PACKAGE LEAFLET

VIZADIS 100 mg Powder for Suspension for SC Injection
Sterile
Cytotoxic
Applied under the skin.

- ***Active substance:*** Each vial contains 100 milligrams (mg) azacitidine. When reconstituted as directed, each mL of suspension will contain 25 mg azacitidine.
- ***Excipient(s):*** Mannitol injectable.

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, please ask your doctor or pharmacist.*
- *This medicine has been prescribed for you. Do not pass it on to others.*
- *When you visit a doctor or hospital while using this medicine, tell them that you are using this medicine.*
- *Please follow the instructions in this leaflet. Do not use any **higher** or **lower** doses than the recommended dose of this medicine.*

What is in this leaflet:

1. What VIZADIS is and what it is used for

- VIZADIS belongs to a group of medicines called anti-neoplastic drugs and is a medicine that prevents the growth of cancer cells.
- It contains 100 mg azacitidine as the active substance and mannitol as an excipient.

It is in the form of white powder for suspension for injection and is available in a glass vial containing 100 mg azacitidine.

- VIZADIS is used in adults who are not able to have a stem cell transplantation to treat:
  - Higher-risk myelodysplastic syndrome (MDS).
  - Chronic myelomonocytic leukemia (CMML).
  - Acute myeloid leukemia (AML) patients aged 65 years and over with 20-30% immature (young) cells and multiple lineage dysplasia (cell development defect) or with more than 30% immature (young) bone marrow cells according to the World Health Organization (WHO) classification.

These are diseases, which affect the bone marrow and can cause problems with normal blood cell production.

VIZADIS works by preventing cancer cells from growing. Azacitidine becomes incorporated into the genetic material of cells (ribonucleic acid [RNA] and deoxyribonucleic acid [DNA]). It is thought to

work by altering the way the cell turns genes on and off and also by interfering with the production of new RNA and DNA. These actions are thought to correct problems with the maturation and growth of young blood cells in the bone marrow that cause myelodysplastic disorders, and to kill cancerous cells in leukemia.

Talk to your doctor if you have any questions about how VIZADIS works or why this medicine has been prescribed for you.

2. What you need to know before you use VIZADIS
DO NOT use VIZADIS in the following conditions:
- If you are hypersensitive (allergic) to azacitidine or any of the other ingredients (see Excipients) of VIZADIS
- If you have advanced malignant liver tumor
- If you are breastfeeding.

Use VIZADIS with SPECIAL CARE in the following conditions:
- If you have decreased counts of platelets, red or white blood cells
- If you have kidney disease
- If you have liver disease
- If you have ever had a heart condition or heart attack or any history of lung disease, tell your doctor.

VIZADIS is not recommended for use in children and adolescents below the age of 18.

You will have blood tests before you begin treatment with VIZADIS and at the start of each period of treatment (called a 'cycle'). This is to check whether you have enough blood cells and whether your liver and kidneys are working properly.

You may have a decrease in your blood cells during VIZADIS treatment, especially in the first 2 cycles. For this reason, your doctor will perform a blood test before each treatment cycle to monitor your response to treatment and for possible side effects on blood cells, and to adjust your treatment dose.

Patients with severe heart failure or clinically uncontrolled heart or lung disease may have heart problems associated with VIZADIS treatment. If you have such diseases, your doctor will monitor your heart and lung functions before and during VİZADIS treatment.

There may be a rapidly spreading infection (necrotizing fasciitis) that can cause death of soft tissues. If necrotizing fasciitis develops, your doctor will immediately stop VIZADIS treatment and begin appropriate treatment.

Patients with a high tumor burden before treatment are at risk for tumor lysis syndrome (when the contents of tumor cells enter the bloodstream and rise to life-threatening levels because of the rapid destruction of tumor cells). Your doctor will monitor your condition closely and take any necessary precautions.

For the use of VIZADIS in men, see section "Pregnancy".

