

Arylia

Denosumab

Package leaflet: Information for the patient Arylia 60 mg solution for injection in pre-filled syringe

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

- 1. What Arylia is and what it is used for
- 2. What you need to know before you use Arylia
- 3. How to use Arylia
- 4. Possible side effects of Arylia
- 5. How to store Arylia
- 6. Contents of the pack and other information

Instructions for preparing and giving an injection of Arylia (See overleaf)

1. What Arylia is and what it is used for

Arylia contains the active substance Denosumab with a protein structure. Denosumab is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to RANKL. RANKL is a protein which is necessary for the formation, function and survival of osteoclast (the cell for bone resorption). Arylia stops RANKL from activating its receptor, RANK, present on the surface of osteoclasts. This prevents osteoclast formation, function, and survival, hence decreasing resorption of bone and increasing bone mass and strength.

Bone is a living tissue that is constantly regenerating. Estrogen (female hormone) helps keep bones strong and healthy. Estrogen levels in the body decrease after menopause and causes weak and brittle bones which ultimately leads to osteoporosis.

Men can also be led to osteoporosis due to certain factors, such as aging and low levels of Testosterone (male hormone) cause osteoporosis. This problem is also found in people taking estrogen and testosterone inhibitors to treat breast and prostate cancer.

Arylia is also used in osteoporosis caused by glucocorticoids in patients at high fracture risk who have been treated with systemic glucocorticoids at daily doses of greater than or equal to 7.5 mg prednisolone for at least 6 months.

Arylia is used to treat

- Osteoporosis in postmenopausal women and in men at increased risk of fractures.
- Bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures and bone loss in females receiving aromatase inhibitor therapy for breast cancer.

- Bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture.

2. What you need to know before you use Arylia

Do not use Arylia

- If you have low calcium levels in the blood (hypocalcaemia).
- If you have ever had an allergic reaction to Denosumab or any of the other ingredients of this medicine (Listed in section 6).
- In pregnancy

Warnings and Precautions

Talk to your doctor, pharmacist or nurse before using Arylia

- You should also take calcium and vitamin D supplements while being on treatment with Arylia. Your doctor will discuss this with you.
- You may have low levels of calcium in your blood while receiving Arylia. Please tell your doctor immediately if you notice any of the following symptoms: spasms, twitches, or cramps in your muscle, and/or numbness or tingling in your fingers, toes or around your mouth, and/or seizures, confusion, or loss of consciousness. Low calcium in the blood may also lead to a change in heart rhythm which is seen by electrocardiogram (ECG).
- Tell your doctor if you have or ever had severe kidney problems, kidney failure or have needed dialysis or are taking medicines called glucocorticoids (such as prednisolone or dexamethasone), which may increase your risk of getting low blood calcium if you do not take calcium supplements.
- Whilst being treated with Arylia you may develop a skin infection with symptoms such as a swollen, red area of skin, most commonly in the lower leg, that feels hot and tender (cellulitis), and possibly with symptoms of fever. Please tell your doctor immediately if you develop any of these symptoms.
- A side effect called osteonecrosis of the jaw (ONJ) (bone damage in the jaw) has been reported rarely in patients receiving Arylia or even after stopping treatment. The risk of ONJ increases in patients treated for a long time. Your doctor may ask you to undergo a dental examination before you start treatment with Arylia. In order to reduce the risk of developing ONJ, take the following precautions:
Before receiving treatment, tell your doctor or nurse (health care professional) if you:

- ✓ Have any problems with your mouth or teeth such as poor dental health, gum disease, or a planned tooth extraction.
- ✓ Are a smoker (as this may increase the risk of dental problems).
- ✓ Do not receive routine dental care or have not had a dental check-up for a long time.
- ✓ Are taking medicines called corticosteroids (such as

prednisolone or dexamethasone).

- ✓ Have previously been treated with a bisphosphonate (used to treat or prevent bone disorders).
- ✓ Have cancer.
- ✓ Are in concomitant therapies: chemotherapy, angiogenesis inhibitors, radiotherapy to head and neck.
- ✓ Have co-morbid conditions (e.g. anaemia, coagulopathies, infection).

