PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986

The medicine is dispensed with a doctor's prescription only

Actemra® 162 mg S.C.

Solution for subcutaneous injection in a pre-filled syringe

Composition:
Each pre-filled syringe contains:
Tocilizumab 162 mg/0.9 ml

- For information on inactive ingredients, see section 6 - "Further Information".

- **Read this leaflet carefully in its entirety before using the medicine.** This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or pharmacist.
- This medicine has been prescribed to treat your ailment. Do not pass it on to others. It may harm them even if it seems to you that their medical condition is similar.

1. WHAT IS THE MEDICINE INTENDED FOR?

Actemra is intended to treat adults with moderate to severe active rheumatoid arthritis, if other accepted treatments were not successful.
Actemra is intended to treat adults with active, severe and progressive rheumatoid arthritis, who have not been previously treated with methotrexate.
Actemra has been shown to slow damage to the cartilage and bone of the joints caused by the disease and also to improve your ability to carry out daily activities normally.
Actemra is usually given in combination with methotrexate. However, if recommended by your doctor, you may receive **Actemra** alone.
Actemra is intended for the treatment of adults with giant cell arteritis (GCA), caused by inflammation of the body's largest arteries, especially those that supply blood to the head and neck.
Actemra, in combination with methotrexate or as monotherapy, is intended for the treatment of children and adolescents over one year of age, with active systemic juvenile idiopathic arthritis who have not responded adequately to previous therapies with systemic corticosteroids or to nonsteroidal anti-inflammatory drugs.
Actemra, in combination with methotrexate or as monotherapy, is intended for the treatment of children and adolescents over two years of age with polyarticular juvenile idiopathic arthritis who have not responded adequately to previous therapy with methotrexate.
Therapeutic group: interleukin inhibitors.

Actemra contains the active substance tocilizumab, which is a protein made from specific immune cells (monoclonal antibody) that blocks the action of a specific protein (cytokine) called interleukin 6. This protein is involved in inflammatory process of the body, and blocking it can reduce the inflammatory process in your body.

2. BEFORE USING THE MEDICINE

☒ Do not use the medicine if:

- you or the child patient whom you look after are sensitive (allergic) to tocilizumab or to any of the other ingredients of this medicine (listed in section 6 "Further Information").
- you or the child patient whom you look after are suffering from an active and severe infection.

❗ Special warnings regarding use of the medicine

Refer to your doctor, pharmacist or nurse before using **Actemra** in the following cases:

- If you experience **allergic reactions** such as chest tightness, wheezing, severe dizziness or light-headedness, swelling of the lips, tongue, face or skin itching, hives or rash during or after the infusion, **inform the doctor immediately**. Do not take the next dose until you have informed the doctor and received an explicit instruction for this, if you have experienced symptoms of an allergic reaction after administration of **Actemra**.
- If you have any kind of **infection**, short- or long-term, or if you often get infections. **Inform the doctor immediately** if you feel unwell. **Actemra** can reduce your body's ability to respond to infections and also make existing infections worse or increase the chance of getting new infections.
- If you have had **tuberculosis**, inform your doctor. The doctor will check for signs and symptoms of tuberculosis before starting treatment with **Actemra**. If symptoms of tuberculosis (persistent cough, weight loss, listlessness, mild fever) or any other infection appear during or after therapy, inform the doctor immediately.
- If you have had **intestinal ulcers or diverticulitis**, inform the doctor. The symptoms could include abdominal pain and unexplained changes in bowel habits accompanied by a fever.
- If you have **liver disease**, inform the doctor. Before starting treatment with **Actemra,** the doctor may send you to do blood tests to examine your liver functions.
- If **you have recently been vaccinated,** or are planning a vaccination, inform the doctor. All patients should get all the vaccinations the doctor has recommended for them before starting treatment with **Actemra**. There are certain types of vaccines that should not be given during the course of treatment with **Actemra**.
- If you have **cancer**, inform your doctor. The doctor will have to decide if you can still be given **Actemra**.
- If you have **risk factors for cardiovascular diseases** such as high blood pressure and high cholesterol levels, inform the doctor. These risk factors need to be monitored while receiving **Actemra**.
- If you have moderate to severe **kidney function disturbances**, your doctor will monitor you.
- If you have **persistent headaches.**