If these warnings apply to you, even at any time in the past, please consult your doctor.

Using VIZADIS with food and drink
There is no interaction with food and drinks in terms of route of administration.
It may be administered on an empty or full stomach.

Pregnancy
Consult your doctor or pharmacist before using this medicine.

Do not use VIZADIS during pregnancy as it may harm the baby.

Use an effective method of birth control during VIZADIS treatment and for 3 months after stopping treatment.

Men should not have children while receiving treatment with VIZADIS. Use an effective method of birth control during VIZADIS treatment and for 3 months after stopping treatment.

Talk to your doctor if you wish to conserve your sperm before starting this treatment.

Immediately tell your doctor or pharmacist if you realize that you are pregnant during the treatment.

Breastfeeding
Consult your doctor or pharmacist before using this medicine.

You should not use VIZADIS if you are breast-feeding. It is not known whether VIZADIS passes into breast milk. Therefore, you should not breastfeed your baby during treatment.

Driving and using machines
If you experience side effects such as tiredness and weakness, do not drive or use machines.

Important information about some of the excipients of VIZADIS
It does not contain any excipients that require a warning.

Using with other medicines
VIZADIS can change the effect of other medicines and other medicines can change the effect of VIZADIS.

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

3. How to use VIZADIS

Instructions for appropriate use and dose/frequency of administration:

- Before giving you VIZADIS, your doctor will give you another medicine to prevent nausea and vomiting at the start of each treatment cycle.
- The daily dose is 75 mg per square meter (m^2) body surface area.
- Your doctor will decide your dose of VIZADIS, depending on your general condition, height and weight. Your doctor will check your progress and may change your dose if necessary.
- VIZADIS is given every day for 1 week, followed by a rest period of 3 weeks.

This treatment cycle will be repeated every 4 weeks.
You will usually receive at least 6 treatment cycles.

Route and method of administration:
VIZADIS will be given to you as an injection under the skin by a doctor or nurse. It may be given under the skin on your thigh, tummy or upper arm.

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

Different age groups:
- **Use in children:**

Azacitidine is not recommended for use in children and adolescents below the age of 18 as its safety and efficacy have not been established.

- **Use in the elderly:**

No special dose adjustment is recommended for the elderly. However, your doctor will monitor your kidney function because it is more likely to decline in older patients.

Special conditions for use:
- **Kidney failure:**

If you have severe organ failure, your doctor will monitor you carefully for side effects.
No special changes in the starting dose prior to the treatment are recommended in patients with kidney failure; your doctor will make possible subsequent dose adjustments based on your blood and kidney laboratory values. Subsequent doses will be adjusted according to changes in your serum bicarbonate, creatinine or blood urea nitrogen levels from baseline.

- **Liver failure:**

If you have severe liver failure, your doctor will monitor you carefully for side effects.
No special changes in the starting dose prior to the treatment are recommended in patients with liver failure; your doctor will adjust any subsequent dose changes based on your blood laboratory values.

You should not use VIZADIS if you have advanced malignant liver tumor.

If you feel that the effect of VIZADIS is too strong or too weak, consult your doctor or pharmacist.

If you have used more VIZADIS than you should:
Your doctor will monitor you with blood counts and provide supportive treatment if needed.

Talk to a doctor or pharmacist if you have used more VIZADIS than you should.

If you forget to use VIZADIS:
Do not use a double dose to make up for the forgotten doses.

Possible effects if you stop using VIZADIS:
No information is available about any side effects that might happen once you stop using VIZADIS. However, use an effective method of birth control during VIZADIS treatment and for 3 months after stopping treatment.

Do not stop using your medicine unless your doctor tells you to.

4. Possible side effects

Like all other medicines, VIZADIS may cause side effects in people with sensitivity to its ingredients.

