SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

VIZADIS 100 mg Powder for Suspension for SC Injection
Sterile
Cytotoxic

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: Each vial contains 100 mg of azacitidine.
When reconstituted as recommended, 25 mg of azacitidine is obtained per mL.

Excipients:
See section 6.1 for excipients.

3. PHARMACEUTICAL FORM

Powder for injection suspension.
White lyophilized powder.
After reconstitution, a homogeneous, cloudy suspension is obtained.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VIZADIS is indicated for adult patients who are not eligible for hematopoietic stem cell transplantation:

- Intermediate 2 and high-risk myelodysplastic syndrome (MDS) according to the International Prognostic Scoring System (IPSS)
- Chronic myelomonocytic leukemia (CMML) with bone marrow blasts between 10-29% without myeloproliferative disorder
- Acute myeloid leukemia (AML) with 20-30% blasts and multisystem dysplasia according to the World Health Organization (WHO) classification
- Acute myeloid leukemia (AML) with more than 30% bone marrow blasts according to the World Health Organization (WHO) classification.

4.2. Posology and method of administration

VIZADIS treatment should be initiated and monitored by a physician experienced in the use of chemotherapeutic agents. Patients should receive antiemetic premedication prior to treatment to prevent nausea and vomiting.

Dosage/administration frequency and duration:
The recommended starting dose in the first treatment cycle should be 75 mg/m^2 based on body surface area for all patients, regardless of pre-treatment hematology laboratory values. This should be administered subcutaneously for 7 days, followed by a 21-day break (28-day treatment cycle).

Patients should receive at least 6 treatment cycles. Treatment should be continued as long as the patient benefits from it or until disease progression is observed.
Patients should be monitored for hematologic response/toxicity and renal toxicity (see Section 4.4); delay or dose reduction as described below may be necessary before starting the next cycle.

VIZADIS should not be substituted for oral azacitidine. Due to differences in exposure, dosage and timing recommendations for oral azacitidine differ from those for injectable azacitidine. Healthcare professionals are advised to verify the name, dosage, and route of administration of the medicinal product.

Laboratory Tests:
Liver function tests, serum creatinine, and serum bicarbonate levels should be measured before starting treatment and before each treatment cycle. Complete blood counts should be performed before starting treatment and at least before each treatment cycle to monitor response and toxicity.

Dose Adjustment Due to Hematologic Toxicity:
In dose adjustment due to hematologic toxicity; hematologic toxicity is defined as the "lowest value" (lowest) reached during the cycle if the platelet count is $\leq 50x10^9$/L and/or the absolute neutrophil count (ANC) is $\leq 1x10^9$/L.

Recovery is defined as an increase of at least half the absolute difference between the baseline values and the lowest value in cell lines with observed hematologic toxicity (recovery ≥ Lowest count + (0.5 x [Baseline count - Lowest count]).

Patients whose blood count values have not decreased from baseline prior to treatment (e.g., white blood cell count - WBC - $\geq 3x10^9$/L and MNS $\geq 1.5x10^9$/L and platelets $\geq 75x10^9$/L), hematologic toxicity associated with VIZADIS *treatment* should be delayed until platelet count and MNS values improve. If improvement in values is achieved within 14 days, no dose adjustment is necessary. However, if improvement is not achieved within 14 days, dose reduction should be performed according to the table below. Following dose adjustments, the cycle should be reset to 28 days.

Lowest value in the cycle		If no improvement is observed within 14 days, the dose that can be administered in the next cycle (%)
MNS ($x10^9$/L)	Platelet ($x10^9$/L)	
≤1	≤50	50
>1	>50	100

*Improvement = Count ≥ Lowest count + (0.5 x [Initial count - Lowest count])

Patients with decreased blood count values compared to baseline prior to treatment (e.g., white blood cell count - WBC - <3x10 ^{9}/L or MNS <1.5x10^{9}/L, or platelets <75x10^{9}/L) following VIZADIS treatment, there is no need for dose adjustment or treatment delay if there is a ≤50% decrease in WBC, MNC, or platelet count compared to pre-treatment levels, or if there is improvement in any cell series differentiation despite a decrease of more than 50%.

