HEMLIBRA

(emicizumab)

Patient information brochure

September 2020 Update

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emicizumab

Dear Patient,

This brochure has been given to you since you have been found eligible for treatment with a drug called HEMLIBRA.

Welcome to the HEMLIBRA instruction guide.

The aim of this brochure is to provide information and support for treatment with HEMLIBRA.
The brochure was updated with information related to the instructions for injection. As part of this update, use of a transfer needle with a 5 micrometre filter has been implemented.

The information provided in the brochure is not a substitute for the judgement or recommendations of the attending physician, and the best source of medical information is the medical team. For further questions, if required, contact the physician, nurse or pharmacist.

For complete information regarding the medication, refer to the Patient Information Leaflet published in the drug database on the Ministry of Health website.
For further information, you may contact the company.

We wish you the best of health

The information about this medication was prepared in accordance with the Israeli Ministry of Health Procedure 137 - "Guidelines for the promotion of educated use and adherence to pharmacological treatment in patients for whom prescription preparations have been prescribed, using non-commercial information."

The information is correct as of September 2020.

For simplicity and ease of reading, this brochure was phrased in the masculine form. However, this brochure is intended for both women and men.

Wherever HEMLIBRA is mentioned in this brochure, the reference is to HEMLIBRA 30 MG/ML or HEMLIBRA 150 MG/ML, which contains the active ingredient emicizumab at a concentration of 30 mg/ml or 150 mg/ml.

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Table of Contents

Chapter 1 **Information about the disease**

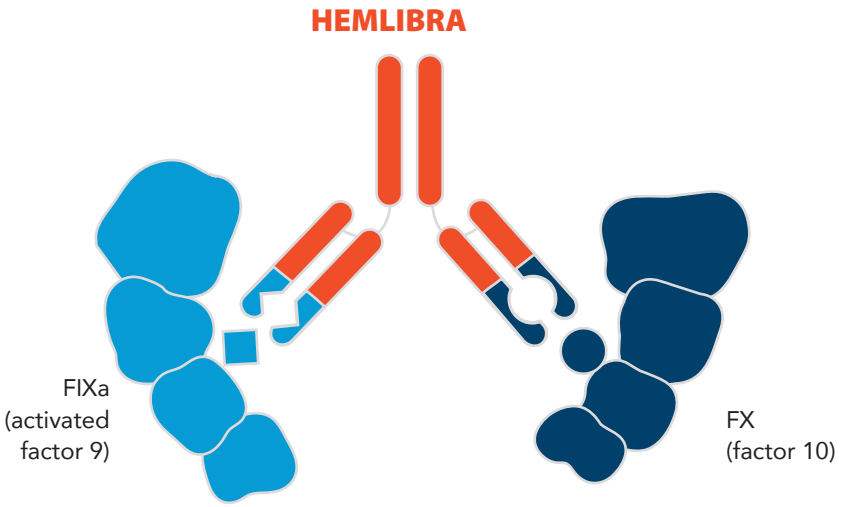
Hemophilia A is a genetic bleeding disease caused by deficiency in factor VIII. The severity of the disease is classified into 3 severity levels in accordance with the level of the factor; half of all patients suffer from severe hemophilia associated with frequent spontaneous bleeds, starting from early childhood, at sites such as the joints, muscles, subcutaneous tissues, skin and mucosa, and even the gastrointestinal system and brain. The recurrent bleeds are the major complication of the disease, starting with recurrent bleeds to the joints manifested by frequent pain with limitations in movement, and in the long term - irreversible damage, up to disability. This complication significantly impairs patient quality of life and leads to the need for surgeries, including joint replacement at young age, and even to hemorrhages in the brain, gastrointestinal system etc., which may be life threatening. Disease complications lead to significant morbidity and shortening of life expectancy. The standard treatment of hemophilia A is based on the use of plasma-derived or recombinant factor VIII concentrates. There are 2 treatment regimens - prophylaxis, administered to most of the patients with moderate or severe hemophilia and to almost 100% of pediatric patients, and treatment on demand administered at the time of bleeding. The development of neutralizing antibodies that target the standard treatment, factor VIII, in patients with hemophilia A is one of the most significant complications resulting from repeated exposure to foreign factor VIII. The inhibitors bind to the factor and neutralize its activity. About 20-30% of patients with severe hemophilia and about 5-10% of patients with mild to moderate hemophilia develop inhibitors. About 20% of the patients remain with persistent inhibitors. Thus, inhibitor development may turn patients with mild to moderate hemophilia to severe hemophilia patients.

