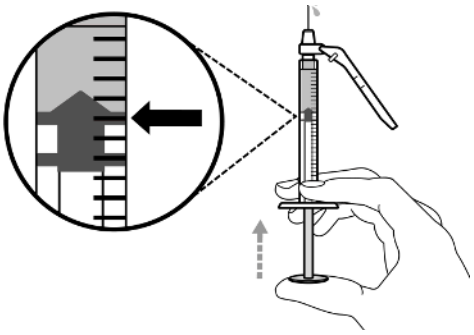
- Move the safety shield away from the needle and **towards** the syringe barrel.

Step 12. Uncap injection needle



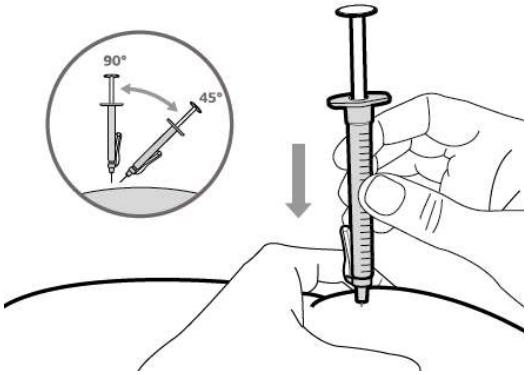
- Carefully pull the injection needle cap **straight away** from the syringe.
- Dispose of (throw away) the cap into a sharps disposal container
- **Do not touch** the needle tip or allow it to touch any surface.
- After the injection needle cap has been removed, the medicine in the syringe must be injected within 5 minutes.

Step 13. Adjust plunger to prescribed dose



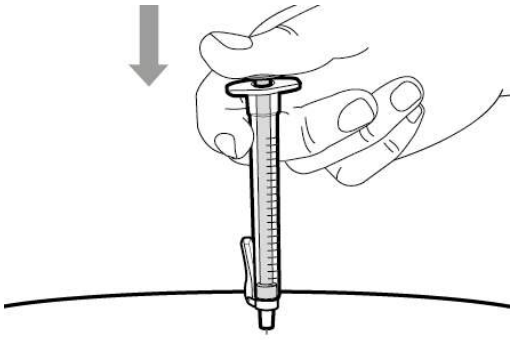
- Hold the syringe with the needle pointing up and slowly push the plunger to your prescribed dose.
- **Check your dose,** ensure the top rim of the plunger is in line with the mark on the syringe for your prescribed dose.

Step 14. Subcutaneous (under the skin) Injection



- Pinch the selected injection site and fully insert the needle at a **45° to 90° angle** with a quick, firm action. **Do not** hold or push on the plunger while inserting the needle.
- Hold the position of the syringe and let go of the pinched injection site.

Step 15. Inject the medicine

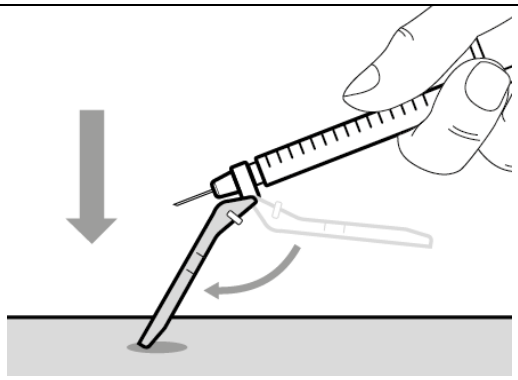


- Slowly inject all of the medicine by gently pushing the plunger all the way down.
- Remove the needle and syringe from the injection site at the same angle as inserted.

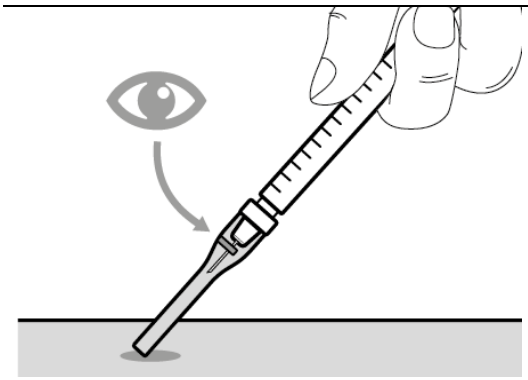
3. DISPOSAL

Step 16. Cover needle with safety shield

- Move the safety shield forward 90°, away from the syringe barrel.
- Holding the syringe with one hand,

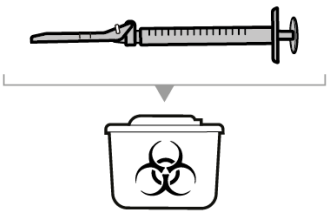


press the safety shield down against a flat surface with a firm, quick motion until you hear a “click”.



- If you do not hear a click, look to see that the needle is fully covered by the safety shield.
- Keep your fingers behind the safety shield and away from the needle at all times.
- **Do not** detach injection needle

Step 17. Dispose of (throw away) the syringe and needle.

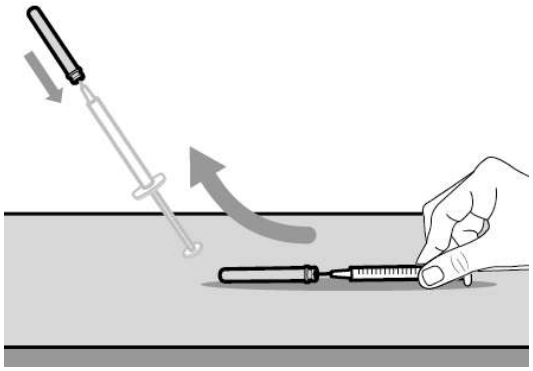


- Put your used needles and syringes in a sharps disposal container right away after use. For further information refer to the section “Disposing of the medicine and supplies”.
- **Do not** try to remove the used injection needle from the used syringe.
- **Do not recap** the injection needle with the cap.
- **Important**: Always keep the sharps disposal container out of reach of children.
- Throw away any used caps, vial(s), needles or adaptors and syringes in a sharps or puncture-proof container.

Combining Vials using the TRANSFER NEEDLE WITH FILTER option

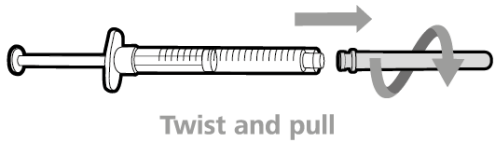
If you need to use more than 1 vial to get to your prescribed dose, follow these steps after you have drawn up the medicine from the first vial as described in step 5. You must use a new transfer needle for each vial.

Step A. Recap transfer needle with filter



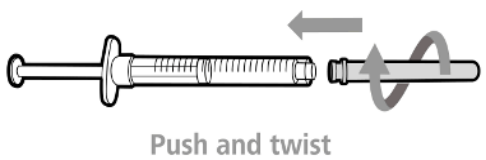
- Remove the syringe and transfer needle with filter from the first vial.
- **Using one hand,** slide the transfer needle with filter into the cap and **scoop upwards** to cover the needle.
- Once the needle is covered, push the transfer needle with filter cap toward the syringe to fully attach it with **one hand** to prevent accidentally injuring yourself with the needle.

Step B. Remove the used transfer needle with filter from the syringe



- Remove the used transfer needle with filter from the syringe by twisting anticlockwise and gently pulling.
- Throw away the used transfer needle with filter into a sharps disposal container.

Step C. Attach a new transfer needle with filter to syringe

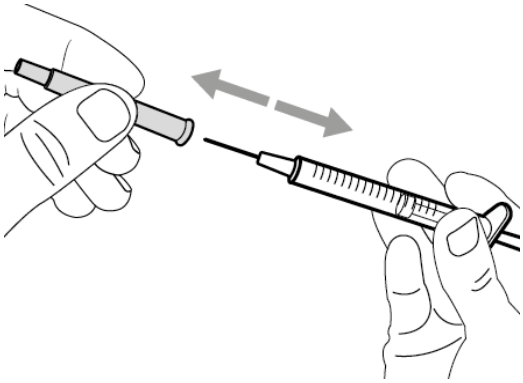


Note: **You must use a new transfer needle with filter each time you withdraw medicine from a new vial.**

- Push and twist a **new** transfer needle with filter clockwise on to the syringe until it is fully attached.

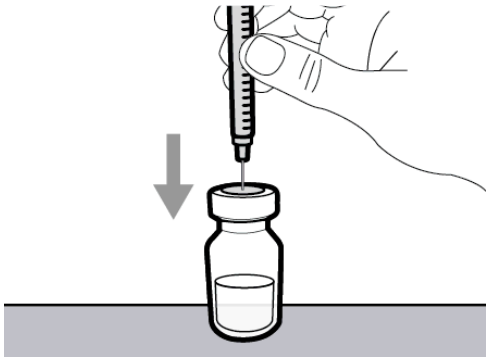
- Slowly pull back the plunger and draw some air into the syringe.