If the decrease in WBC or MNC or platelet count is greater than 50% compared to pre-treatment levels and there is no improvement in any cell series differentiation, the next cycle of VIZADIS treatment should be delayed until the platelet count and MNC improve. If improvement is achieved within 14 days, no dose adjustment is necessary. However, if no improvement is observed within 14 days, the bone marrow cellular structure should be evaluated. If the bone marrow cell level is >50%, no dose change is necessary. If the bone marrow cell level is ≤50%, treatment should be delayed and the dose should be reduced according to the table below:

Bone Marrow Cell Level	Dose adjustment required if no improvement is observed within 14 days (%)	
	Improvement* ≤21 Days	Improvement* >21 Days
15-50	100	50
<15	100	33

*Recovery = Count ≥ Lowest count + (0.5 x [Initial count - Lowest count])

Following dose adjustments, the cycle should be reset to 28 days.

Administration method:
Diluted VIZADIS should be injected subcutaneously into the upper arm, thigh, or abdomen. Injection sites should be rotated. New injections should be made at least 2.5 cm away from the previous one and should never be administered in areas with sensitivity, bruising, redness, or induration. The suspension should not be filtered after dilution. Detailed instructions for the dilution and administration procedure for VIZADIS are provided in Section 6.6.

Additional information for specific populations:
Renal impairment:
Azacitidine can be administered to patients with renal impairment without initial dose adjustment (see Section 5.2). If an unexplained decrease in serum bicarbonate levels below 20 mmol/L occurs, the dose should be reduced by 50% in the next cycle. If serum creatinine or blood urea nitrogen (BUN) levels inexplicably rise to ≥2 times the baseline values and to the upper limit of normal (ULN), the next cycle should be delayed until the values return to normal or baseline levels, and the dose should be reduced by 50% in the following treatment cycle (see Section 4.4).

Hepatic impairment:

No studies have been conducted in patients with hepatic impairment (see Section 4.4). Patients with severe hepatic impairment should be carefully monitored for adverse events. No specific dose adjustment is recommended for the initial dose in patients with hepatic impairment prior to initiating treatment; subsequent dose adjustments should be based on hematological laboratory values. VIZADIS is contraindicated in patients with advanced malignant hepatic tumors (see Sections 4.3 and 4.4).

Pediatric population:
The use of VIZADIS is not recommended in children and adolescents under 18 years of age due to insufficient safety and efficacy data. Currently available data are described in sections 4.8, 5.1, and 5.2, but no recommendations are made regarding posology.

Geriatric population:
No specific dose adjustment is recommended for elderly patients. Monitoring renal function may be beneficial in elderly patients, as renal function is already reduced in this population.

4.3 Contraindications

- Patients with hypersensitivity to azacitidine or any of the components listed in Section 6.1,
- Patients with advanced malignant liver tumors (see Section 4.4),
- During lactation (see Section 4.6).

4.4 Special warnings and precautions for use

Hematologic toxicity

During treatment with azacitidine, anemia, neutropenia, and thrombocytopenia are frequently observed, especially during the first 2 cycles (see Section 4.8). Complete blood counts should be performed at least before each treatment cycle to monitor response and toxicity. After administering the recommended dose for the first cycle, the dose for subsequent cycles may be reduced or administration delayed based on the lowest counts and hematologic response (see Section 4.2).

Patients should be advised to report febrile attacks immediately. Patients and physicians should also be advised to be alert for signs and symptoms of bleeding.

Hepatic impairment

No studies have been conducted in patients with hepatic impairment. In patients with a high tumor burden due to metastatic disease, particularly those with an albumin level below 30 g/L, progressive hepatic coma and death have been rarely reported during azacitidine therapy. Azacitidine is contraindicated in patients with advanced malignant liver tumors (see Section 4.3).

