NOVARTIS

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

The medicine is dispensed with a doctor's prescription only

ACLASTA®

Solution for intravenous infusion (I.V.)

Zoledronic acid 5 mg/100 ml

Each vial of 100 ml solution contains 5 mg zoledronic acid (anhydrous).

Inactive and allergenic ingredients in the preparation - see chapter 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 ailment is similar.

1. WHAT IS THE MEDICINE INTENDED FOR?

Aclasta is used for:

- Treatment of Paget's disease of the bone.
- Treatment of osteoporosis:
  - in postmenopausal women
  - in men

  who are at increased risk of fracture, including those with a recent hip fracture from a minor injury.
- Treatment and prevention of glucocorticoid-induced osteoporosis (a type of steroids).
- Prevention of postmenopausal osteoporosis in women for whom bisphosphonate therapy is indicated.

Therapeutic group: bisphosphonates.

Osteoporosis:

Osteoporosis is a disease that causes thinning and weakening of the bones and is common in women after menopause, but can also occur in men. At menopause, a woman's ovaries stop producing the female hormone estrogen, which helps keep bones healthy. After menopause, bone loss occurs, the bones become weaker and break more easily. Osteoporosis could also occur in men and women because of the long-term use of steroids, which can affect the strength of bones. Many patients with osteoporosis have no symptoms, but they are still at risk of breaking bones because osteoporosis has made their bones weaker. Decreased blood levels of sex hormones, mainly estrogens formed from androgens, also play a role in the more gradual bone loss observed in men. In men and in women, Aclasta strengthens the bone and therefore the likelihood of fractures declines. Aclasta is also used in patients who have recently broken their hip in a minor trauma such as a fall and therefore are at risk of subsequent bone breaks.

Paget's disease of the bone:

Normally, old material that comprises the bone is removed and replaced with new material. This process is called remodeling. In Paget's disease, bone remodeling is too rapid and new bone is formed in a disordered fashion, which makes it weaker than normal. If the disease is not treated, bones may become deformed and painful, and may break. Aclasta works by returning the bone remodeling process to normal, and enables formation of normal bone, thus restoring strength to the bone.

2. BEFORE USING THE MEDICINE

Do not use the medicine if:

- you are sensitive (allergic) to the active ingredient, zoledronic acid, other bisphosphonates or any of the other ingredients of the medicine (listed in chapter 6)
- you have hypocalcaemia (this means that the levels of calcium in your blood are too low)
- you have severe kidney problems
- you are pregnant
- you are breastfeeding

Special warnings regarding use of the medicine

Before treatment with Aclasta, tell the doctor if:

- you are being treated with any other medicine containing zoledronic acid, which is also the active substance of Aclasta (zoledronic acid is used in adult patients with certain types of cancer, to prevent bone complications or to reduce the amount of calcium).
- you have a kidney problem, or had in the past.
- you are unable to take daily calcium and vitamin D supplements.
- some or all of the parathyroid glands in your neck were surgically removed.
- sections of your intestine have been removed.

There have been post-marketing reports of a side effect called osteonecrosis of the jaw (ONJ) (bone damage in the jaw) in patients receiving Aclasta (zoledronic acid) for osteoporosis. ONJ can also occur after stopping treatment.

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

Before receiving Aclasta treatment, tell the doctor, pharmacist or nurse if:

- you have any problems with your mouth or teeth such as poor dental health, gum disease, or a planned tooth extraction
- you do not receive routine dental care or have not had an examination by a dentist for a long time
- you are a smoker (as this may increase the risk of dental problems)
- you have previously been treated with a bisphosphonate (used to treat or prevent bone problems)
- you are taking medicines called corticosteroids (such as prednisolone or dexamethasone)
- you have cancer

Your doctor may ask you to undergo an examination by a dentist before you start treatment with Aclasta.

While being treated with Aclasta, you should maintain good oral hygiene (including regular teeth brushing) and have routine dental check-ups. If you wear dentures, you should make sure these fit properly. If you are under dental treatment or are due to undergo dental surgery (e.g. tooth extraction), inform your doctor about your dental treatment and tell your dentist that you are being treated with Aclasta. Contact your doctor and dentist immediately if you experience any problems with your mouth or teeth such as loose teeth, pain or swelling, or sores that are not healing or are discharging, as these could be signs of ONJ.

Children and adolescents:

Aclasta is not intended for children or adolescents under 18 years of age.

Tests and follow up

- For patients with Paget's disease - it is recommended to measure blood calcium levels before infusion of Aclasta.
- Your doctor should do a blood test to check your kidney function (levels of creatinine) before each dose of Aclasta. It is important for you to drink at least 2 glasses of fluid (such as water), a few hours before receiving treatment with Aclasta, as directed by your healthcare provider.

Drug interactions:

If you are taking, or have recently taken other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist. It is important for your doctor to know all the medicines you are taking, especially if you are taking any medicines known to be harmful to your kidneys (e.g. aminoglycosides [a type of antibiotic used to treat certain infections]) or diuretics (several types of medicines used to treat different states of fluid retention in the body, hypertension and others), that may cause dehydration.

