Patient package insert in accordance with the Pharmacists' Regulations (Preparations) - 1986

The medicine is dispensed with a doctor's prescription only

Hemlibra 30 mg/mL
Hemlibra 150 mg/mL
Solution for injection

Composition:
Each vial contains:
emicizumab

*For information about inactive ingredients see Section 6 - "Additional Information".

Read this leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about this medicine. If you have any further questions, refer to the doctor or pharmacist.

This medicine has been prescribed for the treatment of your ailment. Do not pass it on to others. It may harm them, even if it seems to you that their ailment is similar.

1) WHAT IS THIS MEDICINE INTENDED FOR?

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.

Therapeutic group: anti-hemorrhagic medicines.

Hemlibra contains the active substance emicizumab. The active substance belongs to a group of medicines called "monoclonal antibodies". Monoclonal antibodies are a type of protein that recognizes and binds to a target in the body.

Hemophilia A is an inherited condition caused by a lack of factor VIII, an essential substance required for blood to clot and stop any bleeding.

How Hemlibra works:
The body of some patients with hemophilia A may develop factor VIII inhibitors (antibodies against factor VIII) which stop the replacement factor VIII from working.

Hemlibra restores the function of missing factor VIII (in its active form) that is needed for effective blood clotting. Hemlibra structure is different from factor VIII, therefore it is not affected by factor VIII inhibitors.

2) BEFORE USING THIS MEDICINE

Do not use this medicine if:

you are sensitive (allergic) to the active ingredient emicizumab or to any of the other ingredients that this medicine contains (see Section 6 - "Additional information"). If you are not sure, consult your doctor, pharmacist or nurse before using Hemlibra.

Special warnings regarding use of this medicine

Before you start using Hemlibra, it is very important to talk to your doctor about using "bypassing agents" (medicines that help blood clot but which work in a different way from factor VIII). **This is because treatment with bypassing agents may change while receiving Hemlibra.** Examples of bypassing agents include activated prothrombin complex concentrate (aPCC) and recombinant factor VIIa (rFVIIa). Serious and potentially life-threatening side effects can occur when aPCC is used in patients who are also receiving Hemlibra:

Potentially serious side effects of using aPCC while receiving Hemlibra:

- **Destruction of red blood cells (thrombotic microangiopathy)**
  - This is a serious and potentially life-threatening condition.
  - In patients who have this condition, the lining of the blood vessels can be damaged and blood clots may develop in small blood vessels. In some cases, this can cause damage to the kidneys and other organs.
  - Be cautious if you are at high risk for this condition (you have had this condition in the past, or a member of your family has suffered from it), or if you are taking medicines that can increase the risk of developing this condition, such as cyclosporine, quinine or tacrolimus.
  - It is important to know the symptoms of thrombotic microangiopathy, in case you develop the condition (see section 4, "Side effects" for a list of symptoms).

Stop using Hemlibra and aPCC, and talk to a doctor immediately if you or your caregivers notice any symptoms of thrombotic microangiopathy.

- **Blood clots (thromboembolism)**
  - In rare cases, a blood clot can form inside blood vessels and block them, which may be life-threatening.
  - It is important to know the symptoms of such internal blood clots, in case they develop (see section 4 - "Side effects" for a list of symptoms).

Stop using Hemlibra and aPCC, and talk to a doctor immediately if you or your caregivers notice any symptoms of blood clots in blood vessels.

Other important information about Hemlibra

- **Antibody formation (immunogenicity)**
  - You may notice that bleeding is not being controlled with your prescribed dose of this medicine. This could be due to the development of antibodies to this medicine.

Talk to a doctor immediately if you or your caregivers notice an increase in bleeds. Your doctor may change your treatment if this medicine stops working for you.

Children and adolescents:
There is no information about children less than 1 year old.