Renal impairment

Increased serum creatinine levels, renal impairment, and renal dysfunction leading to death have been reported in patients treated with IV azacitidine in combination with chemotherapeutic agents. Additionally, renal tubular acidosis, defined as a decrease in serum bicarbonate levels to <20 mmol/L accompanied by alkaline urine and hypokalemia (serum potassium <3 mmol/L), developed in 5 chronic myeloid leukemia (CML) patients treated with azacitidine and etoposide. If unexplained increases in serum creatinine or BUN levels or decreases in serum bicarbonate (<20 mmol/L) occur, the dosage should be reduced or administration delayed (see Section 4.2).

Patients should be advised to immediately inform their doctor if they experience oliguria or anuria.

Although there is no clinical difference in the frequency of adverse effects between patients with normal renal function and those with renal impairment, patients with renal impairment should be closely monitored because azacitidine and/or its metabolites are primarily excreted by the kidneys (see Section 4.2).

Laboratory tests:
Liver function tests, serum creatinine, and serum bicarbonate levels should be determined before starting treatment and before each treatment cycle.

Complete blood counts should be performed before starting treatment and at least before each treatment cycle to monitor response and toxicity (see Section 4.8).

Heart and lung disease
Patients with severe congestive heart failure, clinically unstable heart disease, or lung disease were excluded from azacitidine indication studies (AZA PH GL 2003 CL 001 and AZA-AML-001) and therefore the safety and efficacy of azacitidine in these patients have not been established. New data from a clinical study in patients with a known history of heart or lung disease showed a significant increase in the incidence of cardiac events with azacitidine (see Section 4.8). Therefore, caution is advised when using VIZADIS in this patient group. Cardiopulmonary evaluation should be considered before and during treatment with VIZADIS.

Necrotizing fasciitis
Cases of necrotizing fasciitis, including fatal cases, have been reported in patients treated with azacitidine. In patients who develop necrotizing fasciitis, VIZADIS treatment should be discontinued immediately and appropriate treatment initiated urgently.

Tumor lysis syndrome:
Patients with a high tumor burden prior to treatment are at risk for tumor lysis syndrome. These patients should be closely monitored and appropriate precautions should be taken.

Differentiation syndrome
Cases of differentiation syndrome (also known as retinoic acid syndrome) have been reported in patients receiving injectable azacitidine. Differentiation syndrome can be fatal, and symptoms and clinical findings include respiratory distress, pulmonary infiltrates, fever, rash, pulmonary edema, peripheral edema, rapid weight gain, pleural effusions, pericardial effusions, hypotension, and renal failure (see Section 4.8). Treatment with high-dose IV corticosteroids and hemodynamic monitoring should be considered at the first onset of symptoms or findings suggestive of differentiation syndrome. Temporary discontinuation of injectable azacitidine should be considered until symptoms resolve, and caution is advised if treatment is continued.

4.5 Interaction with other medicinal products and other forms of interaction
Based on *in vitro* data, cytochrome P450 isoenzymes (CYPs), UDP-glucuronosyltransferases (UGTs), sulfotransferases (SULTs), and glutathione transferases (GSTs) do not appear to be involved in azacitidine metabolism; therefore, *in vivo* interactions involving these metabolic enzymes are unlikely.

Azasitidine is unlikely to have a clinically significant inhibitory or inducing effect on cytochrome P450 enzymes (see Section 5.2).

No clinical drug interaction studies have been conducted with azacitidine.

Additional information for specific populations
No interaction studies have been conducted.

Pediatric population
No interaction studies have been conducted.

4.6. Pregnancy and lactation
General recommendation
Pregnancy category: D

Women of childbearing potential/Birth control (Contraception)
Women of childbearing potential should use an effective method of contraception during treatment and for at least 6 months after treatment. Men should avoid fathering a child during treatment and should use effective birth control methods during treatment and for at least 3 months after treatment.

Pregnancy
There is insufficient data on the use of azacitidine in pregnant women. Studies in mice have shown reproductive toxicity (see Section 5.3). The potential risk to humans is unknown.