Chapter 2 **What is HEMLIBRA?**

- HEMLIBRA is used as a routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in patients with hemophilia A (an inherited deficiency of coagulation factor VIII) with or without factor VIII inhibitors.
- HEMLIBRA is an antibody which binds coagulation factors together, to assist in blood coagulation.
- HEMLIBRA can reduce the number of bleeds, including joint bleeds and spontaneous bleeds, and can reduce the risk of long term joint damage.

How does HEMLIBRA work?

HEMLIBRA bridges between activated factor 9 and factor 10 to restore the missing function of factor 8, the role of which is to activate factor 10 to continue the coagulation cascade.



Chapter 3 **Dosage and treatment management with HEMLIBRA**

Recommended dosage

The dosage and manner of treatment will be determined by the physician only.

The dosage of HEMLIBRA depends on your weight and the attending physician will calculate the amount (in milligrams) and the corresponding amount of Hemlibra solution (in milliliters) for subcutaneous injection:

- Loading dose: Week 1 to 4: The dosage is 3 milligrams per kilogram of body weight, injected once a week.
- Maintenance dose: Week 5 and onwards: The dosage is 1.5 milligrams per kilogram of body weight, injected once a week, or 3 milligrams per kilogram of body weight, injected every 2 weeks, or 6 milligrams per kilogram of body weight, injected every 4 weeks

Loading dose dosage (week 1 to 4)	Maintenance dose dosage (week 5 and onwards)
3 mg/kg once a week	1.5 mg/kg once a week Or 3 mg/kg every 2 weeks Or 6 mg/kg every 4 weeks

The decision whether to use the maintenance dose of 1.5 mg/kg once per week, 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks should be made in consultation with the attending physician and, possibly with your caregivers as well.

Do not skip any injection. Skipping an injection may increase your risk of bleeding.

What should you do if you forgot a dose?

- Inject the forgotten dose as soon as possible before the day of your next scheduled dose.
- Then, continue to inject the medicine as scheduled.
- Do not inject two doses on the same day to compensate for a forgotten dose.
- If you are not sure what to do, ask your doctor, pharmacist or nurse.

Different strengths and concentrations

HEMLIBRA is available in 4 different strengths.
The strength appears on the package

* The picture is for illustration only

30mg/mL (30mg/mL) | 60mg/0.4mL (150mg/mL) | 105mg/0.7mL (150mg/mL) | 150mg/mL (150mg/mL)

- The dosage of HEMLIBRA is weight-dependent. The attending physician will tell you which vial/s to use, according to your weight.
- **Do not** combine different concentrations of Hemlibra (30 mg/ml and 150 mg/ml) in a single injection when preparing the total volume for injection.
- If your weight changes, do not change the dosage on your own accord; rather, consult the attending physician.
- Prior to each use, check the strength written on the vial.
- Discard any leftovers remaining in the vial following injection.

Chapter 4 **Safety information for HEMLIBRA**

Do not use HEMLIBRA if:

You are sensitive (allergic) to the active ingredient emicizumab or to any of the other ingredients that this medicine contains (listed in the Patient Leaflet).

Safety information

Special warnings regarding the use of HEMLIBRA:

Before you start using HEMLIBRA, it is very important to talk to the attending physician about use of "bypassing agents" (drugs that help the blood clot, but which act in a manner different than factor 8). This is because treatment with bypassing agents may change during the administration of HEMLIBRA. Examples of bypassing agents include aPCC (activated prothrombin complex concentrate) and recombinant factor 7a (rFVIIa). Severe side effects may occur with the use of aPCC during treatment with HEMLIBRA:

- Destruction of red blood cells (thrombotic microangiopathy)
- Blood clots (thromboembolism)

Stop using HEMLIBRA and aPCC and tell your doctor immediately if you notice any symptom of red blood cell destruction or blood clots.