Step D. Uncap transfer needle with filter

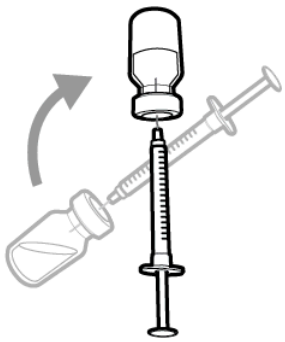


- Hold the syringe by the barrel with the transfer needle with filter cap pointing up.
- Carefully pull the transfer needle with filter cap straight off and away from your body**.** **Do not throw** the cap away. You will need to recap the transfer needle with filter after transferring the medicine.
- **Do not touch** the needle tip.

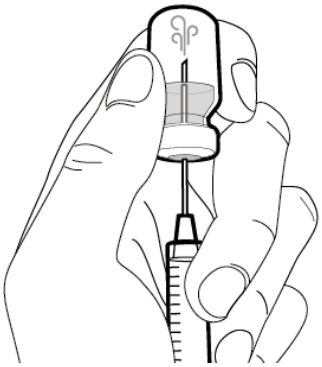
Step E. Inject air into vial



- With the new vial on the flat working surface, insert the new transfer needle with filter and syringe, straight down into the **centre** of the vial stopper.

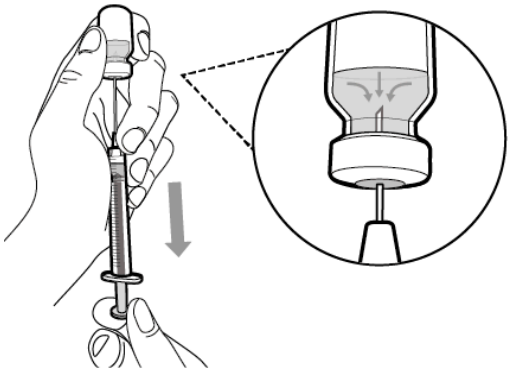


- Keep the transfer needle with filter in the vial and turn the vial upside down.



- With the needle pointing upwards, inject the air from the syringe **above the medicine.**
- Keep your finger pressed down on the syringe plunger.
- **Do not** inject air into the medicine as this could create air bubbles or foam in the medicine.

Step F. Transfer medicine to syringe



- Slide the tip of the needle down so that it is **within the medicine**.
- **Slowly** pull back the plunger to prevent air bubbles/foam. Fill the syringe barrel more than the amount of medicine needed for your prescribed dose.
- Be careful not to pull the plunger out of the syringe.

Note: Ensure you have enough medicine in the syringe to complete your dose before moving onto the next steps. If you cannot remove all of the medicine, turn the vial upright to reach the remaining amount.

Do not use the transfer needle with filter to inject medicine as this may cause harm such as pain and bleeding.

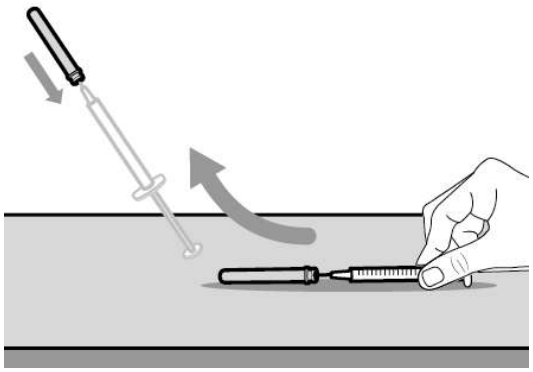
Repeat steps A to F with each additional vial until you have more than the amount of medicine needed for your prescribed dose. Once completed, keep the transfer needle

with filter inserted in the vial and return to Step 6 "Remove air bubbles. Continue with the remaining steps.

Combining Vials using the TRANSFER NEEDLE option

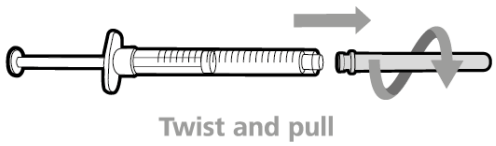
If you need to use more than 1 vial to get to your total prescribed dose, follow these steps after you have drawn up the medicine from the first vial:

Step A. Recap transfer needle



- Remove the syringe and transfer needle from the first vial.
- **Using one hand,** slide the transfer needle into the cap and **scoop upwards** to cover the needle.
- Once the needle is covered, push the transfer needle cap toward the syringe to fully attach it with one hand to prevent accidentally injuring yourself with the needle.

Step B. Remove transfer needle



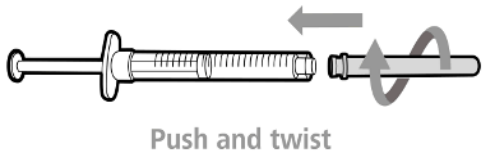
- Remove the transfer needle from the syringe by twisting anticlockwise and gently pulling.
- Dispose of (throw away) the used transfer needle into a sharps disposal container.

Step C. Attach a new transfer needle to Syringe

Note: **You must use a new transfer needle each time you withdraw medicine from a new vial.**

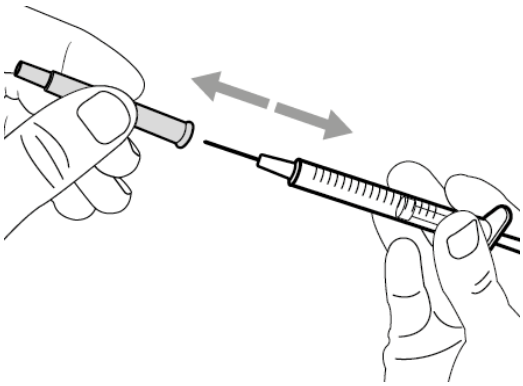
- Push and twist a **new** transfer needle clockwise on to the syringe until it is fully

attached.



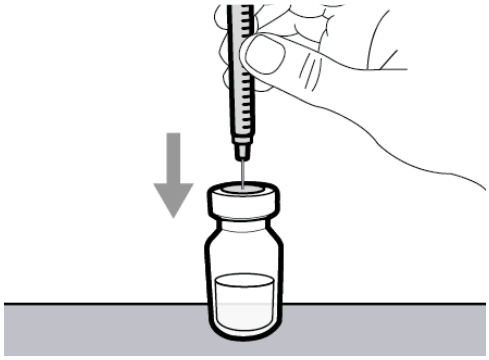
- Slowly pull back the plunger and draw some air into the syringe.

Step D. Uncap transfer needle

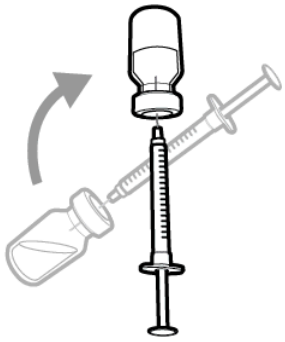


- Hold the syringe by the barrel with the transfer needle cap pointing up.
- Carefully pull the transfer needle cap straight off and away from your body. Do not throw the cap away. You will need to recap the transfer needle after drawing up the medicine.
- Do not touch the needle tip.

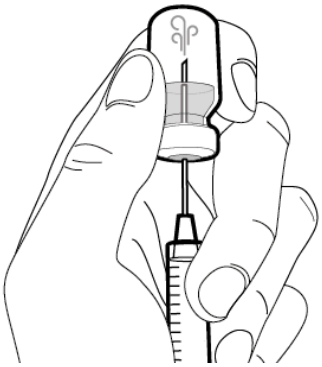
Step E. Inject air into vial



- With the new vial on the flat working surface, insert the new transfer needle and syringe, straight down into the centre of the vial stopper.

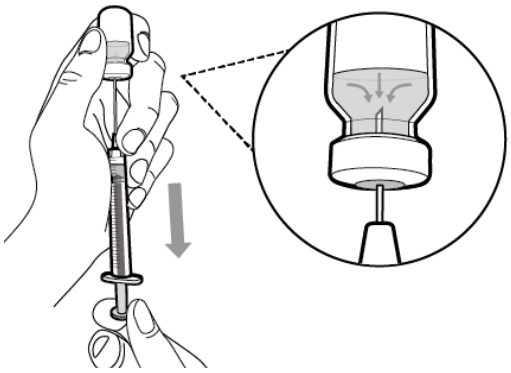


- Keep the transfer needle in the vial and turn the vial upside down.



- With the needle pointing upwards, inject the air from the syringe **above the medicine.**
- Keep your finger pressed down on the syringe plunger.
- Do not inject air into the medicine as this could create air bubbles in the medicine.