Tests and follow-up:
Tell your doctor if you are using Hemlibra before you have laboratory tests to measure how well your blood is clotting. This is because Hemlibra in the blood may interfere with some laboratory tests, and lead to inaccurate results.

Drug interactions:
If you are taking or have recently taken other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist. Particularly if you are taking:

- Using bypassing agents while receiving Hemlibra
    - **Before you start using Hemlibra, talk to your doctor and carefully follow their instructions on when to use a bypassing agent and the dose and schedule you should use.** Hemlibra increases the ability of your blood to clot. Therefore, the dose of bypassing agent required may be lower than the dose you used before starting Hemlibra.
    - Use aPCC **only if** no other treatment can be used. If aPCC is required, talk to your doctor if you think that you need a total of more than 50 units/kg of aPCC. For more information on using aPCC while receiving Hemlibra, see in section 2: “Potentially serious side effects of using aPCC while receiving Hemlibra”.
    - Despite limited experience with concomitant administration of medicines that prevent breakdown of clots (anti-fibrinolytics) with aPCC or rFVIIa in patients treated with Hemlibra, you should know that there is a possibility of clotting (thrombotic) events while using anti-fibrinolytics administered intravenously in combination with aPCC or rFVIIa.

Pregnancy, breast-feeding, and fertility:
- Use an effective method of contraception during treatment with Hemlibra and for 6 months after your last injection of Hemlibra.
- If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine. Your doctor will consider the benefit of you taking Hemlibra against the risk to your baby.

Driving and using machines:
Hemlibra is not likely to affect your ability to drive or use machines.

3) HOW SHOULD YOU USE THIS MEDICINE?

Hemlibra is supplied in single-use vials as ready to use solution which does not need to be diluted.
A doctor qualified to care for patients with hemophilia will start you on treatment with Hemlibra. Always use this medicine as your doctor has told you. Check with your doctor or pharmacist if you are not sure about your dosage or about how to take this medicine.

Keeping a record
Each time you use Hemlibra, record the name and batch number of the medicine.
Recommended dose

Only your doctor will determine your dosage and how you should take the medicine.

The dosage of Hemlibra depends on your weight and your doctor will calculate the amount (in milligrams) and corresponding amount of Hemlibra solution (in milliliters) to be injected:

- Loading dose: Weeks 1 to 4: The dosage is 3 milligrams for every 1 kilogram you weigh, injected once a week.
- Maintenance dose: Week 5 and onward: The dosage is 1.5 milligrams for every 1 kilogram you weigh, injected once a week, or 3 milligrams for every 1 kilogram you weigh, injected every 2 weeks, or 6 milligrams for every 1 kilogram you weigh, injected every 4 weeks.

The decision whether to use either the 1.5 mg/kg once weekly, 3 mg/kg every two weeks, or 6 mg/kg every four weeks maintenance dose, should be made in consultation with your doctor and, where applicable, with your caregivers.

Do not combine different Hemlibra concentrations (30 mg/mL and 150 mg/mL) in a single injection when making up the total volume to be injected.

The amount of Hemlibra solution given in each injection must not be more than 2 mL.

Do not exceed the recommended dose.

How Hemlibra is given

If you inject Hemlibra yourself or if your caregiver injects it, you or your caregiver must carefully read and follow the instructions for using Hemlibra in the information brochure which includes instructions for injection. You can get the brochure from your healthcare provider and it is available at all times in the Drug Registry on Ministry of Health website (www.health.gov.il) and on Roche Israel website (www.roche.co.il).

- Hemlibra is given by injection under the skin (subcutaneously).
- Your doctor or nurse will show you how to inject Hemlibra.
- Once you have been trained, you will be able to inject this medicine at home, by yourself or with the help of your caregiver.
- To correctly insert the needle under the skin, use your free hand to pinch a fold of loose skin at the clean injection site. Pinching the skin is important to ensure that you inject under the skin (into fatty tissue) but not any deeper (into muscle). Injecting into a muscle could cause discomfort.
- Prepare and give the injection in clean and germ-free conditions using aseptic technique. Your doctor or nurse will give you more information about this.