Very common side effects:

- Injection site reaction (redness, itching, pain)
- Headache
- Joint pain

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Common side effects:

- Fever
- Muscle pain
- Diarrhea

For the full list of side effects, see the Patient Leaflet.

Reporting side effects

Side effects can be reported to the Ministry of Health by clicking on the link "Reporting Side Effects of Pharmacological Treatment" on the Ministry of Health homepage at www.health.gov.il, which directs you to the online form for the report of side effects.
You may also report directly to Roche, by email at israel.drugsafety@roche.com or by telephone: 09-9737722.

Inquiries regarding quality

For inquiries regarding quality, contact
israel.productcomplaints@roche.com
or by telephone: 09-9737777

Pregnancy, breastfeeding and fertility

Use an effective method of contraception during treatment with HEMLIBRA and for 6 months after the last injection of HEMLIBRA.

If you are pregnant or breastfeeding, think you may be pregnant or are planning a pregnancy consult your doctor or pharmacist before using HEMLIBRA. Your doctor will weigh the benefit of taking HEMLIBRA against the risk to your baby.

Chapter 5 **Instructions for using HEMLIBRA solution for injection:**

You must read, understand and follow the instructions for use before injecting HEMLIBRA. Your doctor or nurse will show you how to prepare, measure and inject HEMLIBRA properly before you use it for the first time. Consult your doctor or nurse if you have any questions.

Important information:

- **Do not** inject yourself or someone else unless you have been shown how to inject by your doctor or nurse.
- Make sure that the name HEMLIBRA appears on the carton box and on the vial.
- Before opening the vial, read the vial label to ensure that you have the appropriate strength, as prescribed by the attending physician. You may need to use more than one vial to receive the total dose prescribed for you.
- Check the expiration date on the carton box and the vial. **Do not** use if the expiration date has passed.
- **Use the vial one time only**. After you inject the dose, discard any leftover HEMLIBRA remaining in the vial. Do not keep leftover drug remaining in the vial for later use.
- **Use only the syringes, transfer needles and injection needles prescribed for you.**
- **Use the syringes, transfer needles and injection needles one time only.** Discard used syringes and needles.
- If your dose is larger than 2 ml, you will need more than one subcutaneous injection of HEMLIBRA; contact your doctor or nurse for appropriate injection instructions.
- You must inject HEMLIBRA under the skin only.

Storage of HEMLIBRA vials, needles and syringes:

- Store the vial in its original packaging in order to protect it from light.
- Keep the vials, needles and syringes out of the sight and reach of children. Store the vial in the refrigerator (2°C-8°C).
- **Do not** freeze.
- **Do not** shake the vial.
- Take the vial out of the refrigerator 15 minutes before use and allow it to reach room temperature (below 30°C) before preparing the injection.
- Once taken out of the refrigerator, an unopened vial may be kept at room temperature for up to 7 days. After storage at room temperature, unopened vials may be returned to the refrigerator. The total period during which the drug may be stored out of the refrigerator may not exceed 7 days.
- Discard vials that have been kept at room temperature for more than 7 days or at a temperature above 30°C.
- Keep the transfer needle, injection needle and syringe dry.

Inspection of the drug and supplies

- Collect all of the accessories listed below to prepare for the injection and to inject the drug.
- **Check** the expiration date on the carton box, the vial and the accessories listed below. **Do not** use if the expiration date has passed.

Do not use the vial if:

- The drug is cloudy, hazy, or colored.
- The drug contains particles.
- The cap covering the vial stopper is missing.

- Ensure that the accessories required for injection are not damaged. **Do not use** if the accessories appear to be damaged or if they have been dropped.
- Place the accessories required on a clean, well-lit and flat surface.