Step F. Transfer medicine to syringe



- Slide the tip of the needle down so that it is **within the medicine**.
- Slowly pull back the plunger to fill the syringe barrel more that the amount of medicine needed for your prescribed dose.
- Be careful not to pull the plunger out of the syringe.

Note: Ensure you have enough medicine in the syringe to complete your dose before moving onto the next step. If you cannot remove all of the medicine, turn the vial upright to reach the remaining amount.

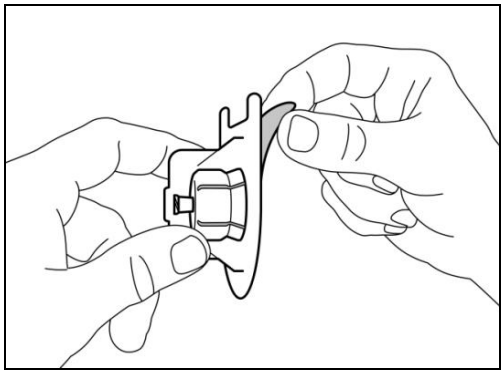
Do not use the transfer needle to inject medicine as this may cause harm such as pain and bleeding.

Repeat steps A to F with each additional vial until you have more than your prescribed dose. Once completed, keep the transfer needle inserted in the vial and return to Step 6. Continue with the remaining steps.

Combining Vials using the VIAL ADAPTOR option

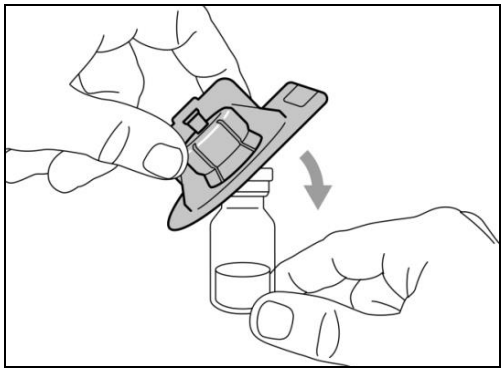
If you need to use more than 1 vial to get to your prescribed dose, follow these steps after you have drawn up the medicine from the first vial:

Step A. Insert new vial adaptor into new vial

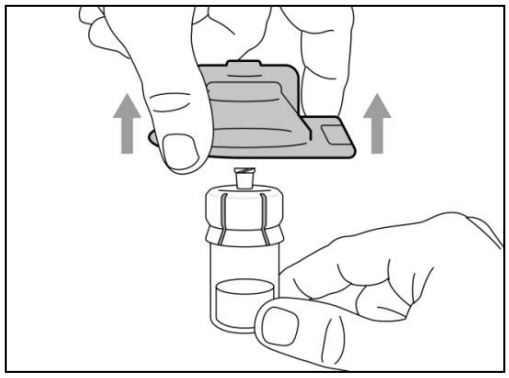


- Peel off back to open the blister pack.

⚠ **Do not remove the vial adaptor from the clear plastic blister pack.**

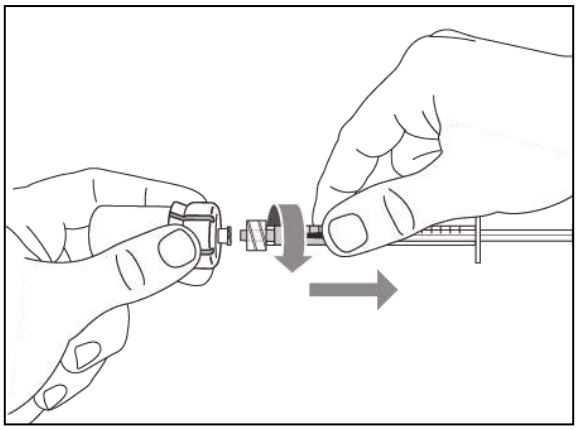


- Firmly press down the plastic blister pack with the vial adaptor onto the new vial at an angle, until you hear a **'click'**.



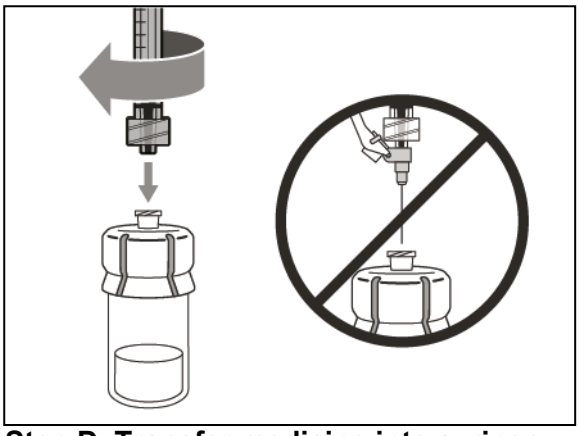
- Remove and throw away the plastic blister pack.
- **Do not** touch the tip of vial adaptor.

Step B. Remove used vial adaptor



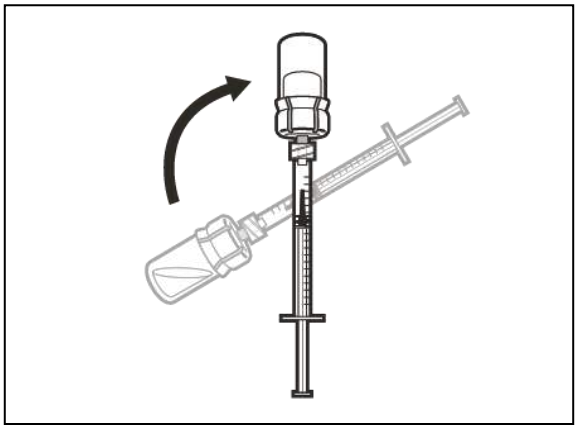
- Remove the used vial adaptor from the syringe by twisting anticlockwise and gently pulling.
- Throw away the used vial/vial adaptor into a sharps disposal container.

Step C. Connect new vial adaptor to syringe

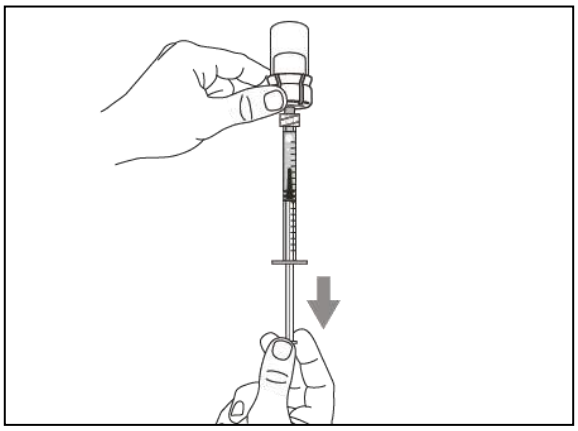


- **Push and twist the syringe clockwise** on to the vial adaptor until it is fully attached.

Step D. Transfer medicine into syringe



- Keep the vial adaptor attached to the syringe and turn the vial upside down.



- With the syringe pointing upwards, slowly pull back the plunger to **fill the syringe with** more than the amount **of the medicine** needed for your prescribed dose.
- **Hold plunger firmly** to ensure it does not pull back in.
- Be careful not to pull the plunger out of the syringe.

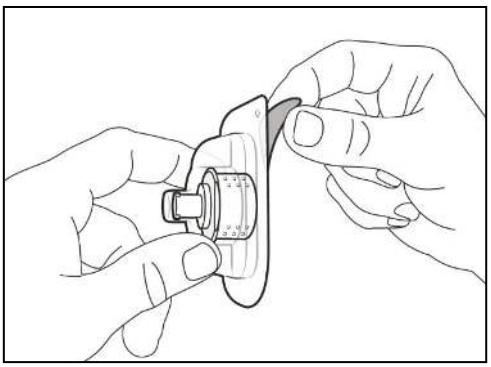
Note: Ensure you have enough medicine in the syringe to complete your dose before moving on to the next step.

Repeat steps A to D with each additional vial until you have more than the amount of medicine needed for your prescribed dose. Once completed, keep the vial adaptor onto the vial and return to Step 6 "Remove air bubbles". Continue with the remaining steps.

Combining Vials using the VIAL ADAPTOR WITH FILTER option

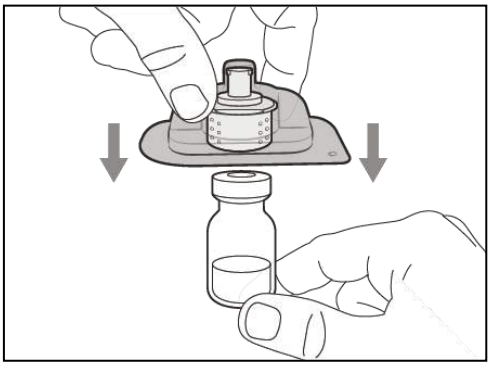
If you need to use more than 1 vial to get to your prescribed dose, follow these steps after you have drawn up the medicine from the first vial as described in step 4. You must use a new vial adapter with filter for each vial.