Pregnancy and breastfeeding

You should not receive Aclasta if you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby. Ask your doctor, pharmacist or nurse for advice before taking this medicine.

Driving and using machines

If you feel dizzy while taking Aclasta, do not drive or use machines until you feel better.

Important information regarding some of the ingredients of the medicine

Aclasta contains less than 1 mmol sodium (23 mg) per each 100 ml vial, i.e., essentially "sodium free".

3. HOW SHOULD YOU USE THE MEDICINE?

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

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

The dosage and treatment regimen will be determined by the doctor only.

Osteoporosis:

The usual dosage is generally 5 mg given as one intravenous infusion per year by your doctor or nurse. The infusion will take at least 15 minutes.

In case you recently broke your hip, it is recommended to administer Aclasta two or more weeks after your hip repair surgery.

It is important to take calcium and vitamin D supplements (for example tablets) as directed by your doctor.

For osteoporosis, Aclasta works for one year. The doctor will let you know when to return for your next dose.

Paget's disease:

For the treatment of Paget's disease, Aclasta must only be prescribed by a doctor with experience in the treatment of Paget's disease of the bone.

The usual dosage is 5 mg, given to you as one initial intravenous infusion by your doctor or nurse. The infusion will take at least 15 minutes. Aclasta may work for longer than one year, and your doctor will let you know if you need to be treated again.

Your doctor may advise you to take calcium and vitamin D supplements (e.g. tablets) for at least the first ten days after treatment with Aclasta. It is important that you follow this advice carefully so that the level of calcium in your blood does not become too low in the period after the infusion. Your doctor will inform you regarding the symptoms associated with hypocalcaemia.

Do not exceed the recommended dose.

Method of administration

Make sure you drink enough fluids (at least one or two glasses) before and after treatment with Aclasta, as directed by your doctor. This will help prevent dehydration. You may eat normally on the day you are treated with Aclasta. This is especially important in patients taking diuretics and in elderly patients (aged 65 and older).

If you took an overdose or if a child has 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 you forgot to take the medicine

Contact your doctor or hospital as soon as possible to reschedule your appointment.

Adhere to the treatment regimen as recommended by the doctor.

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

Before stopping Aclasta therapy

If you are considering stopping Aclasta treatment, please go to your next appointment and discuss this with your doctor. Your doctor will advise you and decide how long you should be treated with Aclasta.

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 further questions regarding use of the medicine, consult a doctor or pharmacist.

4. SIDE EFFECTS

As with any medicine, use of Aclasta 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 related to the first infusion are very common, but are less common following subsequent infusions.

The majority of the side effects, such as fever and chills, pain in the muscles or joints, and headaches, occur within the first three days following the dose of Aclasta. The symptoms are usually mild to moderate and go away within three days. Your doctor can recommend a mild pain reliever such as ibuprofen or paracetamol to reduce these side effects. The chance of experiencing these side effects decreases with subsequent doses of Aclasta.

Some side effects could be serious

Common side effects - effects that occur in 1-10 in 100 users

Cases of heart rhythm disorders (atrial fibrillation) have been observed in postmenopausal female patients who received Aclasta for the treatment of osteoporosis. It is not known whether Aclasta causes these heart rhythm disorders, but you must report to your doctor if you experience symptoms of heart rhythm disorders after receiving Aclasta.

Uncommon side effects - effects that occur in 1-10 in 1,000 users

Swelling, redness, pain and itching in the eyes or eye sensitivity to light.

Very rare side effects - may affect up to 1 in 10,000 users

Talk to your doctor if you have ear pain, discharge from the ear, and/or an ear infection. These could be signs of bone damage in the ear.

Side effects of unknown frequency (effects whose frequency has not yet been determined)

- Pain in the mouth and/or jaw, swelling or non-healing sores in the mouth or jaw, discharge, numbness or a feeling of heaviness in the jaw, or loosening of a tooth; these could be signs of bone damage in the jaw (osteonecrosis). Tell your doctor and dentist immediately if you experience such symptoms while being treated with Aclasta or after stopping treatment.
- Kidney disorders (e.g. decreased urine output) may occur. Your doctor should do a blood test to check your kidney function before each dose of Aclasta. It is important for you to drink at least 2 glasses of fluid (such as water), within a few hours before receiving Aclasta, as directed by your healthcare provider.

If you experience any of these side effects, contact your doctor immediately.

Aclasta may also cause additional side effects

Additional side effects observed for the indications: treatment of osteoporosis in postmenopausal women and in men at increased risk of fracture, including those who recently experienced a low-trauma hip fracture; treatment and prevention of glucocorticoid-induced osteoporosis; treatment of Paget's disease of the bone

Very common side effects - effects that occur in more than one in ten users

Fever.

Common side effects - effects that occur in 1-10 in 100 users

Headache; dizziness; redness of the eye; nausea; vomiting; diarrhea; pain in the muscles; pain in the bones and/or joints; pain in the back, arms or legs; flu-like symptoms (e.g. tiredness, chills, joint and/or muscle pain); chills; feeling of tiredness and lack of interest; weakness; pain; general unwell feeling, pain and/or swelling at the infusion site.