Included in the pack:

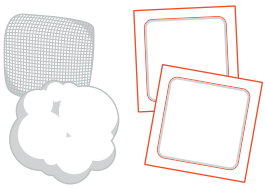
- **A vial, which contains the drug**

- **Hemlibra Patient Leaflet**

Not included in the pack:

- **Alcohol wipes**

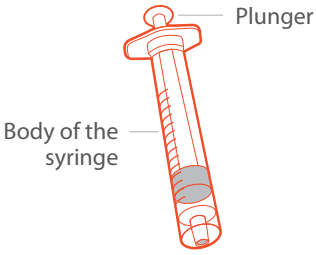
  Attention: If you have to use more than one vial to inject the dose prescribed for you, you must use a new alcohol wipe for each vial
- **Gauze**
- **A cotton ball**



- **A syringe**

  Attention: For an injection volume of up to 1 ml, use a **1 ml syringe.**

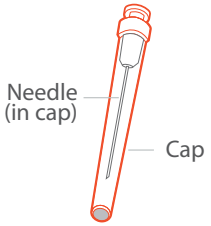
  For an injection amount of 1 ml to 2 ml, use a **2 ml or 3 ml syringe.**



- **An 18G transfer needle with a 5 micrometre filter**

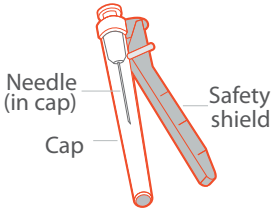
  Attention: If you have to use more than one vial to inject the dose prescribed for you, you must use a new transfer needle for each vial

  Do not use the transfer needle to inject the drug.



- **A 26 G injection needle, with a safety shield**

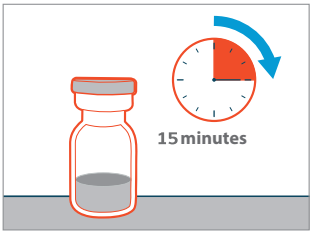
  Do not use the injection needle to draw up the drug from the vial.



- **A sharps disposal container**

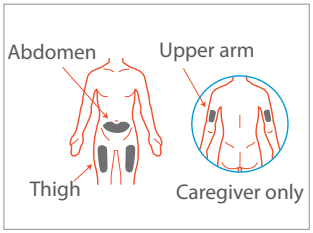
Preparation for injection:

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



Selection and preparation of the injection site:

- Clean the selected injection site area with an alcohol wipe.
- Allow the skin to dry for about 10 seconds. Do not touch, blow or fan the clean injection site before the injection



Possible injection sites:

- Thighs (front and middle area).
- The abdominal area, except for 5 cm around the navel.
- The external area of the upper arm (only if a caregiver is administering the injection).
- You should use a different injection site each time you inject, at least 2.5 cm away from the last injection site.
- Do not inject to areas that may be irritated by a belt. Do not inject into moles, scars, bruises, or areas in which the skin is tender, red, hard or injured.

Preparing the syringe for injection:

- Do not touch exposed needles or place them on the surface after removing the cap.
- After filling the syringe with the drug, use it immediately.
- After the injection needle cap has been removed, inject the drug contained in the syringe under the skin within 5 minutes. Do not use the syringe if the needle has touched any surface.
- **Discard any vials, needles, vial/needle caps and used syringes in a sharps disposal container.**

Important information for after the injection:

- Do not rub the injection site after the injection.
- **If you notice 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 the bleeding stops.**
- If you have bruises (a small area of bleeding under the skin), an ice pack can be gently pressed over the area. If the bleeding does not stop, contact your doctor or nurse.

Disposing of the drug and supplies:

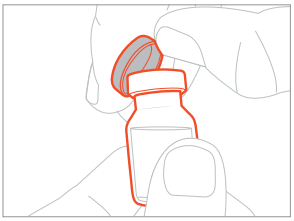
Important: Always keep the sharps disposal container out of the reach of children.