Step A. Insert new vial adapter with filter into new vial

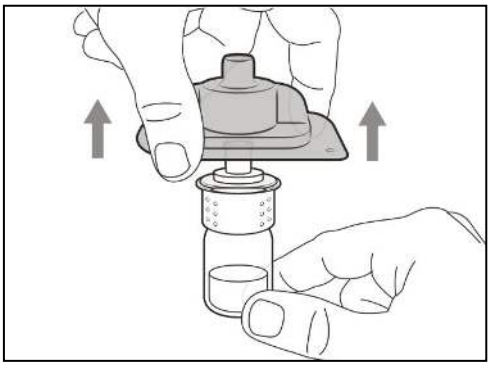


- Peel off back to open the blister pack.

⚠ **Do not** remove the vial adapter with filter from the clear plastic blister pack.

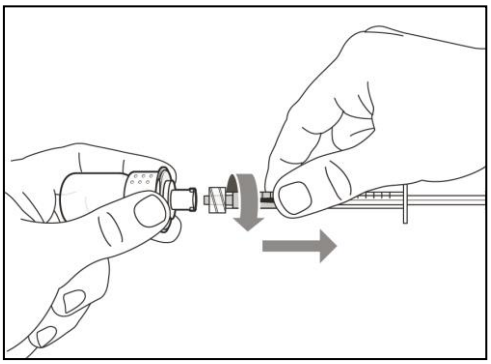


- Firmly press down the plastic blister pack with the vial adapter with filter onto the new vial, until you hear a **"click"**.



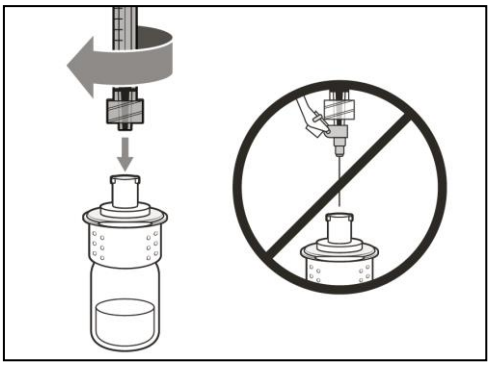
- Remove and throw away the plastic blister pack.
- **Do not** touch the tip of vial adapter with filter.

Step B. Remove syringe from used vial adapter with filter



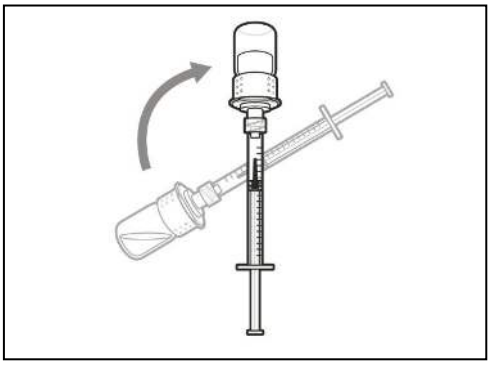
- Remove the syringe from the used vial adapter with filter by twisting anticlockwise and gently pulling.
- Throw away the used vial/vial adapter with filter into a sharps disposal container.

Step C. Connect syringe to new vial adapter with filter

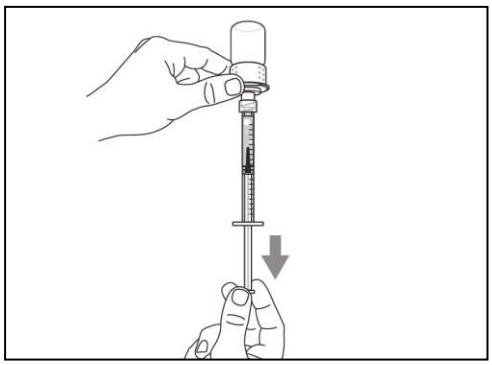


- **Push and twist the same syringe clockwise** on to the next vial adapter with filter until it is fully attached.

Step D. Transfer medicine into syringe



- Keep the vial adapter with filter attached to the syringe and turn the vial upside down.



- With the syringe pointing upwards, slowly pull back the plunger to **fill the syringe** with more than the amount **of the medicine** needed for your prescribed dose.
- **Hold plunger firmly** to ensure it does not pull back in.
- Be careful not to pull the plunger out of the syringe.

Note: Ensure you have enough medicine in the syringe to complete your dose before moving on to the next step.

Repeat steps A to D with each additional vial until you have more than the amount of medicine needed for your prescribed dose. Once completed, keep the vial adapter with filter onto the vial and return to Step 5 "Remove air bubbles". Continue with the remaining steps.

Special Dosage Instructions

Paediatric use

The safety and efficacy of Hemlibra have been established in paediatric patients. Use of Hemlibra in paediatric patients with haemophilia A (with or without FVIII inhibitors) is supported by three randomised studies and two single-arm studies.

These five clinical studies included a total of 137 paediatric patients in the following age groups: 61 adolescents (12 years to < 18 years), 71 children (2 years to < 12 years) and 5 infants (1 month to < 2 years). Safety and efficacy results were consistent with those observed for adults (see section 5.2).

The steady-state plasma trough concentrations of Hemlibra were comparable in adult and paediatric patients at equivalent weight-based doses (see section 5.2).

No dose adjustments are recommended in paediatric patients.

Elderly use

The safety and efficacy of Hemlibra have not been tested in an elderly population. Clinical studies of Hemlibra included 15 patients aged 65 and over. Relative bioavailability decreased with older age, but no clinically important differences were observed in the pharmacokinetics of Hemlibra between patients < 65 years and patients ≥ 65 years (see section 5.2).

No dose adjustments are recommended in patients ≥ 65 years of age (see section 5.2).

Renal impairment

The safety and efficacy of Hemlibra have not been tested in patients with renal impairment. There are limited data available on the use of Hemlibra in patients with mild to moderate renal impairment. No data are available on the use of Hemlibra in patients with severe renal impairment. Hemlibra is a monoclonal antibody and is cleared via catabolism rather than by renal excretion and a change in dose is not expected to be required for patients with renal impairment.

No dose adjustments are recommended in patients with renal impairment (see section 5.2).

Hepatic impairment

The safety and efficacy of Hemlibra have not been tested in patients with hepatic impairment. Patients with mild and moderate hepatic impairment were included in clinical trials. No data are available on the use of Hemlibra in patients with severe hepatic impairment. Hemlibra is a monoclonal antibody and is cleared via catabolism rather than by hepatic metabolism and a change in dose is not expected to be required for patients with hepatic impairment.

No dose adjustments are recommended in patients with hepatic impairment (see section 5.2).

4.3 Contraindications

Hemlibra is contraindicated in patients with known hypersensitivity to emicizumab or to any of the excipients.

4.4 Special warnings and precautions for use

Thrombotic microangiopathy associated with Hemlibra and activated prothrombin complex concentrate

Cases of thrombotic microangiopathy (TMA) were reported from a clinical trial in patients receiving Hemlibra prophylaxis when on average a cumulative amount of > 100 U/kg/24 hours of activated prothrombin complex concentrate (aPCC) for 24 hours or more were administered (see section 4.8). Treatment for the TMA events included supportive care with or without plasmapheresis and haemodialysis. Evidence of improvement was seen within one week following discontinuation of aPCC. This rapid clinical improvement is distinct from the usual clinical course observed in atypical haemolytic uremic syndrome and classic TMAs, such as thrombotic thrombocytopenic purpura, (see section 4.8).

Patients receiving Hemlibra prophylaxis should be monitored for the development of TMA when administering aPCC. The medical practitioner should immediately discontinue aPCC and interrupt Hemlibra therapy if clinical symptoms and/or laboratory findings consistent with TMA occur, and manage as clinically indicated. Medical practitioners should consider the risks of resuming Hemlibra prophylaxis following complete resolution of TMA on a case-by-case basis. In case a bypassing agent is indicated in a patient receiving Hemlibra prophylaxis, see below for dosing recommendations for the use of bypassing agents.

Thromboembolism associated with Hemlibra and activated prothrombin complex concentrate

Thrombotic events were reported from a clinical trial in patients receiving Hemlibra prophylaxis when on average a cumulative amount of > 100 U/kg/24 hours of aPCC for 24 hours or more were administered (see section 4.8). No cases required anticoagulation therapy, which is distinct from the usual treatment of thrombotic events. Evidence of improvement or resolution was seen after discontinuation of aPCC (see section 4.8).

Patients receiving Hemlibra prophylaxis should be monitored for the development of thromboembolism when administering aPCC. The medical practitioner should immediately discontinue aPCC and interrupt Hemlibra therapy if clinical symptoms, imaging, and/or laboratory findings consistent with thrombotic events occur, and manage as clinically indicated.