Based on the results of animal studies and its mechanism of action, azacitidine should not be used during pregnancy, especially during the first trimester, unless absolutely necessary. The decision to treat should be made on a case-by-case basis, weighing the potential benefits to the mother against the potential risks to the fetus.

Lactation
It is unknown whether azacitidine/its metabolites are excreted in human milk. Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is contraindicated during azacitidine therapy.

Reproductive ability/Fertility
There are no data on the effects of azacitidine on fertility in humans. Adverse reactions on male fertility have been observed with the use of azacitidine in animals (see Section 5.3).

Male patients should be advised to seek counseling to store their sperm before starting treatment.

4.7 Effects on the ability to drive and use machines
Azacitidine has a mild to moderate effect on the ability to drive or using machines. Fatigue has been reported with the use of azacitidine. Therefore, caution is advised when driving or operating machinery.

4.8. Undesirable effects

Safety profile summary
In adults with MDS, KMML, and AML with 20-30% bone marrow blasts:
Adverse reactions related to azacitidine administration occurred in 97% of patients.

In the azacitidine indication study (AZA PH GL 2003 CL 001), the most common serious adverse reactions were febrile neutropenia (8%) and anemia (2.3%), and similar serious adverse reactions were reported in studies supporting this study (CALGB 9221 and CALGB 8921). Other less frequently reported serious adverse reactions included infections such as neutropenic sepsis (0.8%) and pneumonia (2.5%), which can sometimes be fatal, thrombocytopenia (3.5%), hypersensitivity reactions (0.25%), and bleeding events [e.g., cerebral hemorrhage (0.5%), gastrointestinal hemorrhage (0.8%), and intracranial hemorrhage (0.5%)].

Adverse reactions commonly seen with azacitidine treatment include hematologic reactions (71.4%) containing thrombocytopenia, neutropenia, and leukopenia (usually Grade 3-4), gastrointestinal events (71.4%) including nausea and vomiting (usually Grade 1-2), or injection site reactions (77.1%; usually Grade 1-2).

In patients aged 65 years and older with >30% bone marrow blasts:

Very common serious adverse reactions (≥10%) identified in the azacitidine treatment arm of the AZA-AML-001 study include febrile neutropenia (25%), pneumonia (20.3%), and pyrexia (10.6%). Additionally, less frequently reported serious adverse reactions include sepsis (5.1%), anemia (4.2%), neutropenic sepsis (3%), urinary tract infection (3%), thrombocytopenia (2.5%), neutropenia (2.1%), cellulitis (2.1%), dizziness (2.1%), and dyspnea (2.1%).

The most frequently reported adverse reactions with azacitidine therapy (seen in 30% of patients in the study) were gastrointestinal events, including constipation (41.9%), nausea (39.8%), and diarrhea (36.9%; generally Grade 1-2), general disorders and administration site conditions including pyrexia (37.7%; generally Grade 1-2), and hematologic events including febrile neutropenia (32.2%) and neutropenia (30.1%; generally Grade 3-4).

Tabulated list of adverse reactions
The following table includes adverse reactions that may be associated with azacitidine treatment. Frequencies are based on pivotal clinical studies in MDS and AML and post-marketing observations.

Frequencies are defined as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), unknown (cannot be estimated from the available data). Within each frequency group, adverse reactions are presented in order of decreasing seriousness. Adverse reactions are presented in the table below according to the highest frequency observed in any of the pivotal clinical studies.