Children and adolescents
Actemra subcutaneous injection is not intended for children under 1 year of age to treat active systemic juvenile idiopathic arthritis and is not intended for children under 2 years of age to treat polyarticular juvenile idiopathic arthritis.
Actemra must not be given to children weighing less than 10 kg.
If a child has a history of macrophage activation syndrome, manifested by activation and uncontrolled proliferation of specific blood cells, tell your doctor. Your doctor will have to decide if **Actemra** can still be given.

Tests and follow-up
Your doctor will perform blood tests before starting and during treatment with **Actemra** to monitor low white blood cell levels, low platelet levels, high liver enzyme levels, blood fat levels, presence of tuberculosis and/or viral hepatitis and risk factors for cardiovascular diseases.

Other medicines and Actemra
If you are taking, or have recently taken, other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist. Actemra can affect the way some medicines work, and the dose of these medicines may have to be adjusted. It is especially important to inform the doctor if you are taking medicines containing the following active substances:

- Methylprednisolone, dexamethasone, used to reduce inflammation
- Simvastatin or atorvastatin, used to reduce cholesterol levels
- Calcium channel blockers (e.g., amlodipine), used to treat high blood pressure
- Theophylline, used to treat asthma
- Warfarin or phenprocoumon, used as blood-thinning agents
- Phenytoin, used to treat convulsions
- Ciclosporin, used to suppress the immune system after organ transplants
- Benzodiazepines (e.g., temazepam), used to relieve anxiety

Actemra is not recommended for use with other biological medicines used for the treatment of rheumatoid arthritis, giant cell arteritis, systemic juvenile idiopathic arthritis or polyarticular juvenile idiopathic arthritis due to lack of clinical experience in this type of combination.

Pregnancy, breast-feeding and fertility
Do not use Actemra during pregnancy unless clearly necessary. If you are pregnant, think you are pregnant, or are planning to become pregnant, consult with your doctor.
Women of child-bearing age must use effective contraception during treatment and up to 3 months after treatment.
Stop breast-feeding if you are to be given Actemra, and consult the doctor. Leave a gap of at least 3 months after the last treatment before starting to breast-feed. It is not known whether **Actemra** is secreted into breast milk.

Driving and use of machines
The medicine may cause dizziness. If you feel dizzy, do not drive or operate machines.

3. HOW SHOULD YOU USE THE MEDICINE?

A doctor experienced in the diagnosis and treatment of rheumatoid arthritis, giant cell arteritis, systemic juvenile idiopathic arthritis or polyarticular juvenile idiopathic arthritis will prescribe and start **Actemra** treatment.

Always use the medicine according to the doctor's instructions. Check with the doctor or pharmacist if you are uncertain regarding the dosage and treatment regimen of the medicine.
The dosage and treatment regimen will be determined by the doctor only.

The usual dosage for patients with rheumatoid arthritis (RA) or giant cell arteritis (GCA) is usually
162 mg (the content of one pre-filled syringe) given once a week.

Children and adolescents with systemic juvenile idiopathic arthritis - from 1 year of age and up
The usual dosage of Actemra depends on the patient's weight.

- If the patient weighs **less than 30 kg**: the usual dosage is 162 mg (the contents of one pre-filled syringe), administered **once every two weeks**. Do not administer **Actemra** subcutaneously to children weighing less than 10 kg.
- If the patient weighs **30 kg or more**: the usual dosage is 162 mg (the contents of one pre-filled syringe), administered **once a week**.

Children and adolescents with polyarticular juvenile idiopathic arthritis - from the age of 2 and up
The usual dosage of Actemra depends on the patient's weight.