In patients with Paget's disease, symptoms due to low blood calcium (hypocalcaemia), such as muscle spasms, or numbness, or a tingling sensation especially in the area around the mouth have been reported.

Uncommon side effects - effects that occur in 1-10 in 1,000 users

Flu; upper respiratory tract infection; decreased red blood cell count; lack of appetite; sleeplessness; sleepiness which may include reduced alertness and awareness; tingling sensation or numbness; extreme tiredness; trembling; temporary loss of consciousness; eye infection or irritation or inflammation with pain and redness; spinning sensation; increased blood pressure; flushing; cough; shortness of breath; upset stomach; abdominal pain; constipation; dry mouth; heartburn; skin rash; excessive sweating; itching; skin reddening; neck pain; stiffness in muscles, bones and/or joints; joint swelling; muscle spasms; shoulder pain; pain in your chest muscles and rib cage; joint inflammation; muscular weakness; abnormal kidney function test results; abnormally frequent urination; swelling of hands, ankles or feet; thirst, toothache, taste disturbances; acute reaction (e.g. fever, increased heart rate, tiredness, lack of appetite); non-cardiac chest pain.

Rare side effects - effects that occur in 1-10 in 10,000 users

Unusual fracture of the thigh bone, particularly in patients receiving long-term treatment for osteoporosis may occur rarely. Contact your doctor if you experience pain, weakness or discomfort in your thigh, hip or groin, as this may be an early indication of a possible fracture of the thigh bone.

Low levels of phosphate in the blood.

Side effects of unknown frequency (effects whose frequency has not yet been determined)

Severe allergic reaction including dizziness and difficulty breathing, swelling mainly of the face and throat, difficulty breathing with wheezing or cough, itchy rash; decreased blood pressure; dehydration secondary to acute phase reactions (post-dose symptoms such as fever, vomiting and diarrhea).

Additional side effects observed for the indication: prevention of osteoporosis in postmenopausal women who require bisphosphonate therapy

The following effects were observed for this indication only, or were reported for this indication at a higher frequency than for the other indications:

Very common side effects - effects that occur in more than one in ten users

Headache; nausea; muscle pain; pain; chills.

Common side effects - effects that occur in 1-10 in 100 users

Lack of appetite; trembling; sleepiness which may include reduced alertness and awareness; eye infection or irritation or inflammation with pain and redness; abdominal pain; upper abdominal pain; constipation; night sweats; muscle pain; bone and/or joint pain; muscle spasms; pain in your chest muscles and rib cage; jaw pain; neck pain; swelling of the hands, ankles or feet; systemic reaction related to the infusion, such as fever, chills, wheezing, itching, flushing, rash, dizziness, light-headedness; non-cardiac chest pain.

Uncommon side effects - effects that occur in 1-10 in 1,000 users

Anxiety; decreased skin sensitivity; blurred vision; flank pain.

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, 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 without explicit instruction from the doctor.
- Do not use the medicine after the expiry date (exp. date) that appears on the carton package and vial. The expiry date refers to the last day of that month.
- Store below 30°C.
- Stability after opening and further instructions for the health care professionals are detailed under "Information for the healthcare professional" chapter, at the end of this leaflet.
- Do not use this medicine if you notice that the package is damaged.

6. FURTHER INFORMATION

- In addition to the active ingredient, the medicine also contains:
  Mannitol, sodium citrate, water for injection
- What the medicine looks like and what are the contents of the package: **The solution**: clear and colorless. **The vial**: plastic, colorless 100 ml vial, with a grey rubber stopper and a flip-off aluminum cap.
  The package contains 1, 3 or 6 vials. Not all package sizes may be marketed.
- **Registration Holder and Importer and its address:** Novartis Israel Ltd., P.O.B 7126, Tel Aviv.
- Revised in December 2020 according to MOH guidelines.
- Registration number of the medicine in the National Drug Registry of the Ministry of Health: 135 99 31323

INFORMATION FOR THE HEALTHCARE PROFESSIONAL

Patients treated with Aclasta should be given the package leaflet following administration.

The following information is intended for healthcare professionals only:

How to prepare and administer Aclasta

Aclasta solution for infusion (Zoledronic acid 5 mg/100 ml) is ready for use.

For single use only. Any unused solution should be discarded. Only clear solution free from particles and discoloration should be used. Aclasta must not be mixed or given intravenously with any other medicinal product and must be given through a separate vented infusion line at a constant infusion rate. The infusion time must not be less than 15 minutes. Aclasta must not be allowed to come into contact with any calcium-containing solutions. If refrigerated, allow the refrigerated solution to reach room temperature before administration. Aseptic techniques must be followed during preparation of the infusion. The infusion must be conducted according to standard medical practice.

How to store Aclasta

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and vial after EXP.
- The unopened vial should be stored below 30°C.
- After opening the vial, the solution is chemically and physically stable for at least 24 hours at 2°C - 8°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C. Allow the refrigerated solution to reach room temperature before administration.