Stop using VIZADIS and IMMEDIATELY tell your doctor or go to the nearest hospital emergency department if any of the following occurs:

- Drowsiness, shaking, jaundice, abdominal bloating and easy bruising. These may be symptoms of liver failure and can be life threatening.
- Swelling of the feet and legs, back pain, reduced passing of water, increased thirst, rapid pulse, dizziness and nausea or reduced appetite and feelings of confusion, restlessness or fatigue. These may be symptoms of kidney failure and can be life threatening.
- **A fever.** This could be due to an infection as a result of having low levels of white blood cells, which can be life-threatening.
- **Chest pain or shortness of breath, which may be accompanied with a fever.** This may be due to an infection of the lung called "pneumonia", and can be life threatening.
- **Bleeding.** Such as blood in the stool due to bleeding in the stomach or gut, or such as bleeding inside your head. These may be symptoms of having low levels of platelets in your blood.
- **Difficulty breathing, swelling of the lips, itching or rash.** This may be due to a hypersensitivity (allergic) reaction.

These are all very serious side effects.
If you have any of these conditions, you may need urgent medical intervention or hospitalization.

Side effects are defined in the categories shown below:

Very common:	May occur in at least 1 in 10 patients.
Common:	May occur in less than 1 in 10 but in more than 1 in 100 patients.
Uncommon:	May occur in less than 1 in 100 but in more than 1 in 1,000 patients.
Rare:	May occur in less than 1 in 1,000 but in more than 1 in 10,000 patients.
Very rare:	May occur in less than 1 in 10,000 patients.
Not known:	Cannot be estimated from the available data.

Very common

- Reduced red blood count (anemia). You may feel tired and pale.
- Reduced white blood cell count. This may be accompanied by a fever. You are also more likely to get infections.
- A low blood platelet count (thrombocytopenia). You are more prone to bleeding and bruising.
- Constipation, diarrhea, nausea, vomiting.
- Pneumonia.
- Chest pain, being short of breath.
- Tiredness (fatigue).
- Injection site reaction including redness, pain, or a skin reaction.
- Loss of appetite.
- Joint aches.
- Bruising.
- Rash.
- Red or purple spots under your skin.
- Pain in your belly.
- Itching.
- Fever.
- Sore nose and throat.
- Dizziness.

- Headache.
- Having trouble sleeping (insomnia)
- Nosebleeds (epistaxis).
- Muscle aches.
- Weakness (asthenia).
- Weight loss.
- Low levels of potassium in your blood.

Common
- Bleeding inside your head (a condition characterized by severe headache, nausea, vomiting, dizziness, slurred speech and loss of consciousness).
- An infection of the blood caused by bacteria (sepsis). This may be due to low levels of white cells in your blood.
- Bone marrow failure. This can cause low levels of red and white blood cells and platelets.
- A type of anemia where your red and white blood cells and platelets are reduced.
- An infection in your urine.
- A viral infection causing cold sores (herpes).
- Bleeding gums, bleeding in the stomach or gut, bleeding from around your back passage (hemorrhoidal hemorrhage), bleeding in your eye, bleeding under your skin, or into your skin (hematoma).
- Blood in your urine.
- Ulcers of your mouth or tongue.
- Changes to your skin at the injection site. These include swelling, a hard lump, bruising, bleeding into your skin (hematoma), rash, itching and changes in the skin color.
- Redness of your skin.
- Skin infection (cellulitis).
- An infection of the nose and throat, or sore throat.
- Sore or runny nose or an inflammation of the air pockets in the facial bones (sinusitis).
- High or low blood pressure (hypertension or hypotension).
- Being short of breath when you move.
- Pain in your throat and voice box.
- Indigestion.
- A very deep and continuous state of abnormal sleep in which vital functions are much weakened (lethargy).
- Feeling generally unwell.
- Anxiety.
- Being confused.
- Hair loss.
- Kidney failure.
- Dehydration.
- White coating covering tongue, inner cheeks, and sometimes on the roof of your mouth, gums and tonsils (oral fungal infection).
- Fainting.
- A fall in blood pressure when standing (orthostatic hypotension) leading to dizziness when moving to a standing or sitting position.
- Sleepiness, drowsiness (somnolence).
- Bleeding due to the catheter line.
- A disease affecting the stomach or gut which can result in fever, vomiting and stomach pain (diverticulitis).
- Fluid around the lungs (pleural effusion).

