Package leaflet: Information for the user

Azacitidine STADA Arzneimittel 25 mg/ml, poeder voor suspensie voor injectie

azacitidine

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.
- 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 <Invented name> is and what it is used for

What <Invented name> is
<Invented name> is an anti-cancer agent which belongs to a group of medicines called 'anti-metabolites'. <Invented name> contains the active substance 'azacitidine'.

What <Invented name> is used for
<Invented name> is used in adults who are not able to have a stem cell transplantation to treat:
- higher-risk myelodysplastic syndromes (MDS)
- chronic myelomonocytic leukaemia (CMML)
- acute myeloid leukaemia (AML)

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

How <Invented name> works
<Invented name> 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 leukaemia.

Talk to your doctor or nurse if you have any questions about how <Invented name> works or why this medicine has been prescribed for you.

2. What you need to know before you use <Invented name>

DO NOT use <Invented name>
- if you are allergic to azacitidine or any of the other ingredients of this medicine (listed in section 6)
- if you have advanced liver cancer

- if you are breast-feeding

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using <Invented name>:
- 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

<Invented name> can cause a serious immune reaction called 'differentiation syndrome' (see section 4).

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

Children and adolescents
<Invented name> is not recommended for use in children and adolescents below the age of 18.

Other medicines and <Invented name>
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines. This is because <Invented name> may affect the way some other medicines work. Also, some other medicines may affect the way <Invented name> works.

Pregnancy, breast-feeding and fertility

Pregnancy
You should not use <Invented name> during pregnancy as it may be harmful to the baby. If you are a woman who can become pregnant you should use an effective method of contraception while taking <Invented name> and for 6 months after stopping treatment with <Invented name>. Tell your doctor straight away if you become pregnant during treatment.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

Breast-feeding
You should not breast-feed when using <Invented name>. It is not known if this medicine passes into human milk.

Fertility
Men should not father a child while receiving treatment with <Invented name>. Men should use an effective method of contraception while taking <Invented name> and for 3 months after stopping treatment with <Invented name>.

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

Driving and using machines
Do not drive or use any tools or machines if you experience side effects, such as tiredness.

3. How to use <Invented name>

Before giving you <Invented name>, your doctor will give you another medicine to prevent nausea and vomiting at the start of each treatment cycle.

- The recommended dose is 75 mg per m^2 body surface area. Your doctor will decide your dose of this medicine, depending on your general condition, height and weight. Your doctor will check your progress and may change your dose if necessary.
- <Invented name> is given every day for one 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.

This medicine will be given to you as an injection under the skin (subcutaneously) 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, pharmacist or nurse.

4. Possible side effects

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

Tell your doctor straight away if you notice any of the following side effects:
- **Drowsiness, shaking, jaundice, abdominal bloating and easy bruising**. These may be symptoms of liver failure and can be life-threatening.
- **Swelling of the legs and feet, back pain, reduced passing of water, increased thirst, rapid pulse, dizziness and nausea, vomiting 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 stools 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 an allergic (hypersensitivity) reaction.

Other side effects include:

Very common (may affect more than 1 in 10 people)
- Reduced red blood count (anaemia). 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, diarrhoea, 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 (abdominal pain).
- 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 (may affect up to 1 in 10 people)
- Bleeding inside your head.
- 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 anaemia 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 due to piles (haemorrhoidal haemorrhage), bleeding in your eye, bleeding under your skin, or into your skin (haematoma).
- 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 (haematoma), rash, itching and changes in the skin colour.
- Redness of your skin.
- Skin infection (cellulitis).
- An infection of the nose and throat, or sore throat.
- Sore or runny nose or sinuses (sinusitis).
- High or low blood pressure (hypertension or hypotension).
- Being short of breath when you move.
- Pain in your throat and voicebox.
- Indigestion.
- 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 a catheter line.
- A disease affecting the gut which can result in fever, vomiting and stomach pain (diverticulitis).
- Fluid around the lungs (pleural effusion).
- Shivering (chills).
- Muscle spasms.
- Raised itchy rash on the skin (urticaria).
- Collection of fluid around the heart (pericardial effusion).

Uncommon (may affect up to 1 in 100 people)
- Allergic (hypersensitivity) reaction.
- Shaking.
- Liver failure.
- Large plum-coloured, raised painful patches on the skin with fever.
- Painful skin ulceration (pyoderma gangrenosum).
- Inflammation of the lining around the heart (pericarditis).

Rare (may affect up to 1 in 1 000 people)
- Dry cough.
- Painless swelling in the finger tips (clubbing).
- Tumour lysis syndrome - Metabolic complications that can occur during treatment of cancer 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 (frequency cannot be estimated from the available data)
- Infection of the deeper layers of skin, which spreads quickly, damaging the skin and tissue, which can be life-threatening (necrotizing fasciitis).
- Serious immune reaction (differentiation syndrome) that may cause fever, cough, difficulty breathing, rash, decreased urine, low blood pressure (hypotension), swelling of the arms or legs and rapid weight gain.
- Inflammation of blood vessels in the skin which may result in rash (cutaneous vasculitis).

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 listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store <Invented name>

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 vial label and the carton. The expiry date refers to the last day of that month.