Where to inject Hemlibra

- Your doctor will show you which areas of the body are suitable for injecting Hemlibra.
- The recommended areas to give an injection are: the front of the waist (lower abdomen), upper outer arms, or the front of the thighs. Give the injection only in the recommended areas.
- For each injection, use a different area of the body to the one you used last time.
- Do not give injections in areas where the skin is red, bruised, tender, hard, or where there are moles or scars.
- When using Hemlibra, any other medicine injected under the skin should be given in a different area.

Using syringes and needles

- Use a syringe, a transfer needle containing a 5 micrometer filter, and an injection needle to draw up the Hemlibra solution from the vial into the syringe and inject it under the skin.
- Syringes, transfer needles with filter, and injection needles are not provided in this pack. For more information, see in section 6 “What is needed for Hemlibra injection and is not contained in this pack”.
- Make sure that you use a new injection needle for each injection and dispose of it after a single use.
- Use a 1 mL syringe for an injection of up to 1 mL of Hemlibra solution.
- Use a 2 to 3 mL syringe for an injection greater than 1 mL and up to 2 mL of Hemlibra solution.

Use in children and adolescents
Hemlibra can be used in adolescents and children of all ages.
- A child can self-inject Hemlibra provided the child’s doctor or nurse, and the child’s parent or caregiver, agree. Self-injection for children below the age of 7 years is not recommended.

If you accidentally took a higher dosage
If you use more Hemlibra than you are supposed to, tell your doctor immediately. This is because you may be at risk of developing side effects such as blood clots. Always use Hemlibra exactly as your doctor has told you, and check with your doctor, pharmacist or nurse if you are not sure.

If you took an overdose or if a child has accidentally swallowed the medicine, immediately refer to a doctor or proceed to a hospital emergency room and bring the package of the medicine with you.

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

Adhere to the treatment as recommended by your doctor.

Even if your health improves, do not stop taking this medicine without consulting your doctor.

If you stop taking this medicine
Do not stop using Hemlibra without talking to your doctor. If you stop using Hemlibra, you may no longer be protected against bleeding.

Do not take medicines in the dark! Check the label and dose <u>each time</u> you take medicine. Wear glasses if you need them.
If you have any further questions regarding use of this medicine, consult the doctor or pharmacist.

4) <u>SIDE EFFECTS</u>

As with any medicine, using Hemlibra may cause side effects in some users. Do not be alarmed by the list of side effects. You may not suffer from any of them.

Serious side effects of using aPCC while receiving Hemlibra
Stop using Hemlibra and aPCC and talk to a doctor immediately if you, or your caregiver, notice any of the following side effects:

- **Destruction of red blood cells (thrombotic microangiopathy):**
  - confusion, weakness, swelling of arms and legs, yellowing of skin and eyes, vague belly (abdominal) or back pain, feeling sick (nausea), vomiting or urinating less – these symptoms may be signs of thrombotic microangiopathy.
- **Blood clots (thromboembolism):**
  - swelling, warmth, pain or redness – these symptoms may be signs of a blood clot in a vein near the surface of the skin.
  - headache, numbness in your face, eye pain or swelling, problems with your vision – these symptoms may be signs of a blood clot in a vein behind your eyes.
  - blackening of the skin – this symptom may be a sign of severe damage to the skin tissue.

