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

This medicine is dispensed with a doctor's prescription only

Darzalex® 20 mg/ml I.V.

Concentrate for solution for infusion

Active ingredient and its concentration

Daratumumab 20 mg/1 ml

Inactive and allergenic ingredients in the preparation: see in section 2 under "Important information about some of the ingredients of the medicine" and 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 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.

Patient Information Card:

In addition to this leaflet, Darzalex is provided with a Patient Safety Information Card. This card contains important safety information you should be aware of before starting and during treatment with Darzalex, and adhere to.

Read the Patient Safety Information Card and the patient leaflet before you start using the preparation.

Keep the card for further reading, if necessary.

1. WHAT IS THE MEDICINE INTENDED FOR?

- In combination with lenalidomide and dexamethasone, or in combination with bortezomib, melphalan and prednisone, is intended for the treatment of adult patients with newly diagnosed multiple myeloma, who are ineligible for autologous stem cell transplant.
- In combination with bortezomib, thalidomide and dexamethasone, is intended for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant.
- In combination with lenalidomide and dexamethasone, or in combination with bortezomib and dexamethasone, is intended for the treatment of adult patients with multiple myeloma who received at least one treatment previously.
- As a monotherapy, is intended for the treatment of adult patients (above the age of 18 years) who have relapsed or refractory multiple myeloma who, despite prior therapy that included a proteasome inhibitor and an immunomodulatory agent, demonstrated disease progression on the last therapy.

Therapeutic group: Darzalex is a medicine for the treatment of bone marrow cancer, which contains the active ingredient daratumumab. It belongs to a group of medicines called "monoclonal antibodies". Monoclonal antibodies are proteins designed to recognize and attach to specific targets in the body. Daratumumab has been designed to attach to certain cancer cells in the body, so that the immune system can destroy the cancer cells.

2. BEFORE USING THE MEDICINE

Do not use the medicine if:

- You are sensitive (allergic) to the active ingredient daratumumab or any of the additional ingredients contained in the medicine. For the list of the additional ingredients, see section 6 "Further Information".
- Do not use Darzalex if the above applies to you. If you are uncertain, talk to the doctor or nurse before you receive Darzalex.

Special warnings regarding use of the medicine

Before treatment with Darzalex, tell the doctor if:

Before treatment, consult the doctor or nurse about:

Infusion-related reactions

Darzalex is given as an infusion (drip) into a vein. Before and after each infusion of Darzalex, you will be given medicines which help to lower the chance of infusion-related reactions (see in section 3 – "Medicines given during treatment with Darzalex"). These reactions may occur during the infusion or during the 3 days after the infusion.

In some cases, you may have a severe allergic reaction, which may be manifested by a swollen face, lips, mouth, tongue or throat, difficulty swallowing or breathing or an itchy rash (hives). Some cases of serious allergic reactions or other severe infusion-related side effects have resulted in death.

Refer to the doctor or nurse immediately if you have any of the infusion-related reactions or related symptoms listed at the top of section 4 – "Side Effects".

If you have any of the infusion-related reactions, you may need other medicines or the infusion may need to be slowed down or stopped. When the reactions go away or get better, the infusion may be started again.

In most cases, these reactions may occur during the first infusion. If you have experienced infusion-related reactions in the past, you are less likely to have these effects a second time.

The doctor may decide not to treat you with Darzalex if you have a severe infusion reaction.

Decreased blood count

Darzalex may cause a decrease in the white blood cell count, which help fight infections, and a decrease in blood cells called platelets, which help with blood clotting. Refer to the doctor or nurse if you develop any symptoms of infection such as fever or symptoms of decreased platelet counts such as bruising or bleeding.

Blood transfusion

If you need a blood transfusion, you need to undergo blood tests to verify your blood type.

Darzalex may affect these blood test results. Please update the medical staff member who performs the tests that you are being treated with Darzalex.

Hepatitis B

Tell your doctor if you might have or have had in the past a hepatitis B infection. This is because Darzalex could cause the hepatitis B virus to become active again. Your doctor may check you for signs of this infection before, during and for some time after treatment with Darzalex. Tell your doctor right away if you notice worsening tiredness or yellowing of your skin or whites of your eyes.

Children and adolescents

This medicine is not intended for children and adolescents below the age of 18.

There is no information regarding the safety and effectiveness of this preparation in children and adolescents.

Drug interactions

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

Pregnancy, breastfeeding and fertility

Pregnancy

If you are pregnant, may be pregnant or are planning to become pregnant, refer to the doctor before beginning treatment with this medicine.

If you become pregnant during treatment with this medicine, please refer to the doctor or nurse straight away.

A joint decision should be made with the doctor as to whether the benefit of treatment with this medicine is greater than the risk to the baby.

Contraception

Women who are being treated with Darzalex should use effective contraception during treatment and for 3 months after treatment.