Your doctor, pharmacist or nurse are responsible for storing <Invented name>. They are also responsible for preparing and disposing of any unused <Invented name> correctly.

For unopened vials of this medicine – there are no special storage conditions.

When using immediately
Once the suspension has been prepared it should be administered within 60 minutes.

When using later on
If the <Invented name> suspension is prepared using water for injections that has not been refrigerated, the suspension must be placed in the refrigerator (2 °C – 8 °C) immediately after it is prepared and kept refrigerated for up to a maximum of 24 hours.

If the <Invented name> suspension is prepared using water for injections that has been stored in the refrigerator (2 °C – 8 °C), the suspension must be placed in the refrigerator

(2 °C – 8 °C) immediately after it is prepared and kept refrigerated for up to a maximum of 36 hours when stored in vial or 30 hours when stored in syringe.

The suspension should be allowed up to 30 minutes prior to administration to reach room temperature (20 °C – 25 °C).

If large particles are present in the suspension it should be discarded.

6. Contents of the pack and other information

What <Invented name> contains
The active substance is azacitidine. One vial contains 100 mg azacitidine. After reconstitution with 4 mL of water for injections, the reconstituted suspension contains 25 mg/mL azacitidine.

The other ingredient is mannitol (E421).

What <Invented name> looks like and contents of the pack
<Invented name> is a white powder for suspension for injection and is supplied in a 30 mL clear, transparent, flint moulded type I glass vial containing 100 mg of azacitidine. The vials may be placed in a polypropylene vial guard if required or may be directly packed in a clean carton box.

Each pack contains one vial of <Invented name>.

Houder van de vergunning voor het in de handel brengen
STADA Arzneimittel AG
Stadastrasse 2-18
61118 Bad Vilbel
Duitsland

Fabrikant
Pharmadox Healthcare Ltd
KW20A Kordin Industrial Park
Paola, PLA3000
Malta

STADA Arzneimittel AG
Stadastr. 2 – 18
61118 Bad Vilbel
Germany

In het register ingeschreven onder:
Azacitidine STADA Arzneimittel 25 mg/ml, poeder voor suspensie voor injectie – RVG 124956

Dit medicijn is geregistreerd in lidstaten van de EEA onder de volgende namen:

Bulgarije	Azacitidine MSN 25 mg/ml прах за инжекционна суспензия
Tsjechië	Azacitidine MSN
Nederland	Azacitidine STADA Arzneimittel 25 mg/ml, poeder voor suspensie voor injectie
Polen	Azacitidine MSN
Hongarije	Azacitidine MSN 25 mg/ml por szuszpenziós injekcióhoz
Roemenië	Azacitidină MSN 25 mg/ml pulbere pentru suspensie injectabila

Slowakije Azacitidine MSN 25 mg/ml prášok na injekčnú suspenziu

Deze bijsluiter is voor het laatst goedgekeurd in februari 2024.

The following information is intended for healthcare professionals only:

Recommendations for safe handling

<Invented name> 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 (see “Reconstitution Procedure”).

Reconstitution procedure

<Invented name> should be reconstituted with water for injections. The shelf life of the reconstituted medicinal product can be extended by reconstituting with refrigerated (2 °C to 8 °C) water for injections. Details on storage of the reconstituted product are provided below.

1. The following supplies should be assembled:
   Vial(s) of azacitidine; vial(s) of water for injections; non-sterile surgical gloves; alcohol wipes; 5 mL injection syringe(s) with needle(s).
2. 4 mL of water for injections 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 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 after reconstitution 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 with needle 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 firmly 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. When 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 must be re-suspended immediately prior to administration. The temperature of the suspension at the time of injection should be approximately 20 °C-25 °C. To re-suspend, vigorously roll the syringe between the palms until a uniform, cloudy suspension is achieved. The product should be discarded if it contains large particles or agglomerates.

Storage of the reconstituted product

For immediate use
The <Invented name> suspension may be prepared immediately before use and the reconstituted suspension should be administered within 60 minutes. If elapsed time is greater than 60 minutes, the reconstituted suspension should be discarded appropriately and a new dose prepared.

For later use
When reconstituting using water for injections that has not been refrigerated, the reconstituted suspension must be placed in a refrigerator (2 °C to 8 °C) immediately after reconstitution, and kept in the refrigerator for a maximum of 24 hours. If the elapsed time in the refrigerator is greater than 24 hours, the suspension should be discarded appropriately and a new dose prepared.

When reconstituting using refrigerated (2 °C to 8 °C) water for injections, the reconstituted suspension must be placed in a refrigerator (2 °C to 8 °C) immediately after reconstitution, and kept in a refrigerator for a maximum of 36 hours when stored in vial or 30 hours when stored in syringe. If the elapsed time in the refrigerator is greater than 36 hours (when stored in vial) or 30 hours (when stored in syringe), 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 °C-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 reconstituted suspension required**
75 mg/m^2 (100 %)	135 mg	2 vials	5.4 mL
37.5 mg/m^2 (50 %)	67.5 mg	1 vial	2.7 mL
25 mg/m^2 (33 %)	45 mg	1 vial	1.8 mL

Method of administration
Do not filter the suspension after reconstitution.
Reconstituted <Invented name> 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.

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