Table 1: Adverse reactions reported in patients with MDS or AML treated with azacitidine (clinical studies and post-marketing experience)

System Organ Class	Very common	Common	Uncommon	Rare	Unknown
Infections and infestations	Pneumonia* (including bacterial, viral, and fungal) Nasopharyngitis	Sepsis* (including bacterial, viral, and fungal) Neutropenic sepsis* Respiratory tract infection (including upper respiratory tract and bronchitis) Urinary tract infections Cellulitis Diverticulitis Oral fungal			Necrotizing fasciitis*

System Organ Class	Very common	Common	Uncommon	Rare	Unknown
		infection Sinusitis Pharyngitis Rhinitis Herpes simplex Skin infection			
Benign and malignant neoplasms (including cysts and polyps)					Differentiation syndrome*,a
Blood and lymphatic system diseases	Febrile neutropenia* Neutropenia Leukopenia Thrombocytopenia Anemia	Pancytopenia* Bone marrow failure			
Immune system disorders			Hypersensitivity reactions		
Metabolic and nutritional disorders	Anorexia Loss of appetite Hypokalemia	Dehydration		Tumor lysis syndrome	
Psychiatric disorders	Insomnia	Confusional state Anxiety			
Nervous system disorders	Dizziness Headache	Intracranial hemorrhage* Fainting Sleepiness Lethargy			
Eye diseases		Eye hemorrhage Conjunctival hemorrhage			
Cardiac diseases		Pericardial effusion	Pericarditis		
Vascular diseases		Hypotension* Hypertension Orthostatic hypotension Hematoma			

System Organ Class	Very common	Common	Uncommon	Rare	Unknown
Respiratory, chest, and mediastinal diseases	Dyspnea Nose bleed	Pleural effusion Exertional dyspnea Pharyngolaryngeal pain		Interstitial lung disease	
Gastrointestinal diseases	Diarrhea Vomiting Constipation Nausea Abdominal pain (including upper abdominal pain and abdominal discomfort)	Gastrointestinal bleeding* (including mouth bleeding) Hemorrhoidal bleeding Stomatitis Gum bleeding Dyspepsia			
Hepatobiliary diseases			Hepatic impairment* Progressive hepatic coma		
Skin and subcutaneous tissue disorders	Petechiae Itching that can occur anywhere on the body, Rash Ecchymosis	Purpura Alopecia Hives Erythema Macular rash	Acute febrile neutrophilic dermatosis Pyoderma Gangrenous		Cutaneous vasculitis
Musculoskeletal disorders and connective tissue and bone diseases	Arthralgia Musculoskeletal pain (including back, bone, and extremity pain)	Muscle spasms Myalgia			
Kidney and urinary tract diseases		Renal impairment* Hematuria Increased serum creatinine levels	Renal tubular acidosis		
General disorders and administration site conditions	Fever* Fatigue Asthenia Chest pain Erythema at the injection site Pain at the	At the injection site: Bruising, hematoma, hardening, rash, itching, inflammation,		Necrosis at the injection site	

System Organ Class	Very common	Common	Uncommon	Rare	Unknown
	injection site e reaction at the injection site (non-specific)	discoloration, nodule, and bleeding. Malaise Chills Catheter site Bleeding			
Research	Weight loss				

* Fatal cases have been reported rarely.
[a] See Section 4.4

Listing of selected adverse reactions
Hematological adverse reactions
Hematological adverse reactions commonly reported (≥10%) in association with azacitidine therapy are generally grade 3 or 4 anemia, thrombocytopenia, neutropenia, febrile neutropenia, and leukopenia.

The risk of these events is higher during the first 2 cycles and occurs less frequently in patients whose hematologic function returns to normal. Most hematologic adverse reactions are managed appropriately with routine monitoring of complete blood counts, delaying azacitidine administration in the next cycle, prophylactic antibiotics and/or growth factor support (e.g., G-CSF) for neutropenia, and transfusions for anemia or thrombocytopenia.

Infections
Myelosuppression can cause neutropenia and an increased risk of infection. Serious adverse reactions, including sepsis and pneumonia, some of which have been fatal, have been reported in patients receiving azacitidine. Infections can be controlled with the use of anti-infective agents and growth factor support (e.g., G-CSF) for neutropenia.

Bleeding
Bleeding may occur in patients receiving azacitidine. Serious adverse reactions, such as gastrointestinal bleeding and intracranial hemorrhage, have been reported. Patients with pre-existing thrombocytopenia or who develop treatment-related thrombocytopenia should be monitored for signs and symptoms of bleeding.