- If the patient weighs **less than 30 kg**: the usual dosage is 162 mg (the contents of one pre-filled syringe), administered **once every three weeks**.
- If the patient weighs **30 kg or more**: the usual dosage is 162 mg (the contents of one pre-filled syringe), administered **once every two weeks**.

Actemra is given by injection under the skin (subcutaneous injection). At the start, the doctor or nurse may inject the medicine, and later, the doctor may decide that you may inject the medicine yourself. In this case, you will get training on how to inject **Actemra** yourself. Detailed instructions for self-injection can be found at the end of the leaflet (see section 7 - "Instructions for Self Injection").
Parents or carers will be trained on how to inject the medicine for patients who cannot inject the medicine themselves, e.g., children.
Do not exceed the recommended dose.

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

If an adult patient with rheumatoid arthritis (RA) or giant cell arteritis (GCA) or a child or adolescent with systemic juvenile idiopathic arthritis (sJIA) missed or forgot the dose
It is very important to use **Actemra** exactly as prescribed by the doctor. Keep track of the next injection time.

- If you have been prescribed one injection per week, and you miss your weekly dose, take the next dose on the next scheduled date.
- If an injection once every two weeks has been prescribed for you, and you miss one injection, the forgotten dose can be injected as soon as you remember, on the condition that no more than 7 days have elapsed from the originally scheduled injection time. Take the next dose at the regular scheduled time.
- If you forgot to take a dose and more than 7 days from the originally scheduled injection time have passed, or if you are not sure when to inject **Actemra**, refer to the doctor or pharmacist.
- If you are not sure when to take the next injection, consult the doctor regarding the next dosing time.

If a child or adolescent with polyarticular juvenile idiopathic arthritis (pJIA) missed or forgot the dose
It is very important to use **Actemra** exactly as instructed by the doctor. Keep track of the next injection date.

- If you forgot to take the dose and fewer than 7 days have passed from the original injection date, inject the forgotten dose as soon as you remember and take the next dose at the regular, planned time.
- If you forgot to take the dose and more than 7 days from the original injection date have passed or if you are unsure about when to inject, refer to your doctor or pharmacist.

Adhere to the treatment regimen as recommended by the doctor.
Even if there is an improvement in your health, do not stop treatment without consulting the doctor.

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

4. SIDE EFFECTS

As with any medicine, use of **Actemra** may cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not suffer from any of them.
Side effects may occur 3 or more months after the last dose of **Actemra**.

Possible serious side effects: refer to the doctor immediately.
These effects are common: they may affect up to 1 in 10 users.
Allergic reactions during or after injection:

- Breathing difficulties, chest tightness or light-headedness
- Rash, itching, hives (urticaria), swelling of the lips, tongue or face

Inform the doctor **immediately** if you notice any of the above-mentioned side effects.
Signs of serious infections:

- Fever and chills
- Mouth or skin blisters
- Stomach ache

Signs and symptoms of liver toxicity (may affect up to 1 in 1,000 users)

- Tiredness
- Abdominal pain
- Jaundice (yellow discoloration of the skin or the eyes)

Inform the doctor **as soon as possible** if you notice any of the above-mentioned side effects.

Very common side effects (may affect 1 or more in 10 users):

- Upper respiratory tract infections with typical symptoms such as cough, blocked nose, runny nose, sore throat and headache
- High blood cholesterol (fat) levels
- Injection site reactions

Common side effects (may affect up to 1 in 10 users):

- Pneumonia
- Shingles (herpes zoster)
- Cold sores (herpes of the lips), blisters
- Skin infection (cellulitis) sometimes with fever and chills
- Rash and itching, hives (urticaria)
- Allergic (hypersensitivity) reactions
- Eye infection (conjunctivitis)
- Headache, dizziness, high blood pressure
- Mouth ulceration, stomach pain
- Fluid retention (edema) in the lower legs, weight gain
- Cough, shortness of breath
- Low white blood cell counts in a blood test (neutropenia, leucopenia)
- Abnormal liver function tests (increase in liver enzymes - transaminases)
- Increased bilirubin in blood tests
- Low fibrinogen levels in the blood (a protein involved in blood clotting)