- Place your used needles and syringes in the special container immediately after use. Do not discard released needles and syringes in household waste.
- If you don't have a sharps disposal container, you can use any container which:
  - is made of durable plastic.
  - can be closed with a tight, puncture-resistant lid, so that the sharps cannot come out.
  - is upright and stable during use.
  - is leak-resistant.
  - has a proper label attached, warning that there is hazardous waste inside the container.
- When the sharps disposal container is almost full, ask the pharmacist how to dispose of the container.
- Do not dispose of the sharps disposal container in household waste and do not recycle it.

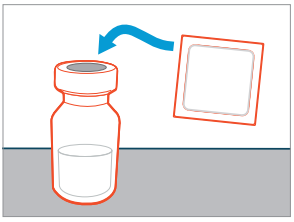
1. Preparation

Stage 1: Removing the vial cap and cleaning the top of the vial

- Remove the vial cap.
- Discard the vial cap into the sharps disposal container.

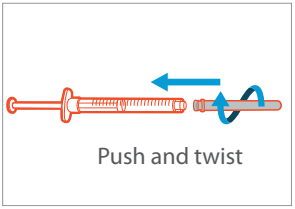


- Clean the top of the vial stopper with an alcohol wipe.

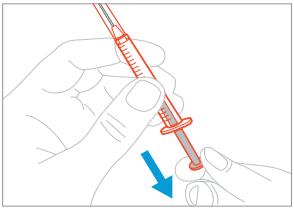


Stage 2: Attaching a transfer needle with a filter to the syringe

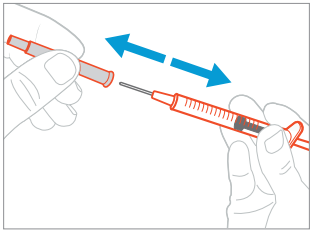
- **Push the transfer needle with the filter onto the syringe and twist it clockwise** until it is fully attached.



- Slowly pull back the plunger and draw air into the syringe, in the same amount as the dose prescribed for you.

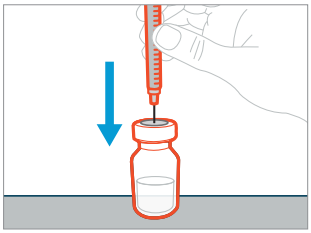


Stage 3: Removing the transfer needle cover

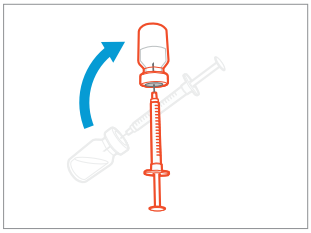


- Hold the syringe by the body of the syringe with the transfer needle pointing upwards.
- Carefully pull the transfer needle cover directly off, pointing away from your body. **Do not discard the cover. Place the transfer needle cover on a clean flat surface.** You will need to cover the transfer needle after transferring the drug.
- **Do not touch** the tip of the needle or place it on the surface after removing the needle cap.

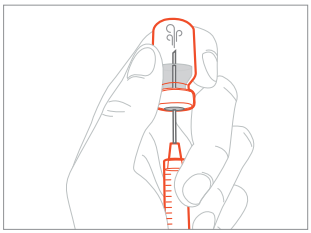
Stage 4: Injecting air into the vial



- Keep the vial on the flat working surface and insert the transfer needle and the syringe directly into the center of the vial stopper.

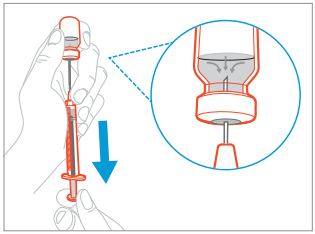


- Keep the needle in the vial and turn the vial upside down.



- With the needle pointing upwards, push the plunger to inject air from the syringe **above the drug.**
- Keep your finger pressed on the syringe plunger.
- **Do not** inject air into the drug. This may cause air bubbles or foam to form in the drug.