- Shivering.
- Muscle spasms.
- Raised itchy rash on the skin (urticaria).
- Collection of fluid around the heart (pericardial effusion).

Uncommon
- Hypersensitivity (allergic) reaction.
- Shaking.
- Liver failure.
- Large plum-colored, raised painful patches on the skin with fever.
- Painful skin ulceration.
- Inflammation of the lining around the heart (pericarditis).

Rare
- Dry cough.
- Painful swelling in the finger tips (clubbing).
- Tumor lysis syndrome - metabolic complications that can occur during cancer treatment and sometimes even without treatment. These complications are caused by the product of dying cancer cells and may include the following: changes to blood chemistry; high potassium, phosphorus, uric acid, and low calcium consequently leading to changes in kidney function, heartbeat, seizures, and sometimes death.

Not known
- Infection of the deeper layers of skin, which spreads quickly, damaging the skin and tissue, which can be life-threatening (necrotizing fasciitis).

If you experience any side effects not listed in this leaflet, please inform your doctor or pharmacist.

Reporting side effects
If you get any side effects including any possible side effects not listed in this leaflet, talk to your doctor, pharmacist or nurse. You can also report side effects directly via the national reporting system. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store VIZADIS
Keep VIZADIS out of the reach and sight of children, and in its original package.
Store at room temperature below 25°C.

The suspension prepared with water for injection that is not stored in the refrigerator can be stored at room temperature below 25°C for up to 45 minutes or at 2-8°C for up to 8 hours.

When prepared with water for injection stored in the refrigerator (2-8°C), it can be stored for up to 22 hours at 2-8°C.

Your doctor or pharmacist is responsible for storing VIZADIS and disposing of any unused product correctly.

Use the medicine in line with its expiry date.
Do not use VIZADIS after the expiry date written on the vial and cardboard box.
The expiry date refers to the last day of the specified month.

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 protect the environment.

Waste of inner packaging of cytotoxic and cytostatic medicinal products for human use is **HAZARDOUS WASTE** and the management of this waste is carried out in accordance with the local requirements.

Marketing authorization holder:
DEVA Holding A.Ş.
Küçükçekmece / İSTANBUL / TÜRKİYE

Manufacturing site:
DEVA Holding A.Ş.
Kapaklı / TEKİRDAĞ / TÜRKİYE

This package leaflet was approved on 24/02/2021.

THE FOLLOWING INFORMATION IS INTENDED FOR HEALTHCARE PROFESSIONALS ONLY:

Recommendations for safe handling:
Azacitidine is a cytotoxic medicinal product and, as with other potentially toxic compounds, caution should be exercised when handling and preparing azacitidine suspensions. Procedures for proper handling and disposal of anticancer medicinal products should be applied.

If reconstituted azacitidine comes into contact with the skin, immediately and thoroughly wash with soap and water. If it comes into contact with mucous membranes, flush thoroughly with water.

Incompatibilities:
This medicinal product must not be mixed with other medicinal products except those mentioned below, in the section "Reconstitution procedure".