Uncommon side effects (may affect up to 1 in 100 users):

- Diverticulitis, including fever, nausea, diarrhea, constipation, stomach pain
- Red swollen areas in the mouth
- High blood triglyceride levels
- Stomach ulcer
- Kidney stones
- Underactive thyroid

Rare side effects (may affect up to 1 in 1,000 users):

- Stevens-Johnson syndrome - skin rash that may worsen to severe blistering and peeling of the skin
- Fatal allergic reactions (anaphylaxis [fatal])
- Inflammation of the liver (hepatitis), jaundice

Very rare side effects (may affect up to 1 in 10,000 users):

- Low counts of white blood cells, red blood cells and platelets, observed in blood tests
- Liver failure

Side effects in children and adolescents with systemic juvenile idiopathic arthritis (sJIA) or polyarticular juvenile idiopathic arthritis (pJIA)
Side effects in children and adolescents with systemic juvenile idiopathic arthritis (sJIA) or polyarticular juvenile idiopathic arthritis (pJIA) are generally similar to those of adults. Some of the side effects seen more frequently among children and adolescents: inflamed nose and throat, headache, nausea and low white blood cell count.

If a side effect occurs, if one of the side effects worsens or if you suffer from a side effect not mentioned in this leaflet, consult with the 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 SHOULD THE MEDICINE BE STORED?

Avoid poisoning! This medicine and any other medicine must be kept in a safe place out of the reach and sight of children and/or infants 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 label of the pre-filled syringe and on the package. The expiry date refers to the last day of that month.
Storage conditions: store in a refrigerator (2-8°C). Do not freeze.
Store the pre-filled syringe in its outer package to protect from light.
Once removed from the refrigerator, use **Actemra** within 8 hours and do not keep at a temperature that exceeds 30°C.
Do not use the medicine if the solution is cloudy or contains particles, or if its color is not colorless to yellowish or if parts of the pre-filled syringe seem damaged.
The pre-filled syringe should not be shaken. After removing the cap, the injection must be started within 5 minutes to prevent the medicine from drying out and blocking the needle. If the pre-filled syringe is not used within 5 minutes of cap removal, dispose of it in a closed, sharps container and use a new pre-filled syringe.
If following insertion of the needle, you cannot depress the plunger, you must dispose of the pre-filled syringe in a closed, sharps container and use a new pre-filled syringe.

6. FURTHER INFORMATION

In addition to the active ingredient, the medicine also contains:
L-arginine hydrochloride, L-methionine, L-histidine hydrochloride monohydrate, L-histidine, Polysorbate 80, L-arginine and water for injections.

What does the medicine look like and what are the contents of the package?
Actemra is a solution for injection. The solution is colorless to yellowish.
Actemra is supplied as a pre-filled syringe (0.9 ml) containing 162 mg tocilizumab solution for injection.
Each **Actemra** package contains 1 or 4 syringes*
* Not all package sizes may be marketed.

License holder and address: Roche Pharmaceuticals (Israel) Ltd., 6 Haharash St., P.O.B. 6391, Hod Hasharon 4524079, www.roche.co.il.

Manufacturer and address: F. Hoffmann-La Roche Ltd., Basel, Switzerland.

The leaflet was approved in April 2020

Registration number of the medicine in the National Drug Registry of the Ministry of Health:
153-15-34111-00

7. INSTRUCTIONS FOR SELF INJECTION

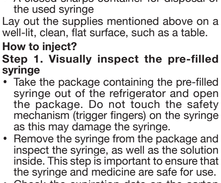
It is very important that you read, understand and follow these instructions so that you or your caregiver will know how to use the pre-filled syringe (hereinafter referred to as a "syringe") correctly. These instructions do not replace training by the healthcare team.
A healthcare provider will show you how to prepare the syringe for injecting and how to inject properly before you use the syringe for the first time. Refer to your healthcare team with any question. Do not attempt to administer an injection until you are sure that you understand how to use the syringe.