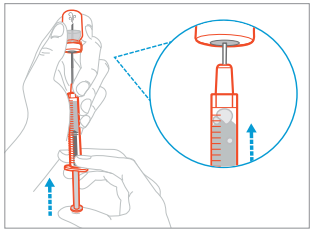
Stage 5: Transferring the drug to the syringe

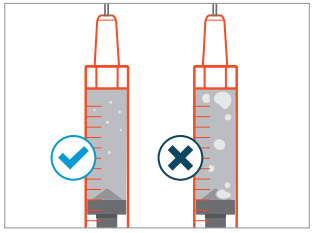


- Slide the tip of the needle down so that it is **in the drug.**
- Pull the plunger backwards **slowly** to prevent the formation of air bubbles or foam. Fill the syringe with more than the amount of drug required for the dose prescribed for you.
- Be careful not to pull the plunger out of the syringe.

Important: If the dose prescribed for you is larger than the amount of drug in the vial, **withdraw all of the drug** and go to the section **"Combining Vials".**

Stage 6: Removing air bubbles





- Keep the needle in the vial and check the syringe for the presence of large air bubbles. Air bubbles that are too large can reduce the dose of the drug received.
- **Remove the large air bubbles** by gently **tapping** on the body of the syringe with your fingers until the air bubbles rise to the top of the syringe. Move the needle tip **above the drug** and slowly push the plunger upwards to remove the air bubbles from the syringe.
- If the amount of the drug in the syringe is equal or to or smaller than the dose prescribed for you, move the tip of the needle **into the drug and slowly pull** back the plunger until you have **more** than the amount required for **the dose prescribed** for you.
- Be careful not to pull the plunger out of the syringe.
- Repeat the steps detailed above until you have removed the large air bubbles.

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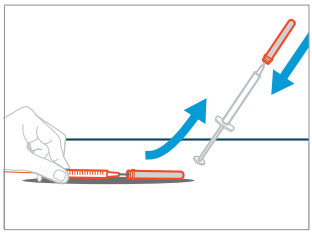
Attention: Ensure that you have enough drug in the syringe to complete the dose before moving to the next stage. If you cannot remove all of the drug, turn the vial upright to reach the remaining amount

Do not use the transfer needle to inject the drug. This may cause pain and bleeding.

2. Injection

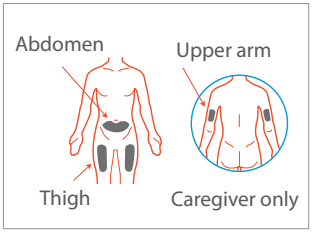
Stage 7: Covering the transfer needle

- Remove the syringe and transfer needle from the vial.
- **Using one hand, insert** the transfer needle into the cap **and lift upwards** to cover the needle.
- Once the needle is covered, use **one hand** to push the transfer needle cap towards the syringe to fully attach it, to prevent an accidental needle prick.



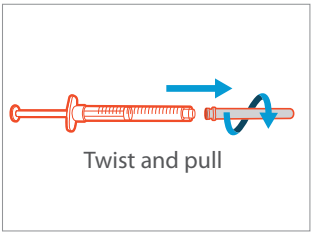
Stage 8: Cleaning the injection area

- Select the injection site **and clean** it using an alcohol wipe.



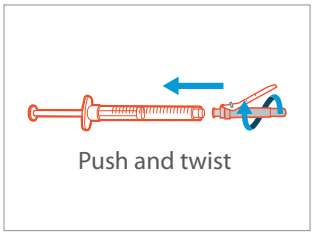
Stage 9: Removing the transfer needle

- Remove the transfer needle from the syringe by twisting counter-clockwise and pulling gently.
- Discard the used transfer needle into the sharps disposal container.



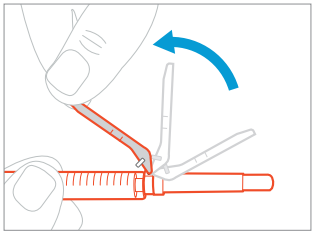
Stage 10: Attaching the injection needle to the syringe

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



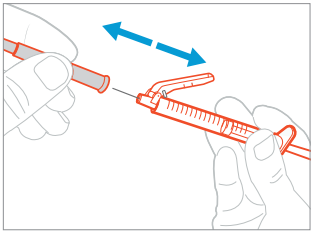
Stage 11: Moving the safety shield

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



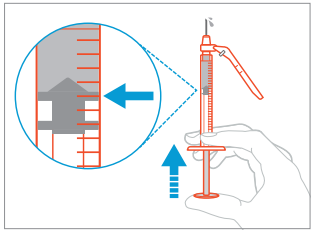
Stage 12: Removing the injection needle cover

- Carefully **pull** the injection needle cap away from the syringe in a straight line.
- Discard the cap in the sharps disposal container.
- **Do not touch** the tip of the needle or allow it to touch any surface.
- After the injection needle cap has been removed, inject the drug in the syringe within 5 minutes.