Hypersensitivity
Serious hypersensitivity reactions have been reported in patients receiving azacitidine. In the event of an anaphylactoid reaction, azacitidine treatment should be discontinued immediately and appropriate symptomatic treatment initiated.

Skin and subcutaneous tissue disorders
Most skin and subcutaneous adverse reactions are related to the injection site. None of these adverse reactions led to discontinuation of azacitidine or reduction of the azacitidine dose in the main studies. Most adverse reactions occurred during the first 2 cycles of treatment and tended to decrease in subsequent cycles. Subcutaneous adverse reactions such as rash/inflammation/pruritus, rash, erythema, and skin lesions at the injection site may require the concomitant use of medications such as antihistamines, corticosteroids, and non-steroidal anti-inflammatory drugs (NSAIDs). These cutaneous reactions should sometimes be distinguished from soft tissue infections occurring at the injection site. In post-marketing observations, soft tissue infections such as cellulitis and necrotizing fasciitis, which in rare cases led to death, have been reported with azacitidine. Refer to section 4.8 Infections for the clinical management of infectious adverse reactions.

Gastrointestinal adverse reactions
The most commonly reported adverse reactions with azacitidine therapy are constipation, diarrhea, nausea, and vomiting. These adverse reactions should be treated symptomatically with antiemetics for nausea and vomiting; antidiarrheals for diarrhea; and laxatives and/or stool softeners for constipation.

Renal adverse reactions
In patients treated with azacitidine, renal disorders ranging from increased serum creatinine levels and hematuria to renal tubular acidosis, renal failure, and death have been reported (see Section 4.4).

Hepatic adverse reactions
During azacitidine therapy, hepatic failure, progressive hepatic coma, and death have been observed in patients with a high tumor burden due to metastatic disease (see Section 4.4).

Cardiac events
Data from a clinical study including patients with known cardiovascular or pulmonary disease history showed an increase in cardiac events in newly diagnosed AML patients treated with azacitidine (see Section 4.4).

Elderly patients
There is limited information on the safety of azacitidine in patients aged 85 years and older (14 patients aged 85 years and older [5.9%] were treated in the AZA-AML-001 study).

Pediatric population
In the AZA-JMML-001 study, 28 pediatric patients (aged 1 month to 18 years) were treated with azacitidine for MDS (n=10) or juvenile myelomonocytic leukemia (JMML) (n=18) (see Section 5.1).

All 28 patients experienced at least 1 adverse event, and 17 (60.7%) experienced at least 1 treatment-related event. The most commonly reported adverse events in the overall pediatric population were hematologic events, including fever, anemia, thrombocytopenia, and febrile neutropenia, and gastrointestinal events, including constipation and vomiting.

Three (3) patients in the clinical trial experienced treatment-related events that led to discontinuation of the drug (fever, disease progression, and abdominal pain).

In the AZA-AML-004 study, 7 pediatric patients (aged 2-12 years) with molecular relapse were treated with azacitidine after achieving first complete remission [CR1] (see Section 5.1).

All 7 patients experienced at least 1 treatment-related adverse event. The most commonly reported side effects were neutropenia, nausea, leukopenia, thrombocytopenia, diarrhea, and alanine aminotransferase (ALT) elevation. Two patients experienced a treatment-related event leading to dose discontinuation (febrile neutropenia, neutropenia).

No new safety signals were identified in the limited number of pediatric patients treated with azacitidine during the clinical trial. The overall safety profile is consistent with the safety profile in the adult population.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit / risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9. Overdose
During clinical trials, one case of azacitidine overdose was reported. After receiving a single IV dose of approximately 290 mg/m^2, which is nearly 4 times the recommended starting dose, the patient experienced diarrhea, nausea, and vomiting.