Important Information:

- Do not use the syringe if it appears to be damaged.
- Do not use the medicine if the solution looks cloudy, discolored or contains particles.
- Do not try to open or take apart the syringe.
- Do not remove the needle-cap (see the syringe components below) until you are ready to inject.
- Do not inject through clothing that covers the skin.
- Do not try to re-use the same syringe.
- Do not touch the safety mechanism (trigger fingers – see the syringe components below) as this may damage the syringe.

Storage:
See section 5 - "How Should the Medicine be Stored?".

Syringe parts:



You will need the following items for the injection:
Included in the package:

- Pre-filled syringe

Not included in the package:

- Alcohol pad
- Sterile cotton ball or gauze
- A closed sharps container for disposal of the used syringe

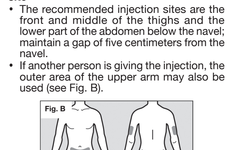
Lay out the supplies mentioned above on a well-lit, clean, flat surface, such as a table.

How to inject?

Step 1. Visually inspect the pre-filled syringe

- Take the package containing the pre-filled syringe out of the refrigerator and open the package. Do not touch the safety mechanism (trigger fingers) on the syringe as this may damage the syringe.
- Remove the syringe from the package and inspect the syringe, as well as the solution inside. This step is important to ensure that the syringe and medicine are safe for use.
- Check the expiration date on the carton package and the syringe (see Fig. A) to make sure that it has not passed (expired). Do not use the syringe if the expiration date has passed.

Fig. A



Dispose of the syringe and do not use in the following cases:

- If the solution is cloudy
- If the solution contains particles
- If the solution is **not** colorless to yellowish
- If parts of the syringe appear to be damaged

Step 2. Allow the syringe to reach room temperature

- Do not remove the needle-cap until Step 5. Early removal of the needle-cap can cause the medicine to dry out and block the needle.
- Place the syringe on a clean and flat surface and allow it to reach room temperature (18 to 28 degrees) for about 25-30 minutes in order to prevent discomfort caused during the injection and from difficulty in depressing the plunger.
- Do not warm up the syringe in any other way.

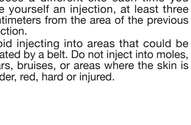
Step 3. Sanitize your hands

- Wash your hands with soap and water.

Step 4. Choose and prepare the injection site

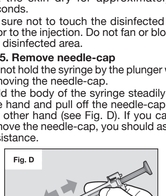
- The recommended injection sites are the front and middle of the thighs and the lower part of the abdomen below the navel; maintain a gap of five centimeters from the navel.
- If another person is giving the injection, the outer area of the upper arm may also be used (see Fig. B).

Fig. B



- Choose a different site each time you give yourself an injection, at least three centimeters from the area of the previous injection.
- Avoid injecting into areas that could be irritated by a belt. Do not inject into moles, scars, bruises, or areas where the skin is tender, red, hard or injured.
- Disinfect the selected injection site using an alcohol pad (see Fig. C), to reduce the risk of infection.

Fig. C

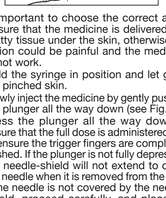


- Let the skin dry for approximately 10 seconds.
- Be sure not to touch the disinfected area prior to the injection. Do not fan or blow on the disinfected area.

Step 5. Remove needle-cap

- Do not hold the syringe by the plunger while removing the needle-cap.
- Hold the body of the syringe steadily with one hand and pull off the needle-cap with the other hand (see Fig. D). If you cannot remove the needle-cap, you should ask for assistance.

Fig. D



- Do not touch the needle or let it touch any surface.
- You may notice a drop of liquid at the end of the needle. This is normal.
- Throw the needle-cap into a closed and safe sharps container.

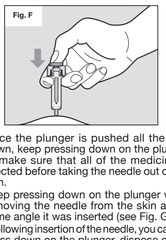
NOTE: Once the needle-cap is removed, use the syringe immediately.