Medical practitioners should consider the risks of resuming Hemlibra prophylaxis following complete resolution of thrombotic events on a case-by-case basis. In case a bypassing agent is indicated in a patient receiving Hemlibra prophylaxis, see below for dosing recommendations for the use of bypassing agents.

Guidance on the use of bypassing agents in patients receiving Hemlibra prophylaxis

Treatment with bypassing agents should be discontinued the day before starting Hemlibra therapy.

Medical practitioners should discuss with all patients and/or caregivers the exact dose and schedule of bypassing agents to use, if required while receiving Hemlibra prophylaxis.

Hemlibra increases the patients' coagulation potential. The bypassing agent dose required may therefore be lower than that used without Hemlibra prophylaxis. The dose and duration of treatment with bypassing agents will depend on the location and extent of bleeding and on the patient's clinical condition. Avoid use of aPCC unless no other treatment options/alternatives are available. If aPCC is indicated in a patient receiving Hemlibra prophylaxis, the initial dose should not exceed 50 U/kg. If bleeding is not controlled with the initial dose of aPCC up to 50 U/kg, additional aPCC doses should be administered under medical guidance or supervision, and the total aPCC dose should not exceed 100 U/kg in the first 24-hours of treatment. Treating medical practitioners must carefully weigh the risk of TMA and thromboembolism against the risk of bleeding when considering aPCC treatment beyond a maximum of 100 U/kg in the first 24-hours.

In clinical trials, no cases of thrombotic microangiopathy (TMA) or thrombotic events were observed with use of activated recombinant human FVII (rFVIIa) alone in patients receiving Hemlibra prophylaxis.

Bypassing agent dosing guidance should be followed for at least 6 months following discontinuation of Hemlibra prophylaxis (see section 5.2).

Immunogenicity

Anti-hemlibra antibodies have been reported in a small number of patients treated with Hemlibra in clinical trials. Most patients found to have anti-hemlibra antibodies did not experience a change in Hemlibra plasma concentrations or an increase in bleeding events; however, in uncommon (≥ 1/1,000 to < 1/100) cases, the presence of neutralising anti-hemlibra antibodies with decreasing Hemlibra concentration may be associated with loss of efficacy (see section 4.8).

In case of clinical signs of loss of efficacy (e.g. increase in breakthrough bleeding events), prompt evaluation by a medical practitioner should be sought to assess the etiology and a possible change in treatment should be considered.

Laboratory coagulation test interference

Hemlibra affects intrinsic pathway clotting-based laboratory tests, including the activated clotting time (ACT), activated partial thromboplastin time (aPTT) and all assays based on aPTT, such as one-stage factor VIII activity (see Table 1 below). Therefore, intrinsic pathway clotting-based laboratory test results in patients treated with Hemlibra prophylaxis should not be used to monitor Hemlibra activity, determine dosing for factor replacement or anti-coagulation, or measure factor VIII inhibitor titres. Laboratory tests affected and unaffected by Hemlibra are also shown in Table 1 below (see section 4.5).

Table 1 Coagulation Test Results Affected and Unaffected by Hemlibra

Results affected by Hemlibra	Results unaffected by Hemlibra
Activated partial thromboplastin time (aPTT) Bethesda assays (clotting-based) for FVIII inhibitor titres One-stage, aPTT–based, single-factor assays (e.g. FVIII activity) aPTT-based activated protein C resistance (APC-R) Activated clotting time (ACT)	Bethesda assays (bovine-chromogenic) for FVIII inhibitor titres Thrombin time (TT) One-stage, prothrombin time (PT)-based, single-factor assays Chromogenic-based single-factor assays other than FVIII* Immuno-based assays (e.g. ELISA, turbidimetric methods) Genetic tests of coagulation factors (e.g. Factor V Leiden, Prothrombin 20210)
*For important considerations regarding FVIII chromogenic activity assays, see Interactions.	

Traceability

In order to improve traceability of Hemlibra, the trade name and the batch number of the Hemlibra should be clearly recorded (or stated) in the patient file.

Advise patients/caregivers to record the batch number of the product whenever Hemlibra is administered outside of a healthcare setting.

4.5 Interaction with other medicines and other forms of interaction

No adequate or well-controlled interaction studies have been conducted with Hemlibra.

Clinical experience suggests that a medicine interaction exists with Hemlibra and aPCC (see sections 4.3 and 4.8).

There is a possibility for hypercoagulability with rFVIIa or FVIII with Hemlibra based on preclinical experiments. Hemlibra increases coagulation potential, therefore the coagulation factor dose required to achieve haemostatis may be lower than when used without Hemlibra prophylaxis.

Effect of Hemlibra on coagulation tests

Hemlibra restores the tenase cofactor activity of missing activated factor VIII (FVIIIa). Coagulation laboratory tests based on intrinsic clotting (e.g. aPTT) measure the total clotting time including time needed for activation of FVIII to FVIIIa by thrombin. Such intrinsic pathway-based tests will yield overly shortened clotting times with Hemlibra, which does not require activation by thrombin. The overly shortened intrinsic clotting time will then disturb all single-factor assays based on aPTT, such as the one-stage FVIII activity assay (see section 4.4, Table 1). However, single-factor assays utilising chromogenic or immuno-based methods are unaffected by Hemlibra and may be used to monitor coagulation parameters during treatment, with specific considerations for FVIII chromogenic activity assays as described below.

Chromogenic FVIII activity tests may be manufactured with either human or bovine coagulation proteins. Assays containing human coagulation factors are responsive to Hemlibra but may overestimate the clinical haemostatic potential of Hemlibra. In contrast, assays containing bovine coagulation factors are insensitive to Hemlibra (no activity measured) and can be used to monitor endogenous or infused factor VIII activity, or to measure anti-FVIII inhibitors.

Hemlibra remains active in the presence of inhibitors against factor VIII and so will produce a false-negative result in clotting-based Bethesda assays for functional inhibition of FVIII. Instead, a chromogenic Bethesda assay utilising a bovine-based FVIII chromogenic test that is insensitive to Hemlibra may be used.

Due to the long half-life of Hemlibra, effects on coagulation assays may persist for up to 6 months after the last dose (see section 5.2).

4.6 Fertility, pregnancy and lactation

Safety and efficacy has not been established.

Pregnancy

Safe use during pregnancy has not been established. It is not known whether Hemlibra can cause foetal harm when administered to a pregnant woman or can affect reproductive capacity. As antibodies, such as Hemlibra, crosses the placenta, pregnant women are advised not to use Hemlibra.

Contraception

Women of childbearing potential receiving Hemlibra should use effective contraception during, and for at least 6 months after cessation of Hemlibra treatment (see section 5.2).

Lactation

Women should not breastfeed while using Hemlibra.

4.7 Effects on ability to drive and use machines

There is no evidence that treatment with Hemlibra results in an increase in adverse reactions that might lead to the impairment of the ability to drive and use machines.

4.8 Undesirable effects

a) Summary of the safety profile

Clinical Trials

The following adverse drug reactions (ADRs) are based on pooled data from five phase III clinical trials (three adult and adolescent studies, a paediatric study, and an all-age group study [HAVEN 6]. A total of 444 patients with haemophilia A received at least one dose of Hemlibra as

routine prophylaxis. Three hundred and seven (69,1 %) patients were adults (of which two were female) (≥ 18 years), 61 (13,7 %) were adolescents (≥12 to <18 years), 71 (16,0 %) were children (≥ 2 to < 12 years) and five (1,1 %) were infants (≥ 1 month to < 2 years). The median duration of exposure across the studies was 32,0 weeks (range: 0,1 to 94,3 weeks).

Three patients (0,7 % in the pooled phase III clinical trials receiving Hemlibra prophylaxis withdrew from treatment due to ADRs, which were thrombotic microangiopathy, skin necrosis contemporaneous with superficial thrombophlebitis, and headache.

b) Tabulated list of adverse reactions

Adverse drug reactions (ADRs) from the pooled phase III clinical trials in patients who received Hemlibra are listed by MedDRA system organ class (see Table 2 below). The corresponding frequency categories for each ADR are based on the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), and uncommon (≥ 1/1,000 to < 1/100).