Breastfeeding

A joint decision should be made with the doctor whether the benefit of breastfeeding is greater than the risk to your baby. This is because the medicine may pass into the mother's milk and it is not known how it will affect the baby.

Driving and using machines

After treatment with Darzalex, you may feel tired, which may affect your ability to drive or operate machines.

Important information about some of the ingredients of the medicine

Darzalex contains sorbitol:

Sorbitol is a source of fructose. If you have hereditary fructose intolerance (HFI), a rare genetic disorder, you must not receive this medicine. Patients with HFI cannot break down fructose, which may cause serious side effects.

You must tell your doctor before receiving this medicine if you have HFI.

Darzalex contains polysorbate:

This medicine contains 0.4 mg of polysorbate 20 in each ml, which is equivalent to 2.0 mg per 5 ml vial. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

This medicine contains 0.4 mg of polysorbate 20 in each ml, which is equivalent to 8.0 mg per 20 ml vial. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. HOW SHOULD THE MEDICINE BE USED?

Always use the preparation according to the doctor's instructions.

Check with the doctor or nurse if you are uncertain regarding the dosage and treatment regimen of the preparation.

The dosage, treatment regimen and manner of treatment with Darzalex will be determined by the doctor only, depending on your body weight.

The usual starting dose of Darzalex is 16 mg per kg of body weight. Darzalex can be given to you as a monotherapy or in combination with other medicines to treat multiple myeloma.

Darzalex is administered as a monotherapy in the following manner:

- once a week for the first 8 weeks
- then, once every 2 weeks, for 16 weeks
- then, once every 4 weeks as long as your condition does not worsen.

When Darzalex is given in combination with other medicines, the doctor may change the time between doses as well as how many treatments you will receive.

In the first week, the doctor may give you the Darzalex dose split over two consecutive days.

Do not exceed the recommended dose.

How the medicine is given

Darzalex will be given to you by a doctor or nurse as a drip into the vein (intravenous infusion) over several hours.

Medicines given during treatment with Darzalex

You may be given medicines to lower the chance of getting shingles.

Before each infusion of Darzalex you will be given medicines which help to lower the chance of infusion-related reactions. These medicines may include:

- medicines for an allergic reaction (anti-histamines)
- medicines for inflammation (corticosteroids)
- medicines to reduce fever (such as paracetamol)

After each infusion of Darzalex you will be given medicines (such as corticosteroids) to lower the chance of infusion-related reactions.

Patients with breathing problems

If you have breathing problems, such as asthma or Chronic Obstructive Pulmonary Disease (COPD), you will be given medicines to inhale which will help your breathing problems:

- medicines to help the airways in your lungs stay open (bronchodilators)
- medicines to lower swelling and irritation in your lungs (corticosteroids)

If you received an overdose of Darzalex

Darzalex will be given to you by your doctor or nurse; therefore, it is unlikely that you will receive an overdose. Your doctor will check you for side effects.

If you forgot a scheduled appointment to have Darzalex

It is very important to receive all the prescribed treatments in order for the treatment to work. If you miss an appointment for treatment, make another appointment as soon as possible.

Adhere to the treatment regimen as recommended by the doctor.

Even if there is an improvement in your health, do not stop treatment with the medicine without consulting the doctor.

If you have further questions regarding use of the medicine, consult the doctor, pharmacist or nurse.

4. SIDE EFFECTS

As with any medicine, use of Darzalex 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.

Infusion-related reactions

Refer to the doctor or nurse straight away if you experience any of the following effects related to the infusion during or in the 3 days after the infusion. You may need other medicines, or the infusion may need to be slowed down or stopped.

These side effects include the following symptoms:

Very common side effects – effects that may affect more than 1 in 10 users:

- chills
- sore throat, cough
- nausea
- vomiting
- itchy, runny or blocked nose
- feeling short of breath or other breathing problems

Common side effects – effects that may affect up to 1 in 10 users:

- chest discomfort
- dizziness (associated with hypotension)
- itching
- wheezing

Rare side effects – effects that may affect up to 1 in 1,000 users:

- severe allergic reaction which may include a swollen face, lips, mouth, tongue or throat, difficulty swallowing or breathing or an itchy rash (hives). See section 2 "Before using the medicine"
- eye pain
- blurred vision

If you experience any of the infusion-related reactions above, refer to the doctor or nurse straight away.