Stage 13: Adjusting the plunger to the prescribed dose

- Keep the syringe with the needle pointing upwards and slowly push the plunger until you reach the dose prescribed for you.
- **Check your dose.** Make sure that the upper rim of the plunger is aligned with the mark on the syringe for the dose prescribed for you.



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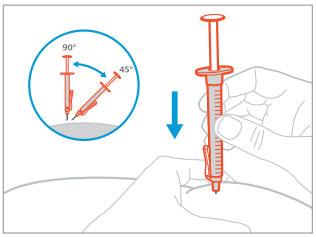
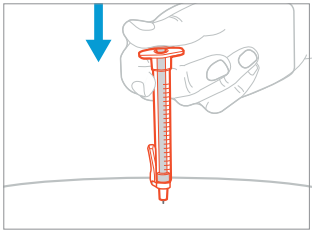
Stage 14: Subcutaneous injection (under the skin)



- Pinch the selected injection site and fully insert the needle at a **45° to 90°** angle in a quick and firm motion. **Do not** hold or push the plunger while inserting the needle.
- Maintain the position of the syringe and release the fold of skin at the injection site.

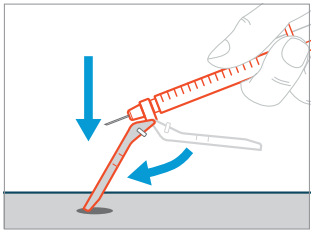
Stage 15: Injecting the drug



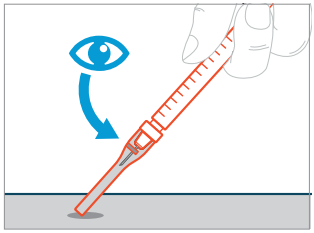
- Slowly inject all of the drug by gently pushing the plunger all the way down.
- Remove the needle and the syringe from the injection site at the same angle used for insertion.

3. Disposal

Stage 16: Covering the needle with the safety shield

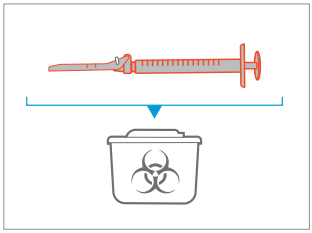


- Move the safety shield forward at 90°, away from the body of the syringe.
- While holding the syringe with one hand, **press the safety shield down** against a flat surface using a quick and firm motion until you hear a "click".



- If you do not hear a click, look to check that the needle is fully covered by the safety shield.
- Always hold your fingers behind the safety shield and away from the needle.
- **Do not** separate the injection needle.

Stage 17: Discarding the syringe and needle

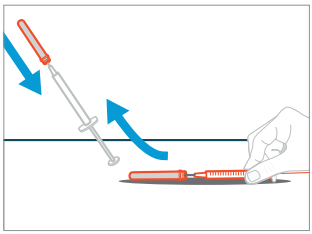


- Place **your** used needles and syringes in a sharps disposal container immediately after use. For further information, see the section "Disposing of the drug and accessories".
- **Do not** try to remove the used injection needle from the used syringe.
- **Do not cover** the injection needle with the cap again.
- **Important:** Always keep the sharps disposal container out of the reach of children.
- Discard caps, vials, used needles and syringes in a sharps container.