Table 2: Summary of Adverse Drug Reactions from Pooled Clinical Trials with Hemlibra

System Organ Class ADR (preferred term, MedDRA)	**Number of patients (N = 444)**	**Percentage of patients**	**Frequency**
General disorders and administration site conditions			
Injection site reactions	86	19,4 %	Very common
Pyrexia	23	5,2 %	Common
Nervous system disorders			
Headache	62	14,0 %	Very common
Gastrointestinal disorders			
Diarrhoea	21	4,7 %	Common
Musculoskeletal and connective tissue disorders			
Arthralgia	63	14,2 %	Very Common
Myalgia	13	2,9 %	Common

Blood and Lymphatic system disorders			
Thrombotic microangiopathy	3	< 1 %	Uncommon
Infections and Infestations			
Cavernous sinus thrombosis	1	<1 %	Uncommon
Skin and subcutaneous tissue disorders			
Skin necrosis	1	<1 %	Uncommon
Vascular Disorders			
Superficial thrombophlebitis	1	<1 %	Uncommon

Post Marketing

The following adverse drug reactions have been identified from post marketing surveillance with Hemlibra (see Table 4). Adverse drug reactions from post marketing surveillance are listed by MedDRA system organ class.

Table 3 Adverse Drug Reactions from Post marketing Surveillance

System Organ Class	**Frequency**
ADR (preferred term, MedDRA)	
Immune system disorders	
Hypersensitivity[b]	Uncommon
Skin and subcutaneous tissue disorders	
Angioedema[a]	Uncommon
Urticaria[b]	Common
Rash[b]	Common
[a]Frequency estimated at the upper limit of the 95 % confidence interval utilising the clinical trial safety population. [b]Frequency derived from clinical trial data.	

c) Description of selected adverse drug reactions:

The most serious adverse drug reactions reported from the pooled phase III clinical trials with Hemlibra were TMA and thrombotic events, including cavernous sinus thrombosis and superficial vein thrombosis contemporaneous with skin necrosis (see below and section 4.4).

***Thrombotic microangiopathy*:**

In the pooled phase III clinical trials, thrombotic microangiopathy events were reported in < 1 % of patients (3/444) and in 9,7 % of patients (3/31) who received at least one dose of aPCC. Each patient was reported to have received on average a cumulative amount of > 100 U/Kg/24 hours of aPCC for 24 hours or more while receiving Hemlibra prophylaxis prior to the development of TMA events (presenting with thrombocytopenia, microangiopathic haemolytic anaemia, and acute kidney injury, without severe deficiencies in ADAMTS13 activity). One patient resumed Hemlibra following resolution of TMA without recurrence (see section 4.4).

***Thrombotic events*:**

In the pooled phase III clinical trials, serious thrombotic events were reported in <1 % of patients (2/444) and in 6,5 % of patients (2/31) who received at least one dose of aPCC. Each patient was reported to have received on average a cumulative amount of > 100 U/Kg/24 hours of aPCC for 24 hours or more while receiving Hemlibra prophylaxis, prior to the development of the thrombotic events. One patient resumed Hemlibra following resolution of the thrombotic event without recurrence (see section 4.4).

Characterisation of aPCC Treatment (in the pooled phase III clinical trials)

There were 82 instances of aPCC treatment*, of which 8 instances (10 %) consisted of on average a cumulative amount of > 100 U/kg/24 hours of aPCC for 24 hours or more; two of the 8 instances were associated with thrombotic events and three of the 8 instances were

associated with TMA (see Table 3). No TMA or thrombotic events were associated with the remaining instances of aPCC treatment. Of all instances of aPCC treatment, 68 % consisted of a single infusion ≤ 100 U/kg.

Table 4 Characterisation of aPCC Treatment* in the Pooled Phase III Clinical Trials

Duration of aPCC treatment	Average cumulative amount of aPCC over 24 hours (U/Kg/24 hours)		
	< 50	50 – 100	> 100
< 24 hours	9	47	13
24-48 hours	0	3	1[a]
> 48 hours	1	1	7[a, b, b, b]

* An instance of aPCC treatment is defined as all doses of aPCC received by a patient, for any reason, until there was a 36-hour treatment-free break. Includes all instances of aPCC treatment excluding those in the first 7 days and those that occurred 30 days after the discontinuation of Hemlibra.

[a] Thrombotic event

[b] Thrombotic microangiopathy

***Injection site reactions*:**

Injection site reactions (ISRs) were reported very commonly (19,4 %) from clinical trials. All ISRs observed in the Hemlibra clinical trials were reported as being non-serious and generally mild to moderate in intensity, and 94,9 % resolved without treatment. The commonly reported ISR symptoms were injection site erythema (10,6 %), injection site pruritus (2,9 %), injection site pain (4,1 %) and injection site swelling (2,7 %).

Immunogenicity

In the pooled phase III clinical trials with Hemlibra, development of neutralising anti-hemlibra antibodies associated with decreasing emicizumab concentration was uncommon. One patient,

who developed neutralising anti-hemlibra antibodies with decreasing emicizumab concentration, experienced loss of efficacy (manifest as breakthrough bleeding) after 5 weeks of treatment and later discontinued Hemlibra treatment (see section 4.4). Overall, the safety profile of Hemlibra was similar between those patients with anti-hemlibra antibodies (including neutralising antibodies) and those without.

Patients with mild or moderate haemophilia A without FVIII inhibitors (HAVEN 6)

The safety profile of Hemlibra in patients with mild or moderate haemophilia A without FVIII inhibitors (HAVEN 6) was consistent with the known safety profile in previous HAVEN studies, conducted primarily in patients with severe haemophilia A with or without FVIII inhibitors. There were no new adverse drug reactions reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Accidental overdose may result in hypercoagulability.

Patients who receive an accidental overdose should immediately contact their medical practitioner/ medicine control centre and be monitored closely.

Treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-haemorrhagics, other systemic haemostatics; ATC code: B02BX06.

Emicizumab bridges activated factor IX and factor X to restore the function of missing activated factor VIII that is needed for effective haemostasis.

Emicizumab has no structural relationship or sequence homology to factor VIII and, as such, does not induce or enhance the development of direct inhibitors to factor VIII.

Prophylactic therapy with emicizumab shortens the activated partial thromboplastin time (aPTT) and increases the reported FVIII activity (using a chromogenic assay with human coagulation factors). These two pharmacodynamic markers do not reflect the true haemostatic effect of emicizumab *in vivo* (aPTT is overly shortened and reported FVIII activity may be overestimated) but provide a relative indication of the pro-coagulant effect of emicizumab.

CLINICAL EFFICACY

HAVEN 6

Patients (all ages) with mild or moderate haemophilia A without FVIII inhibitors

The HAVEN 6 study was a multicenter, open-label, single-arm study in 71 emicizumab-treated patients (all ages) with mild (n = 20 [28,2 %]) or moderate (n = 51 [71,8 %]) haemophilia A without FVIII inhibitors for whom prophylaxis was indicated, as assessed by the investigator. Most patients were male (69 patients [97,2 %]), and 2 were female (2,8 %). At study entry, 34 patients (47,9 %) were on episodic and 37 patients (52,1 %) were on prophylactic treatment with FVIII. Patients received subcutaneous emicizumab, 3 mg/kg once weekly for the first four weeks followed by patient preference for one of the following maintenance regimens, from week 5: 1,5 mg/kg once weekly (n = 24 [33,8 %]), 3 mg/kg every two weeks (n = 39 [54,9 %]) or 6 mg/kg every four weeks (n = 8 [11,3 %]), thereafter. Dose up-titration was allowed after 24 weeks for patients who experienced two or more qualified bleeds (i.e., spontaneous and clinically significant bleeds occurring at steady state). At the time of interim analysis, no patients underwent up-titration of their maintenance dose.

The primary efficacy objective of the study was to evaluate the efficacy of emiczumab prophylaxis based on the number of bleeds requiring treatment with coagulation factors over time (i.e., bleed rate of treated bleeds, see Table 5). Other objectives were to evaluate the efficacy of emicizumab prophylaxis based on the number of all bleeds, spontaneous bleeds, joint bleeds, and target joint bleeds over time, as well as assessing patient reported health-related quality of life HRQoL with the Comprehensive Assessment Tool of Challenges in Haemophilia (CATCH) questionnaire over time.

Efficacy results

HAVEN 6 (interim analysis)

Interim efficacy results for the HAVEN 6 clinical study are summarised below. In the study, 71 patients aged 2 to 71 years old were evaluated for efficacy with a median observation time of 27,6 weeks (range: 6,7 – 61,7 weeks). The efficacy results of emicizumab prophylaxis in patients with mild or moderate haemophilia A without FVIII inhibitors with respect to rate of treated bleeds, all bleeds, treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds are shown in Table 5.