Other side effects

Very common side effects – effects that may affect more than 1 in 10 users:

- fever
- feeling very tired
- diarrhea
- abdominal pain
- constipation
- decreased appetite
- difficulty sleeping
- headache
- feeling dizzy
- nerve damage that may cause sensation of slight tingling, numbness or pain
- high blood pressure
- skin rash
- muscle spasms
- swelling of the hands, ankles or feet
- feeling weak
- muscle and joint pains (including back pains and chest muscle pains)
- lung infection (pneumonia)
- bronchitis
- respiratory tract infection – e.g., in the nose, sinuses or throat
- low count of red blood cells, which carry oxygen in the blood (anemia)
- low count of white blood cells, which help fight infections (neutropenia, lymphopenia, leukopenia)
- low count of platelets, blood cells which help with blood clotting (thrombocytopenia)
- low level of potassium in the blood (hypokalemia)
- unusual feeling in the skin (such as a tingling or a feeling of crawling in the skin)
- COVID-19

Common side effects – effects that may affect up to 1 in 10 users:

- irregular heart beat (atrial fibrillation)
- build-up of fluid in the lungs, making you short of breath
- urinary tract infection
- severe infection throughout the body (sepsis)
- dehydration
- fainting
- chills
- high level of sugar in the blood
- low level of calcium in the blood
- low level of antibodies called immunoglobulins in the blood, which help fight infections (hypogammaglobulinemia)
- inflamed pancreas
- itching
- type of herpes virus infection (cytomegalovirus infection)

Uncommon side effects – effects that may affect up to 1 in 100 users:

- inflamed liver (hepatitis)

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.

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?

- Darzalex will be stored at the hospital, pharmacy or clinic.
- Avoid poisoning! This medicine, and any other medicine, should be kept in a safe place out of the reach and sight 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 package. The expiry date refers to the last day of that month.
- Store in a refrigerator at 2°C-8°C. Do not freeze.
- Do not shake.
- Store in the original package in order to protect from light.

Do not discard the medicine in the wastewater or household waste. The medical staff will discard the medicines that are no longer in use. These measures will help protect the environment.

6. FURTHER INFORMATION

The active substance is daratumumab. Every 1 ml contains 20 mg daratumumab.

Each vial of 5 ml contains 100 mg of daratumumab

Each vial of 20 ml contains 400 mg of daratumumab

- In addition to the active ingredient, the medicine also contains:
  Sorbitol, L-histidine hydrochloride monohydrate, L-methionine, Polysorbate 20, L-histidine, Water for injections.

What the medicine looks like and the contents of the package:

- Darzalex 20 mg/ml I.V. is a concentrate for solution for infusion and is colorless to yellow.
- Package size: 1 glass vial of 5 ml or 20 ml in a carton pack.

Manufacturer and Address: Janssen Cilag International N.V., Turnhoutseweg 30, B-2340, Beerse, Belgium .

Registration Holder and Address: J-C Health Care Ltd., Kibbutz Shefayim 6099000, Israel.

Revised in November 2025.

Registration number of the medicine in the National Drug Registry of the Ministry of Health: 157-75-34719

הנחיות שימוש לצוות הרפואי:

تعليمات الإستعمال للطاقم الطبي:

Instructions for use for healthcare professionals:

This medicinal product is for single-use only.

Prepare the solution for infusion using aseptic technique as follows:

- Calculate the dose (mg), total volume (ml) of Darzalex solution required and the number of Darzalex vials needed based on patient weight.
- Check that the Darzalex solution is colorless to yellow. Do not use if opaque particles, discoloration or other foreign particles are present.
- Using aseptic technique, remove a volume of sodium chloride 9 mg/ml (0.9%) solution for injection from the infusion bag/container that is equal to the required volume of Darzalex solution.
- Withdraw the necessary amount of Darzalex solution and dilute to the appropriate volume by adding to an infusion bag/container containing sodium chloride 9 mg/ml (0.9%) solution for injection. Infusion bags/containers must be made of polyvinylchloride (PVC), polypropylene (PP), polyethylene (PE) or polyolefin blend (PP+PE). Dilute under appropriate aseptic conditions. Discard any unused portion left in the vial.
- Gently invert the bag/container to mix the solution. Do not shake.
- Visually inspect parenteral medicinal products for particulate matter and discoloration prior to administration. The diluted solution may develop very small, translucent to white proteinaceous particles, as daratumumab is a protein. Do not use if visibly opaque particles, discoloration or foreign particles are observed.
- Since Darzalex does not contain a preservative, diluted solutions should be administered within 15 hours (including infusion time) at room temperature (15°C-25°C) and in room light.
- If not used immediately, the diluted solution can be stored prior to administration for up to 24 hours at refrigerated conditions (2°C-8°C) and protected from light. Do not freeze.
- Administer the diluted solution by intravenous infusion using an infusion set fitted with a flow regulator and with an in-line, sterile, non-pyrogenic, low protein-binding polyethersulfone (PES) filter (pore size 0.22 or 0.2 micrometer). Polyurethane (PU), polybutadiene (PBD), PVC, PP or PE administration sets must be used.
- Do not infuse Darzalex concomitantly in the same intravenous line with other agents.
- Do not store any unused portion of the infusion solution for reuse. Any unused product or waste material should be disposed of in accordance with local requirements.
- Traceability
  In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.