- If the syringe was not used within 5 minutes, it should be disposed of in a closed safe sharps container and a new syringe should be used. If the needle-cap is removed for more than 5 minutes, it may be more difficult to perform an injection as the medicine can dry out and block the needle.
- Never try to re-attach the needle-cap after removing it.

Step 6. Giving the injection

- Hold the syringe comfortably in one hand.
- To make sure the needle can be inserted correctly under the skin, pinch a fold of loose skin at the disinfected injection site with your free hand. Pinching the skin is important to ensure that you inject into fatty tissue under the skin but not any deeper (into the muscle). Injection into muscle could cause discomfort.
- Do not hold or push on the plunger while inserting the needle into the skin.
- Quickly and steadily insert the needle all the way into the pinched skin at a 45°-90° angle (see Fig. E).

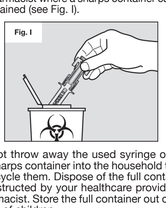
Fig. E



It is important to choose the correct angle to ensure that the medicine is delivered into the fatty tissue under the skin, otherwise the injection could be painful and the medicine may not work.

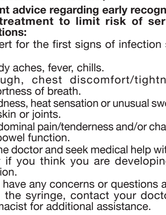
- Hold the syringe in position and let go of the pinched skin.
- Slowly inject the medicine by gently pushing the plunger all the way down (see Fig. F). Press the plunger all the way down to ensure that the full dose is administered and to ensure the trigger fingers are completely pushed. If the plunger is not fully depressed, the needle-shield will not extend to cover the needle when it is removed from the skin. If the needle is not covered by the needle-shield, proceed carefully, and place the syringe into the closed safe sharps container to avoid injury by the needle.

Fig. F



- Once the plunger is pushed all the way down, keep pressing down on the plunger to make sure that all of the medicine is injected before taking the needle out of the skin.
- Keep pressing down on the plunger while removing the needle from the skin at the same angle it was inserted (see Fig. G).
- If following insertion of the needle, you cannot press down on the plunger, dispose of the syringe in a closed safe sharps container and use a new pre-filled syringe (starting again at Step 2). If you still experience difficulty, consult the healthcare team.

Fig. G



- Once the needle is completely removed from the skin, the plunger can be released, allowing the needle-shield to cover the needle (see Fig. H).

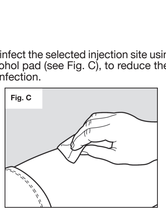
Fig. H

- If you see drops of blood at the injection site, attach a cotton ball or gauze over the injection site for approximately 10 seconds.
- Do not rub the injection site.

Step 7. Dispose of the used syringe

- Do not try to re-cap the syringe.
- Throw away the used syringe in a closed and safe sharps container. Ask the doctor/nurse/pharmacist where a sharps container can be obtained (see Fig. I).

Fig. I



Do not throw away the used syringe or the full sharps container into the household trash or recycle them. Dispose of the full container as instructed by your healthcare provider or pharmacist. Store the full container out of the reach of children.

Patient advice regarding development of hypersensitivity reactions (a situation that can lead to shock in severe cases):

- If you develop symptoms such as, but not limited to: skin rash, itching, chills, swelling of face, lips, tongue or throat, chest pain, wheezing, difficulty breathing or swallowing or feeling dizzy or faint at any time and you are not at the clinic during or following injection of the medicine, you should seek medical care immediately.

Patient advice regarding early recognition and treatment to limit risk of serious infections:
Be alert for the first signs of infection such as:

- Body aches, fever, chills.
- Cough, chest discomfort/tightness, shortness of breath.
- Redness, heat sensation or unusual swelling of skin or joints.
- Abdominal pain/tenderness and/or changes in bowel function.

Call the doctor and seek medical help without delay if you think you are developing an infection.
If you have any concerns or questions about using the syringe, contact your doctor or pharmacist for additional assistance.