Table 5 HAVEN 6: Annualised Bleed Rate with Emicizumab Prophylaxis in Patients with Mild or Moderate Haemophilia without FVIII Inhibitors

	[c]Hemlibra 1,5 mg/kg QW, 3 mg/kg Q2W or 6 mg/kg Q4W		
Endpoints	**[a]ABR (95 % CI)**	**[b]Median ABR (IQR)**	**% Zero Bleeds (95 %CI)**
N	71	71	71
Treated Bleeds	0,8 [0,41;1,46]	0,0 [0,00; 0,00]	80,3 [69,1; 88,8]
All Bleeds	2,7 [1,87; 3,83]	1,7 [0,00; 3,80]	45,1 [33,2; 57,3]
Treated Spontaneous	0,1 [0,02;0,23]	0,0 [0,00; 0,00]	95,8 [88,1; 99,1]

Bleeds			
Treated Joint Bleeds	0,3 [0,12;0,65]	0,0 [0,00; 0,00]	90,1 [80,7; 95,9]
Treated Target Joint Bleeds	*Did not converge	0,0 [0,00; 0,00]	94,4 [86,2; 98,4]

[a] Calculated with negative binomial regression (NBR) model

[b] Calculated ABR

Bleed definitions adapted based on ISTH criteria

Treated bleeds: bleeds treated with FVIII.

All bleeds: bleeds treated and not treated with FVIII.

Patients exposed to emicizumab started with a loading dose of 3 mg/kg/week for 4 weeks.

ABR=Annualized Bleed Rate, CI=confidence interval; IQR=interquartile range; 25th percentile to 75th percentile; QW=once every week; Q2W=once every two weeks; Q4W=once every four weeks prophylaxis

[c] 1,5 mg/kg QW (n = 24); 3 mg/kg Q2W, (n = 39); 6 mg/kg Q4W (n = 8)

*Model may not converge due to too short follow-up times combined with a low number of bleeds

Health-related outcome measures

HAVEN 6 assessed HRQoL in adult and paediatric patients, as well as caregivers of paediatric patients, using the CATCH questionnaire. The domains of risk perception and impact of hemophilia on daily activities, social activities, recreational activities, and work/school, as well as preoccupation and treatment burden were examined.

Health-related outcomes results

HAVEN 6 health-related outcomes

In HAVEN 6, HRQoL for patients with mild or moderate haemophilia A of all ages was evaluated at week 25 based on the CATCH questionnaire. The CATCH questionnaire (version 1.0) is a

validated instrument that assesses the effect of haemophilia and its treatment. Different versions of the questionnaire exist for adult patients, paediatric patients and caregivers of paediatric patients. HRQoL on Hemlibra prophylaxis remained generally stable, with improvement in the treatment burden domain of CATCH consistently observed across the respondent group.

5.2 Pharmacokinetic properties

The pharmacokinetics of emicizumab were determined via a non-compartmental analysis in healthy subjects and using a population pharmacokinetic analysis on a database composed of 389 patients with haemophilia A.

Absorption

Following subcutaneous administration in haemophilia A patients, the absorption half-life was 1,6 days.

Following multiple subcutaneous administrations of 3 mg/kg once weekly for the first 4 weeks in haemophilia A patients, mean (±SD) trough plasma concentrations of emicizumab achieved 52,6 ±13,6 µg/mL at Week 5. Sustained mean trough plasma concentrations of emicizumab at steady-state were 51,2 µg/mL, 46,9 µg/mL and 38,5 µg/mL with the recommended maintenance doses of 1,5 mg/kg once weekly, 3 mg/kg every two weeks or 6 mg/kg every four weeks, respectively (see Figure 1).

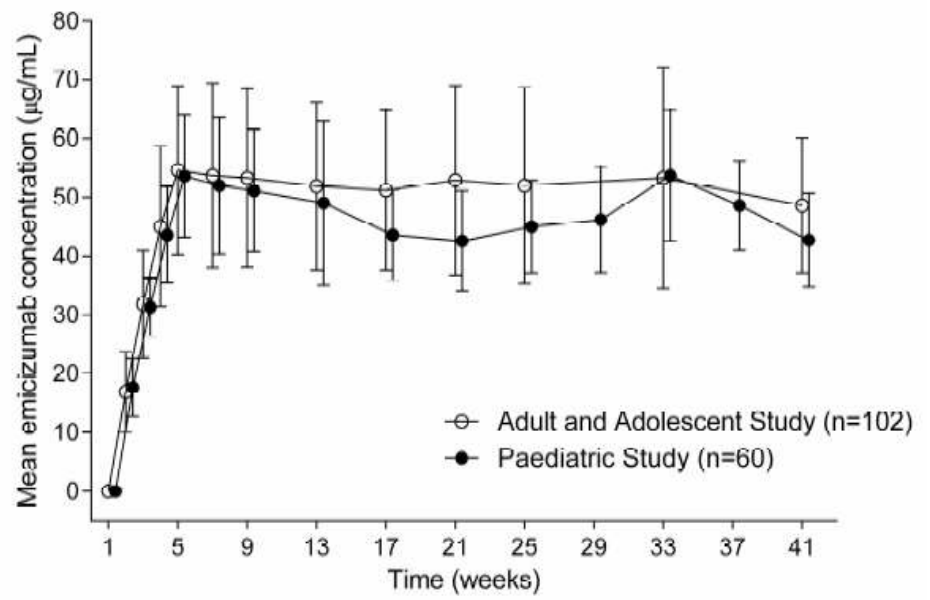
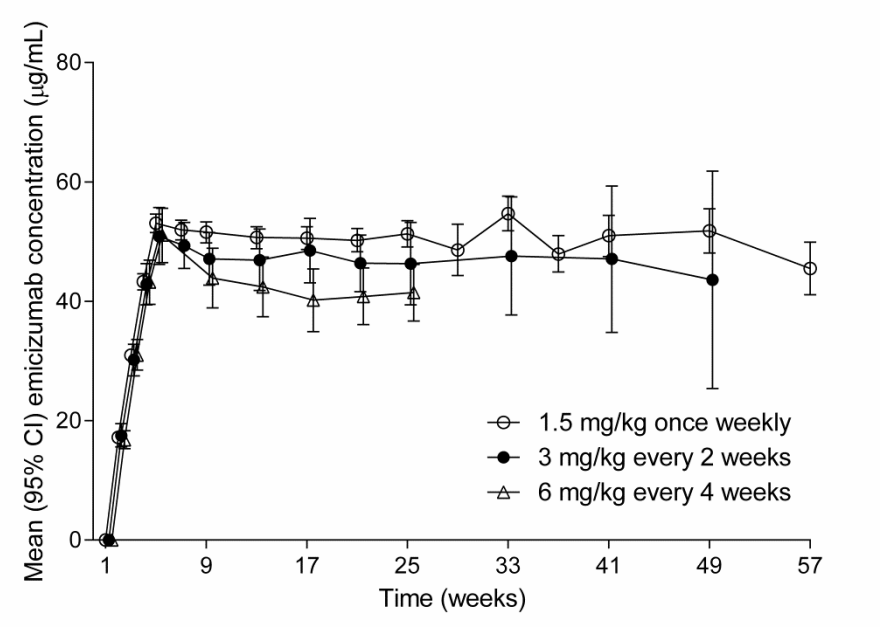


Figure 1: Mean (±95 % CI) Emicizumab Trough Concentrations for Maintenance Doses

The mean (±SD) C_{trough}, C_{max} and ratios of C_{max}/C_{trough} at steady-state for the recommended maintenance doses of 1,5 mg/kg once weekly, 3 mg/kg every two weeks or 6 mg/kg every four weeks are shown in below.

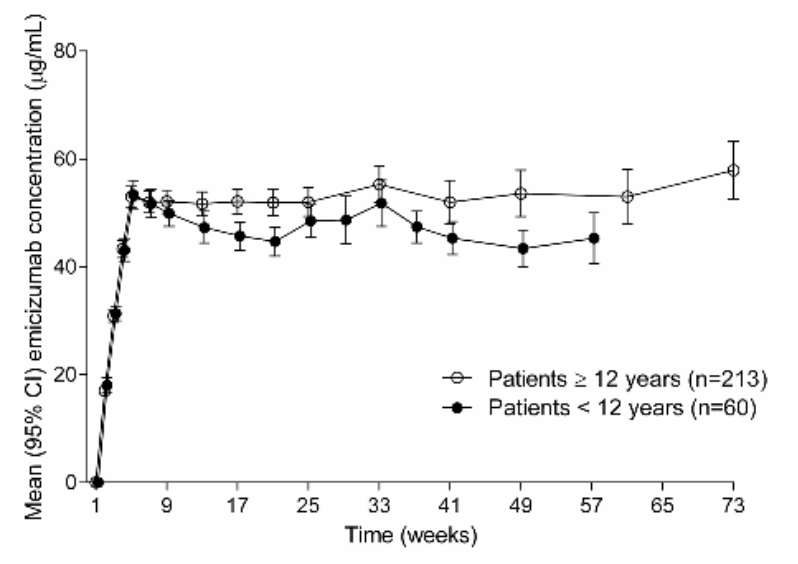


Mean (± SD) Steady-State Emicizumab Concentrations

	Maintenance Dose		
Parameters	1,5 mg/kg once weekly	3 mg/kg every two weeks	6 mg/kg every four weeks
$C_{max, ss}$ (µg/mL)	55,1 ±15,9	58,3 ±16,4	67,0 ±17,7
$C_{avg, ss}$ (µg/mL)	53,7 ±15,6	53,7 ±15,6	53,7 ±15,6
$C_{trough, ss}$ (µg/mL)	51,2 ±15,2	46,9 ±14,8	38,5 ±14,2
$C_{max}/C_{trough\ ratio}$	1,08 ±0,03	1,26 ±0,12	1,85 ±0,47
$C_{avg, ss}$ = average concentration at steady state; $C_{max, ss}$ = maximum plasma concentration at steady state; $C_{trough, ss}$ = trough concentration at steady state; Pharmacokinetic parameters derived from the population PK model.			