Reconstitution procedure:
1. The following materials should be available:
   - Vial(s) of azacitidine; water for injection vial(s); non-sterile surgical gloves;
   - Alcohol wipes; 5 mL injection syringe(s) with needle.
2. 4 mL of water for injection should be drawn into the syringe, making sure to purge any air trapped within the syringe.
3. The needle of the syringe containing the 4 mL of water for injections should be inserted through the rubber top of the azacitidine vial followed by injection of the water for injections into the vial.
4. Following removal of the syringe and needle, the azacitidine vial should be vigorously shaken until a uniform cloudy suspension is achieved. After reconstitution, each mL of suspension will contain 25 mg of azacitidine (100 mg/4 mL). The reconstituted product is a homogeneous, cloudy suspension, free of agglomerates. The product should be discarded if it contains large particles or agglomerates. Do not filter the suspension since this could remove the active substance. It must be taken into account that filters are present in some adaptors, spikes and closed systems. Therefore, such systems should not be used for administration of the medicinal product after reconstitution.
5. The rubber top should be cleaned and a new syringe inserted into the vial. The vial should then be turned upside down, making sure the needle tip is below the level of the liquid. The plunger should then be pulled back to withdraw the amount of medicinal product required for the proper dose, making sure to purge any air trapped within the syringe. The syringe with needle should then be removed from the vial and the needle disposed of.
6. A fresh subcutaneous needle (recommended 25-gauge) should then be attached to the syringe. The needle should not be purged prior to injection, in order to reduce the incidence of local injection site reactions.
7. If more than 1 vial is needed, all the above steps for preparation of the suspension should be repeated. For doses requiring more than 1 vial, the dose should be equally divided (e.g., dose 150 mg = 6 mL, 2 syringes with 3 mL in each syringe). Due to retention in the vial and needle, it may not be feasible to withdraw all of the suspension from the vial.
8. The contents of the dosing syringe should be re-suspended immediately prior to administration. The temperature of the suspension at the time injection should be approximately 20-25°C. To re-suspend, vigorously roll the syringe between the palms until a cloudy suspension is achieved. The product should be discarded if it contains large particles or agglomerates.

VIZADIS suspension should be prepared immediately before administration, and the resulting suspension should be used within 45 minutes. If the elapsed time is longer than 45 minutes, the suspension should be discarded appropriately and a new dose prepared. Alternatively, if the

suspension must be prepared in advance before administration to the patient, the reconstituted suspension must be place in a refrigerator (2°C to 8°C) immediately after reconstitution. This suspension is stable for a maximum of 8 hours when stored in a refrigerator. If the elapsed time in the refrigerator is greater than 8 hours, the suspension should be discarded appropriately and a new dose prepared.

If reconstituted with water for injection stored in the refrigerator (2-8°C), it should be placed in a refrigerator (2-8°C) immediately after reconstitution. The suspension is stable for a maximum of 22 hours when stored in a refrigerator. If the elapsed time in the refrigerator is greater than 22 hours, the suspension should be discarded appropriately and a new dose prepared.

The syringe filled with reconstituted suspension should be allowed up to 30 minutes prior to administration to reach a temperature of approximately 20-25°C. If the elapsed time is longer than 30 minutes, the suspension should be discarded appropriately and a new dose prepared.

Calculation of an individual dose
The total dose, according to the body surface area (BSA) can be calculated as follows:
Total dose (mg) = Dose (mg/m^2) x BSA (m^2)

The following table is provided only as an example of how to calculate individual azacitidine doses based on an average BSA value of 1.8 m^2.

Dose mg/m^2 (% of recommended starting dose)	**Total dose based on BSA value of 1.8 m^2**	**Number of vials required**	**Total volume of suspension required**
75 mg/m^2 (100%)	135 mg	2 vials	5.4 mL
37.5 mg/m^2 (50%)	67.5 mg	1 vials	2.7 mL
25 mg/m^2 (33%)	45 mg	1 vials	1.8 mL

Method of administration:
Do not filter the suspension after reconstitution.

Reconstituted VIZADIS should be injected subcutaneously (insert the needle at a 45-90° angle) using a 25-gauge needle into the upper arm, thigh or abdomen.

Doses greater than 4 mL should be injected into two separate sites.

Injection sites should be rotated. New injections should be given at least 2.5 cm from the previous site and never into areas where the site is tender, bruised, red, or hardened.