Combining vials

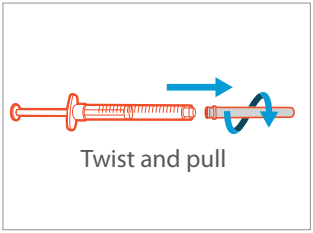
If you need to use more than one vial to obtain the total dose prescribed for you, follow the instructions below after you have drawn up the drug from the first vial:

Stage A: Covering the transfer needle



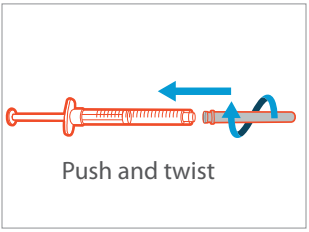
- Remove the syringe and transfer needle from the first vial.
- **Using one hand,** insert the transfer needle into the cap **and lift upwards** to cover the needle.
- Once the needle is covered, use **one hand** to push the cap of the transfer needle towards the syringe to fully attach it, to prevent an accidental needle prick.

Stage B: Removing the transfer needle



- Remove the transfer needle from the syringe by twisting counter-clockwise and pulling gently.
- Discard the used transfer needle into the sharps disposal container.

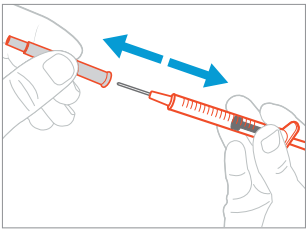
Stage C: Attaching a new transfer needle with a filter to the syringe



Attention: You must use a new transfer needle with a filter each time you withdraw the drug from a new vial.

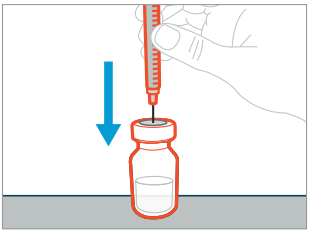
- Push a **new** transfer needle onto the syringe and twist it clockwise until it is fully attached.
- Slowly pull back the plunger and draw air into the syringe.

Stage D: Removing the transfer needle cover

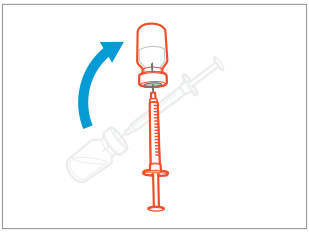


- Hold the syringe by the body of the syringe with the transfer needle cap pointing upwards.
- Carefully pull the transfer needle cover directly off and away from your body. **Do not discard the cover.** You will need to cover the transfer needle after drawing the drug.
- **Do not touch** the tip of the needle.

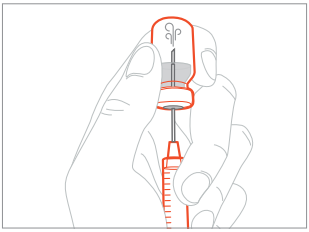
Stage E: Injecting air into the vial



- With the new vial placed on the flat working surface, insert the new transfer needle and the syringe, directly down into the **center** of the vial stopper.

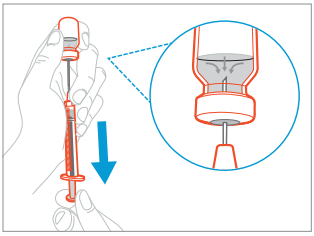


- Keep the transfer needle in the vial and turn the vial upside down.



- With the needle pointing upwards, inject the air from the syringe **above the drug.**
- Keep your finger pressed on the syringe plunger.
- **Do not** inject air into the drug. This may cause air bubbles or foam to form in the drug.

Stage F: Transferring the drug to the syringe



- Slide the tip of the needle down so that it is **in the drug.**
- Pull the plunger backwards **slowly** to prevent the formation of air bubbles or foam. Fill the syringe with more than the amount of drug required for the dose prescribed for you.
- Be careful not to pull the plunger out of the syringe.

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

Do not use the transfer needle to inject the drug. This may cause harm, such as pain and bleeding.

Repeat steps A to F with each additional vial until you have more than the dose prescribed for you. After finishing, keep the transfer needle inserted in the vial and return to step 6. Continue with the remaining steps.

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For complete information, see the product leaflet as approved by the Ministry of Health, available in the drug database on the Ministry of Health website at www.health.gov.il

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