Similar PK profiles were observed following once weekly dosing (3 mg/kg/week for 4 weeks followed by 1,5 mg/kg/week) in adults/adolescents (≥ 12 years) and children (< 12 years) (see Figure 2).

Figure 2: Mean Plasma Emicizumab Concentration versus Time Profiles for Patients ≥ 12 Years Compared with Patients <12 Years



In healthy subjects, the absolute bioavailability following subcutaneous administration of 1 mg/kg was between 80,4 % and 93,1 % depending on the injection site. Similar pharmacokinetic profiles were observed following subcutaneous administration in the abdomen, upper arm, and thigh. Emicizumab can be administered interchangeably at these anatomical sites (see section 4.2).

Distribution

Following a single intravenous dose of 0,25 mg/kg emicizumab in healthy subjects, the volume of distribution at steady state was 106 mL/kg (i.e. 7,4 L for a 70 kg adult). Emicizumab is not intended for intravenous use (see section 4.2).

The apparent volume of distribution (V/F), estimated from the population pharmacokinetic analysis, in haemophilia A patients following multiple subcutaneous doses of emicizumab was 10,4 L.

Metabolism

The metabolism of emicizumab has not been studied. IgG antibodies are mainly catabolised by lysosomal proteolysis and then eliminated from or reused by the body.

Elimination

Following intravenous administration of 0,25 mg/kg in healthy subjects, the total clearance of emicizumab was 3,26 mL/kg/day (i.e. 0,228 L/d for a 70 kg adult) and the mean terminal half-life was 26,7 days.

Following single subcutaneous injection in healthy subjects, the elimination half-life was approximately 4 to 5 weeks.

Following multiple subcutaneous injections in haemophilia A patients, the apparent clearance was 0,271 L/day and the elimination apparent half-life was 26,9 days.

Dose linearity

Emicizumab exhibited dose-proportional pharmacokinetics in patients with haemophilia A over a dose range from 0,3 to 6 mg/kg once weekly following subcutaneous administration.

Pharmacokinetics in Special Populations

Renal impairment

No studies on the effect of renal impairment on the pharmacokinetics of emicizumab have been conducted. Most of the patients with haemophilia A in the population pharmacokinetic analysis had normal renal function (N = 332; creatinine clearance [CLcr] ≥ 90 mL/min) or mild renal impairment (N = 27; CLcr of 60-89 mL/min). Only 2 patients had moderate renal impairment (CLcr of 30-59 mL/min). No patients had severe renal impairment. Mild or moderate renal impairment did not appear to have an impact on the pharmacokinetics of emicizumab (see section 4.2)

Hepatic impairment

No studies on the effect of hepatic impairment on the pharmacokinetics of emicizumab have been conducted.

Paediatrics

The effect of age on the pharmacokinetics of emicizumab was assessed in a population pharmacokinetic analysis which included 5 infants (≥ 1 month to < 2 years, 55 children (≥ 2 years to < 12 years) and 50 adolescents (12 - < 18 years) with haemophilia A. Age did not affect the pharmacokinetics of emicizumab in paediatric patients (see section 4.2).

Elderly

The effect of age on the pharmacokinetics of emicizumab was assessed in a population pharmacokinetic analysis which included 13 patients aged 65 years and older (no subjects were older than 77 years of age). Relative bioavailability decreased with older age, but no clinically important differences were observed in the pharmacokinetics of emicizumab between patients < 65 years and patients ≥ 65 years.

Gender

Limited data in female patients suggests that gender did not affect the pharmacokinetics of emicizumab.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-arginine

L-aspartic acid

L-histidine

Polaxamer 188

Water for injection

6.2 Incompatibilities

No incompatibilities between Hemlibra and polypropylene or polycarbonate syringes, polycarbonate vial adapters and stainless steel needles have been observed.

In the absence of compatibility studies, Hemlibra must not be mixed with other medicines.

6.3 Shelf life

Hemlibra® 30 mg/1 mL: 24 months

Hemlibra® 60 mg/0,4 mL: 24 months

Hemlibra® 105 mg/0,7 mL: 24 months

Hemlibra® 150 mg/1 mL: 24 months

Once removed from the refrigerator, unopened vials can be kept at room temperature (below 30 °C) for up to 7 days.

After storage at room temperature, unopened vials may be returned to the refrigerator. Cumulative storage time at room temperature should not exceed 7 days.

Once transferred from the vial to the syringe Hemlibra should be used immediately since it does not contain any antimicrobial preservative.

Refer to the Hemlibra “Instructions for Use” for handling instructions when combining vials in a syringe. Do not use different Hemlibra vial concentrations (30 mg/mL and 150 mg/mL) in a single syringe when combining vials to administer the prescribed dose.

6.4 Special precautions for storage

Store vial in a refrigerator at 2 - 8 °C.

Do not freeze. Do not shake.

Keep vial in the outer carton in order to protect from light.

Store out of reach of children.

Do not use after the expiry date (EXP) shown on the pack.

Disposal of unused/expired medicines

Hemlibra should not be disposed of via wastewater and disposal through household waste should be avoided.

6.5 Nature and contents of container

Hemlibra is supplied in single-use 3 mL clear glass vial containing:

- 1 mL of Hemlibra solution (30 mg/mL),
- 0,4 mL of Hemlibra solution (150 mg/mL),
- 0,7 mL of Hemlibra solution (150 mg/mL),
- 1 mL of Hemlibra solution (150 mg/mL).

Each pack of Hemlibra contains 1 glass vial.

Once transferred from the vial to the syringe, Hemlibra should be used immediately.

Not all strengths may be marketed.

6.6 Special precautions for disposal and other handling

Hemlibra solution is a sterile, preservative-free, and ready to use solution for subcutaneous injection that does not need to be diluted. Hemlibra solution should be discarded if particulate matter is visible or the product is discoloured.

- Once removed from the refrigerator, unopened vials can be kept at room temperature (below 30 °C) for up to 7 days.
- After storage at room temperature, unopened vials may be returned to the refrigerator. Cumulative storage time at room temperature should not exceed 7 days.
- Once transferred from the vial to the syringe Hemlibra should be used immediately.
- Return all unused medicine to your pharmacist.
- Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

A syringe, a transfer needle (with or without filter) or a vial adaptor (with or without filter) and an injection needle are needed to withdraw Hemlibra solution from the vial and inject it subcutaneously.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Roche Products (Pty) Ltd

90 Bekker Road, Hertford Office Park,

Building E, Vorna Valley, Midrand,

Johannesburg, 1686

South Africa

Roche Ethical Assistance Line (REAL) toll-free: 0800 21 21 25

8. REGISTRATION NUMBERS

Hemlibra® 30 mg/1 mL solution for injection: 53/30.1/0071

Hemlibra® 60 mg/0,4 mL solution for injection: 53/30.1/0072

Hemlibra® 105 mg/0,7 mL solution for injection: 53/30.1/0073

Hemlibra® 150 mg/1 mL solution for injection: 53/30.1/0074

9. DATE OF FIRST AUTHORISATION

Date of registration: 9 May 2019

10. DATE OF REVISION OF THE TEXT

30 October 2025

Hemlibra® 30 mg/1 mL:	Namibia: NS2 19/30/0033	Zimbabwe: PP 2019/10.7/5815	Botswana: S2 BOT2103738	Zambia: POM ZAMRA-HM-23-15
Hemlibra® 60 mg/0,4 mL:	Namibia: NS2 19/30/0034	Zimbabwe: PP 2019/10.7/5814	Botswana: S2 BOT2103737	Zambia: POM ZAMRA-HM-23-17
Hemlibra® 105 mg/0,7 mL:	Namibia: NS2 19/30/0035	Zimbabwe: PP 2019/10.7/5813	Botswana: S2 BOT2103736	Zambia: POM ZAMRA-HM-23-25
Hemlibra® 150 mg/1 mL:	Namibia: NS2 19/30/0036	Zimbabwe: PP 2019/10.7/5812	Botswana: S2 BOT2103730	Zambia: POM ZAMRA-HM-23-35

Approved manufacturer(s):

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