• You always need to keep a good oral hygiene while on Arylia and you may need to tell your dentist that you are taking Arylia. If you use dentures, make sure they are completely fitted in your mouth. If you are under dental treatment or will undergo dental surgery (e.g. tooth extractions), inform your doctor about your dental treatment and tell your dentist that you are being treated with Arylia.

- Immediately inform your doctor or dentist if you ever get a problem in your mouth such as pain, loose teeth, swelling, discharge or sores in your mouth which do not heal, as these may be signs of ONJ.
- Tell your doctor if you develop unusual pain in your thigh, hip and groin. Some people have developed thigh (femoral) bone fracture due to treatment with Arylia.
- Tell your doctor if you have an allergy to latex (the needle cap on the pre-filled syringe contains a derivative of latex).
- The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving denosumab who present with ear symptoms including chronic ear infections.

Children and Adolescents

Denosumab 60 mg solution for injection (Arylia) should not be used in children aged < 18 years because of safety concerns of serious hypercalcaemia, and potential inhibition of bone growth and lack of tooth eruption.

Other medicines and Arylia

- Tell your doctor or pharmacist if you are using or have recently used any other medicine.
- Tell your doctor or pharmacist if you are using any other medicine containing Denosumab.

Pregnancy and Breast-feeding

Pregnancy

Arylia is not recommended for use in pregnant women and women of child-bearing potential not using contraception. Women of child-bearing potential should use effective methods of contraception while being treated with Arylia for at least 5 months after stopping treatment with Arylia. If you become pregnant during treatment with Arylia or less than 5 months after stopping treatment with Arylia, please inform your doctor.

Breast-feeding

It is unknown if Arylia is excreted in breast milk. Tell your doctor if you are breast-feeding. Your doctor will then help you decide whether to stop breast-feeding, or whether to stop taking Arylia, considering the benefit of breast-feeding to the baby and the benefit of Arylia to the mother.

Effects on ability to drive and use machines

Arylia does not have any significant effect on using machines or ability to drive.

Excipients Warning

- Arylia contains Sorbitol. This medicine contains 47 mg sorbitol in each mL of solution. The additive effect of concomitantly administered products containing sorbitol (or fructose) should be taken into account.
- If you are on a controlled Sodium diet; this medicinal product contains less than 1 mmol (23 mg) Sodium per 60 mg that is to say essentially sodium-free.

3. How to use Arylia

- Arylia is available on prescription only. Always take this medicine exactly as your doctor or pharmacist have told you. Check with your doctor or pharmacist if you are not sure about the dose.
- The recommended dose is one pre-filled syringe of 60 mg administered once every 6 months, as a single injection under the skin (subcutaneous). You should also take calcium and vitamin D supplements while being on treatment with Arylia. Your doctor will discuss this with you.

Use in children and adolescents

Denosumab 60 mg solution for injection (Arylia) should not be used in children aged < 18 years because of safety concerns of serious hypercalcaemia, and potential inhibition of bone growth and lack of tooth eruption.

Route and method of administration

Arylia is given as an injection under the skin (subcutaneous) and The best places to inject are the top of your thighs (from 5 cm below the groin to 5 cm above the knee) and the abdomen (5 cm from the navel). Your carer can also use the outer area of your upper arm.

If you use more Arylia than you should

If you have used more Arylia than you should, talk to a doctor or pharmacist immediately.

If you forget to use Arylia

If a dose of Arylia is missed, the injection should be administered as soon as possible. Thereafter, injections should be scheduled every 6 months from the date of the last injection.

Do not take a double dose (two doses on the same day) to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor.

To avoid forgetting, you can write down your current injection date and your next injection date (6 months later) in the box located on the medicine box.

