Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) – 1986
The medicine is dispensed according to a physician's prescription only

XGEVA®, Solution for subcutaneous injection

Each vial contains 120 mg of denosumab in 1.7 mL of solution (corresponding to 70 mg/mL).

List of the additional ingredients detailed in section 6.

Read the entire leaflet carefully before using the medicine. This leaflet contains concise information about the medicine. If you have any other questions, refer to the physician or the pharmacist.

This medicine has been prescribed for you only. Do not pass it on to others. It may harm them even if it seems to you that their medical condition is similar.

XGEVA is not intended for children and adolescents under 18 years of age except for adolescents with giant cell tumor of the bone whose bones have stopped growing.

In addition to the patient leaflet, XGEVA has patient safety information card. This card includes important safety information that you should know, before treatment initiation and during the treatment with XGEVA and act according to it. The patient safety information card and the patient leaflet should be read prior treatment initiation with this product. The card should be kept for additional reading as needed.

1. What is the medicine intended for?

XGEVA is used in adults with cancer to prevent serious complications caused by bone metastasis (e.g. fracture, pressure on the spinal cord or the need to receive radiation therapy or surgery) and in adults with multiple myeloma. In adults and adolescents whose bones have stopped growing, XGEVA is also used to treat giant cell tumor of bone, which cannot be treated by surgery or where surgery is not the best option.

XGEVA contains denosumab, a protein (monoclonal antibody) that works to slow down bone destruction caused by cancer spreading to the bone (bone metastasis) or by giant cell tumor of bone.

Therapeutic group:
Drugs for the treatment of bone disease-other drugs affecting bone structure and mineralization.

2. Before using the medicine

Do not use the medicine:
- if you are sensitive (allergic) to denosumab or to any of the additional ingredients contained in the medicine (listed in section 6).
- your physician will not administer XGEVA to you if you have a very low level of calcium in your blood which has not been treated.
- your physician will not administer XGEVA to you if you have unhealed wounds from dental or oral surgery.

Special warnings regarding the use of the medicine

Talk to your physician before using XGEVA.

Calcium and vitamin D supplementation
You should take calcium and vitamin D supplements while being treated with XGEVA unless your blood calcium is high. Your physician will discuss this with you. If the level of calcium in your blood is low, your physician may decide to give you calcium supplements before you start treatment with XGEVA.

Low calcium levels in the blood
Please tell your physician immediately if you have spasms, twitches, or cramps in your muscles, and/or numbness or tingling in your fingers, toes or around your mouth and/or seizures, confusion or loss of consciousness while being treated with XGEVA. You may have low levels of calcium in your blood.

Renal impairment
Tell your physician if you have or have had severe kidney problems, kidney failure or have needed dialysis, which may increase your risk of getting low blood calcium, especially if you do not take calcium supplements.

Problems with your mouth, teeth or jaw
A side effect called osteonecrosis of the jaw (bone damage in the jaw) has been reported commonly (may affect up to 1 in 10 people) in patients receiving XGEVA injections for cancer-related conditions. Osteonecrosis of the jaw can also occur after stopping treatment.

It is important to try to prevent osteonecrosis of the jaw developing as it may be a painful condition that can be difficult to treat. In order to reduce the risk of developing osteonecrosis of the jaw, there are some precautions you should take:

- Before receiving treatment, tell your physician or nurse if you have any problems with your mouth or teeth. Your physician should delay the start of your treatment if you have unhealed wounds in your mouth from dental procedures or oral surgery. Your physician may recommend a dental examination before you start treatment with XGEVA.
- While being treated, you should maintain good oral hygiene and receive routine dental check-ups. If you wear dentures you should make sure these fit properly.
- If you are under dental treatment or will undergo dental surgery (e.g. tooth extractions), inform your physician about your dental treatment and tell your dentist that you are being treated with XGEVA.
- Contact your physician and dentist immediately if you experience any problems with your mouth or teeth such as loose teeth, pain or swelling, non-healing of sores or discharge, as these could be signs of osteonecrosis of the jaw.