Additional side effects when using Hemlibra
Very common side effects (may affect more than 1 in 10 users):

- a reaction in the area where the injection is given (redness, itching, pain)
- headache
- joint pain

Common side effects (may affect 1-10 in 100 users):

- fever
- muscle aches
- diarrhea
- itchy rash or hives (urticaria)
- skin rash

Uncommon side effects (may affect 1-10 in 1000 users):

- destruction of red blood cells (thrombotic microangiopathy)
- blood clot in a vein behind your eye (cavernous sinus thrombosis)
- severe damage of the skin tissue (skin necrosis)
- blood clot in a vein near the surface of the skin (superficial thrombophlebitis)
- swollen face, tongue and/or throat and/or difficulty in swallowing, or hives, together with difficulty in breathing which are suggestive of an angioedema
- lack of effect or decreased response to treatment
- allergic reaction

If a side effect occurs, if any of the side effects worsens, or if you suffer from a side effect not mentioned in this leaflet, consult your doctor.

Reporting side effects
Side effects can be reported to the Ministry of Health by clicking on the link “Report Side Effects of Drug Treatment” found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or by entering the link: https://sideeffects.health.gov.il

5) HOW TO STORE THE MEDICINE?

Prevent poisoning! This medicine and any other medicine must be kept in a closed place out of the sight and reach of children and/or infants in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.
Do not use the medicine after the expiry date (exp. date) that appears on the outer package and the vial. The expiry date refers to the last day of that month.

Storage conditions

- Store this medicine in a refrigerator at 2°C to 8°C. Do not freeze.
- Store this medicine in the original pack in order to protect from light.
- Once removed from the refrigerator, unopened vials may be kept at room temperature (below 30°C) for up to 7 days. After storage at room temperature, unopened vials may be put back in the refrigerator. The total time the medicine is stored at room temperature should not be more than 7 days.
- Discard vials that have been kept at room temperature for more than 7 days or exposed to temperatures above 30°C.
- Once transferred from the vial to the syringe, use Hemlibra straight away. Do not refrigerate the solution in the syringe.
- Before using the medicine, check the solution for particles or discoloration. The solution should be colorless to slightly yellow. Do not use this medicine if it is cloudy, discolored, or contains visible particles.
- Throw away any unused solution appropriately. Do not throw away the medicine via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6) ADDITIONAL INFORMATION

The active substance is emicizumab. Each vial of Hemlibra contains 30 mg (1 mL at a concentration of 30 mg/mL), 60 mg (0.4 mL at a concentration of 150 mg/mL), 105 mg (0.7 mL at a concentration of 150 mg/mL), or 150 mg (1 mL at a concentration of 150 mg/mL) of emicizumab.*

*Not all pack sizes may be available.

In addition to the active substance this medicine also contains:
L-arginine, L-histidine, poloxamer 188, L-aspartic acid, and Water for injections.

What the medicine looks like and contents of the pack:
Hemlibra is a solution for injection. The solution is a colorless to slightly yellow liquid.

Each pack of Hemlibra contains one glass vial.

What is needed for Hemlibra injection and is not contained in this pack
A syringe, a transfer needle, and an injection needle are needed to draw up the Hemlibra solution from the vial into the syringe and to inject it under the skin (see information brochure which includes instructions for using Hemlibra. You can get the brochure from your healthcare provider and it is available at all times in the Drug Registry on Ministry of Health website (www.health.gov.il) and on Roche Israel website (www.roche.co.il)).

Syringes

- **1 mL syringe:** transparent, 0.01 mL graduation **or**
- **2 or 3 mL syringe:** transparent, 0.1 mL graduation

Needles

- **Transfer needle with filter:** 18 G gauge, 35 mm long (1½″), containing a 5 micrometer filter and preferably with semi-blunted tip, **and in addition**
- **Injection needle:** 26 G gauge (acceptable range: 25-27 gauge), length preferably 9 mm (3/8") or maximally 13 mm (1/2"), preferably including a needle safety feature

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Manufacturer name and address: F. Hoffmann-La Roche Ltd., Grenzacherstrasse 124, CH-4058 Basel, Switzerland
Registration number of the medicine in the National Drug Registry of the Ministry of Health:
Hemlibra 30 mg/mL: 161-18-35414-00
Hemlibra 150 mg/mL: 161-19-35415-00

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