If you stop taking Arylia

Never stop using your medicine before consulting your physician. In order to take the complete benefit from your medicine, always complete the treatment course recommended by your doctor.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Important side effects

Denosumab can rarely cause Important side effects. If you ever experience any of the following, treatment is needed immediately. These side effects include:

- Uncommonly, patients receiving Arylia may develop skin infections (predominantly cellulitis) with symptoms of: swollen, red area of skin, most commonly in the lower leg, that feels hot and tender, and possibly fever.
- Rarely, patients receiving Arylia may develop pain in the mouth and/or jaw, swelling or non-healing of 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 (ONJ). Tell your doctor and dentist immediately if you experience such symptoms
- Rarely, patients receiving Arylia may have low calcium levels in the blood (hypocalcaemia). Symptoms include 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. If any of these apply to you, tell your doctor immediately. Low calcium in the blood may also lead to a change in heart rhythm which can be seen in electrocardiogram (ECG).
- Rarely unusual fractures of the thigh bone may occur in patients receiving Arylia. Contact your doctor if you experience new or unusual pain in your hip, groin or thigh as this may be an early indication of a possible fracture of the thigh bone.
- Rarely, allergic reactions may occur in patients receiving Arylia. Symptoms include swelling of the face, lips, tongue, throat or other parts of the body; rash, itching or hives on the skin, wheezing or difficulty breathing. Please tell your doctor if you develop any of these symptoms while being treated with Arylia.

The side effects observed with Denosumab are listed below in decreasing frequency order

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

- Bone, joint, and/or muscle pain which is sometimes severe,
- Arm or leg pain (pain in extremity).

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

- Urinary infection with painful urination, frequent urination, blood in the urine, inability to hold your urine,
- Upper respiratory tract infection,
- Pain, tingling or numbness that moves down your leg (sciatica),
- Cataract
- Abdominal discomfort,
- Constipation,
- Rash, skin lesion
- Skin condition with itching, redness and/or dryness (eczema)

- Hair loss (alopecia)

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

- Fever, vomiting and abdominal pain or discomfort (diverticulitis)
- Ear infection
- Cellulitis
- Lichen planus-like reactions (inflammatory skin disease)

Rare side effects (may affect up to 1 in 1000 people)

- Allergic reactions with symptoms of difficult breathing, wheezing, increased heartbeat, swollen throat, lips, tongue, face or other parts of the body, rash, hives or itching on skin.
- Thigh (femoral) fracture may happen with Arylia. Contact your doctor upon unusual pain in the thigh, groin or the hip.
- Anaphylactic reaction
- Hypocalcaemia
- Osteonecrosis of the jaw

Very rare side effects (may affect up to 1 in 10000 people)

Allergic reaction that can damage blood vessels mainly in the skin (e.g., purple or brownish-red spots, hives or skin sores) (hypersensitivity vasculitis).

Not known

(frequency cannot be estimated from the available data)

- Osteonecrosis of the external auditory canal (ear pain, discharge from the ear and/or an ear infection)

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

You can also report side effects directly via the national reporting system fda.gov.ir.

5. How to store Arylia

- 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 label and outer carton after "EXP". The expiry date refers to the last day of that month.
- Store in a refrigerator (2-8 °C).
- Do not freeze.
- Keep in the original outer carton to protect from light.
- Do not shake excessively.
- To reduce pain at the injection site, inject the medicine after reaching room temperature (about 30 minutes after removing from the refrigerator).
- Check the solution in pre-filled syringe before injection. Do not use the solution if it is discoloured, cloudy, or if other than those described above are present. If you are concerned with the appearance of the solution, then contact your pharmacist for assistance.
- 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. Contents of the pack and other information

What Arylia contains

The active substance of Arylia is Denosumab. Each 1 mL pre-filled syringe contains 60 mg of Denosumab (60 mg/mL).

- The other ingredients are acetic acid glacial, sodium hydroxide, sorbitol, polysorbate 20 and water for injections.

What Arylia looks like and contents of the pack

Arylia is a clear, colourless to slightly yellow solution for injection provided in a ready to use pre-filled syringe.

Each small box contains one pre-filled syringe, one alcohol swab and a patient information leaflet.