Patients undergoing chemotherapy and/or radiotherapy, taking steroids or anti-angiogenic medicines (used to treat cancer), undergoing dental surgery, who do not receive routine dental care, have gum disease or who are smokers, may have a higher risk of developing osteonecrosis of the jaw.

Unusual thigh bone fractures
Some people have developed unusual fractures in their thigh bone while being treated with XGEVA. Contact your physician if you experience new or unusual pain in your hip, groin, or thigh.

High calcium levels in the blood after stopping treatment with XGEVA
Some patients with giant cell tumor of the bone have developed high calcium levels in the blood weeks to months after stopping treatment. Your physician will monitor you for signs and symptoms of high levels of calcium, after you stop receiving XGEVA.

Risk of broken bones in the spine after stopping treatment with XGEVA
Treatment discontinuation with XGEVA may increase the risk of having broken bones in the spine, particularly in post-menopausal women with malignancies and which had a fracture in the past or are with a background of osteoporosis (a condition in which bones become thin and fragile). Do not stop taking XGEVA without first talking with your physician. If your XGEVA treatment is stopped, discuss other available treatment options with your physician.

Children and adolescents
XGEVA is not intended for children and adolescents under 18 years of age except for adolescents with giant cell tumor of the bone whose bones have stopped growing. The use of XGEVA has not been studied in children and adolescents with other cancers that have spread to bone.

Other medicines and XGEVA
If you are taking or have recently taken other medicines including non-prescription medicines and food supplements, tell the physician or the pharmacist. It is especially important that you tell your physician if you are being treated with:
- another medicine containing denosumab
- a bisphosphonate

You should not take XGEVA together with other medicines containing denosumab or bisphosphonates.

Pregnancy and breast-feeding
XGEVA has not been tested in pregnant women. It is important to tell your physician if you are pregnant, think you may be pregnant, or plan to get pregnant. XGEVA is not recommended for use if you are pregnant. Women of child-bearing potential should use effective methods of contraception while being treated with XGEVA and for at least 5 months after stopping treatment with XGEVA.

If you become pregnant during treatment with XGEVA or less than 5 months after stopping treatment with XGEVA, please inform your physician.

It is not known whether XGEVA is excreted in breast milk. It is important to tell your physician if you are breast-feeding or plan to do so. Your physician will then help you decide whether to stop breast-feeding or whether to stop taking XGEVA, considering the benefit of breast-feeding to the baby and the benefit of XGEVA to the mother.

If you are nursing during treatment with XGEVA, please inform your physician.

Ask your physician or pharmacist for advice before taking any medicine.

Driving and using machines
XGEVA has no or negligible influence on the ability to drive and use machines.

Important information about some ingredients of the medicine

XGEVA contains sorbitol
This medicine contains 78 mg sorbitol in each vial.

XGEVA contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per 120 mg dose, that is to say essentially 'sodium-free'.

3. How should you use the medicine?

Always use according to the physician's instructions.

You should check with the physician or the pharmacist if you are unsure.

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

XGEVA should be administered under the responsibility of a healthcare professional.

The recommended dose of XGEVA is 120 mg administered once every 4 weeks, as a single injection under the skin (subcutaneous). The physician or the nurse will give XGEVA as an injection into your thigh,

abdomen or upper arm. If you are being treated for giant cell tumor of bone, you will receive an additional dose 1 week and 2 weeks after the first dose.

Do not exceed the recommended dose.

Do not shake.

You should also take calcium and vitamin D supplements while being treated with XGEVA unless you have an excess of calcium in the blood. Your physician will discuss this with you.

It is important that you follow the instructions of your physician or nurse regarding return visits. If you forget to go back to your physician at the scheduled time, ask your physician for advice.

Persist with the treatment as recommended by the physician.

If a child has accidentally swallowed the medicine, refer immediately to a physician or to a hospital emergency room and bring the package of the medicine with you.

Do not take medicines in the dark! Check the label and the dose each time you take a medicine. Wear glasses if you need them.

If you have any further questions on the use of this medicine, ask your physician, pharmacist or nurse.

4. Side effects

As with any medicine, use of XGEVA may cause side effects in some of the users. Do not be alarmed by reading the list of side effects. You may not experience any of them.

Please tell your physician immediately if you develop any of these symptoms while being treated with XGEVA (may affect more than 1 in 10 people):

- spasms, twitches, cramps in your muscles, numbness or tingling in your fingers, toes or around your mouth and/or fits (seizures), confusion or loss of consciousness. These could be signs that you have low calcium levels in the blood. Low calcium in the blood may also lead to a change in heart rhythm called QT prolongation, which is seen by electrocardiogram (ECG).

Please tell your physician and dentist immediately if you experience any of these symptoms while being treated with XGEVA or after stopping treatment (may affect up to 1 in 10 people):

- persistent pain in the mouth and/or jaw, and/or swelling or non-healing of sores in the mouth or jaw, discharge, numbness or feeling of heaviness in the jaw, or loosening of a tooth could be signs of bone damage in the jaw (osteonecrosis).

Very common side effects (may affect more than 1 in 10 people):

- bone, joint, and/or muscle pain which is sometimes severe,
- shortness of breath,
- diarrhea.

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

- low phosphate levels in the blood (hypophosphatemia),
- removal of a tooth,
- excessive sweating,
- in patients with advanced cancer: development of another form of cancer.

Uncommon side effects (may affect up to 1 in 100 people):
- high calcium levels in the blood (hypercalcemia) after stopping treatment in patients with giant cell tumor of the bone,
- new or unusual pain in your hip, groin or thigh (this may be an early indication of a possible fracture of the thigh bone),
- rash that may occur on the skin or sores in the mouth (lichenoid drug eruptions).

Rare side effects (may affect up to 1 in 1,000 people):
- allergic reactions (e.g. wheezing or difficulty breathing; swelling of the face, lips, tongue, throat or other parts of the body; rash, itching or hives on the skin). In rare cases, allergic reactions may be severe,
- broken bones in your spine after stopping treatment with XGEVA (multiple vertebral fractures).

Not known (frequency cannot be estimated from the available data):
- talk to your physician if you have ear pain, discharge from the ear, and/or an ear infection. These could be signs of bone damage in the ear.

If a side effect has appeared, if any of the side effects get worse or when you suffer from a side effect that has not been mentioned in the leaflet, you should consult the physician.

Reporting of side effects
Side effects can be reported to the Ministry of Health by clicking the link "Report Side Effects of Drug Treatment" found on the Ministry of Health home page 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?

Avoid poisoning! This medicine and any other medicine should 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 without an explicit instruction from the physician.

Do not use the medicine after the expiry date (exp. date) appearing on the package. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C–8°C).
Do not freeze.
Store in the original carton in order to protect from light.
The vial may be left outside the refrigerator to reach room temperature (up to 25°C) before injection. This will make the injection more comfortable. Once your vial has been left to reach room temperature (up to 25°C), it must be used within 30 days.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Additional information

In addition to the active ingredient the medicine also contains: sorbitol, glacial acetic acid, polysorbate 20, sodium hydroxide, water for injection.

What does the medicine look like and what is the content of the package:
XGEVA is a solution for injection (injection).
XGEVA is a clear, colorless to slightly yellow solution. It may contain trace amounts of clear to white particles.
Each pack contains one or four single use vials.
Not all pack sizes may be marketed.

Manufacturer:
Amgen Europe B.V., Minervum 7061, Breda, The Netherlands.

License Holder:
Amgen Europe B.V., P.O. BOX 53313, Tel - Aviv.

Revised in September 2022.

Registration number of the medicine in the National Drug Registry of the Ministry of Health: 147-01-33411

The following information is intended for healthcare professionals only:

- Before administration, the XGEVA solution should be inspected visually. The solution may contain trace amounts of translucent to white proteinaceous particles. Do not inject the solution if it is cloudy or discolored.
- Do not shake.
- To avoid discomfort at the site of injection, allow the vial to reach room temperature (up to 25°C) before injecting and inject slowly.
- The entire contents of the vial should be injected.
- A 27 gauge needle is recommended for the administration of denosumab.
- The vial should not be re-entered.

Any unused product or waste material should be disposed of in accordance with local requirements.