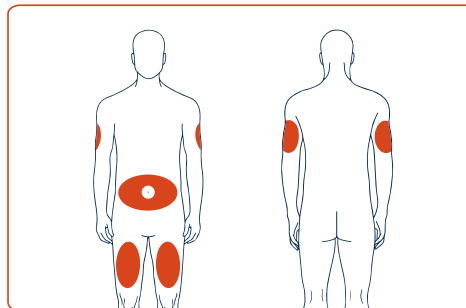
Instructions for preparing and giving an injection of Arylia

Step 1: Setting up for an injection

- Select a clean, well-lit, flat working surface.
- Take the Arylia carton containing the pre-filled syringe out of the refrigerator and place it on the flat work surface. Do not shake the pre-filled syringe of Arylia.
- Check the expiration date on the pre-filled syringe.
- Do NOT use the pre-filled syringe if the needle cover is missing or not securely attached.
- For a more comfortable injection, allow the Arylia in the pre-filled syringe to reach room temperature (approximately 30 minutes). Do NOT remove the needle cover while allowing it to reach room temperature. Do NOT warm Arylia in any other way.
- Assemble the additional supplies you will need for your injection. These include an alcohol swab, a cotton ball or gauze if available.
- Wash your hands thoroughly with soap and warm water.
- Make sure the solution in the pre-filled syringe is clear, colorless or slightly yellow.
- Do NOT use the pre-filled syringe if any part of it appears cracked or broken.

STEP 2: Choosing and Preparing an Injection Site

Three recommended injection sites for using Arylia pre-filled syringe include: The best places to inject are the top of your thighs (from 5 cm below the groin to 5 cm above the knee) and the abdomen (5 cm from the navel). Your carer can also use the outer area of your upper arm.

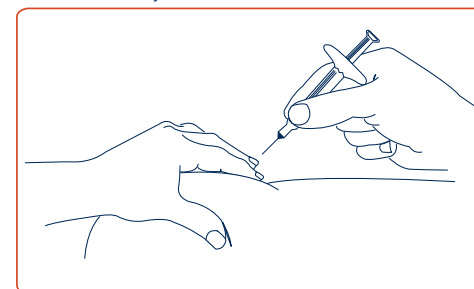


Rotate the site for each injection. Make sure that the new injection is given at least one inch from sites of recent injections. Do NOT inject into areas where the skin is tender, bruised, red, or hard. Avoid areas with scars or stretch marks. To prepare the area of skin where Arylia is to be injected, wipe the injection site with an alcohol swab. Do NOT touch this area again before giving the injection.

STEP 3: Injecting Arylia Using a Pre-filled Syringe

Do NOT remove the needle cover from the pre-filled syringe until you are ready to inject.

Pick up the pre-filled syringe from your flat working surface. Hold the barrel of the pre-filled syringe with one hand and pull the needle cover straight off. To avoid damaging the needle, do NOT twist or bend the needle cover while you are removing it, and do NOT try to put the needle cover back on to the pre-filled syringe. When you remove the needle cover, there may be a drop of liquid at the top of the needle, this is normal. Do NOT touch the needle or allow it to touch any surface. Do NOT touch or bump the plunger. Doing so could cause the liquid to leak out. Hold the syringe in one hand like a pencil, use the other hand to gently pinch a fold of skin at the cleaned injection site and hold it firmly.



With a quick, short motion, push the needle all the way into the skin at an angle between °45 and °90

After the needle is inserted, let go of the skin. Slowly push the plunger all the way down to injects Arylia. When the syringe is empty, remove the needle from the skin, being careful to keep it at the same angle as it was inserted.

If there is blood, press a cotton ball or gauze pad on your injection site for 10 seconds. Do not rub the injection site.

STEP 4: Disposing of Supplies

- The syringe should NEVER be reused. After injecting, drop the syringe into the bin for sharp objects and avoid throwing it away in the household bin.
- Dispose of used syringes and alcohol pads immediately after injection.

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