In case of overdose, the patient should be monitored with appropriate blood counts and receive supportive treatment as needed. There is no known specific antidote for azacitidine overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties
Pharmacotherapeutic group: Antineoplastic agents. Pyrimidine analogs
ATC code: L01BC07

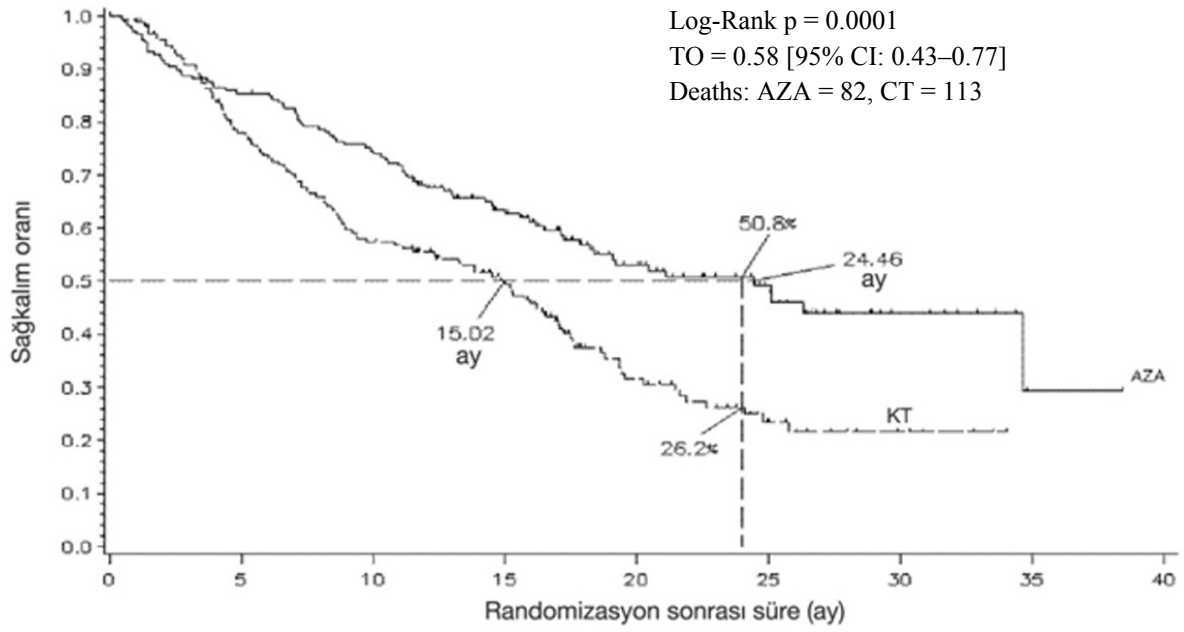
Mechanism of action:

The antineoplastic effects of azacitidine are believed to be mediated by multiple mechanisms, including cytotoxicity on abnormal hematopoietic cells in the bone marrow and hypomethylation of DNA. The cytotoxic effects of azacitidine may result from the following mechanisms: inhibition of DNA, RNA, and protein synthesis; binding to RNA and DNA; and activation of DNA degradation pathways. Non-proliferative cells are relatively resistant to azacitidine. The incorporation of azacitidine into DNA results in the inactivation of DNA methyltransferases and DNA hypomethylation. DNA hypomethylation of abnormally methylated genes involved in normal cell cycle control, differentiation, and death pathways may result in gene re-expression and restoration of tumor suppressor functions. The relative importance of DNA hypomethylation and azacitidine's cytotoxic or other activities on clinical outcomes is not yet known.

Clinical efficacy and safety:
In adults diagnosed with MDS, KMML, and AML with 20-30% blasts in the bone marrow

The efficacy and safety of azacitidine were evaluated in an international, multicenter, controlled, open-label, randomized, parallel-group, Phase 3 comparative study (AZA PH GL 2003 CL 001). Patients with MDS classified as intermediate-2 to high risk according to the International Prognostic Scoring System (UPSS) and RAEB, RAEB-T (21-30% blasts) or mKMML according to the French-American-British (FAB) classification system were included in the study; patients with secondary MDS were excluded. Azacitidine (n=179) was compared with conventional treatment regimens (n=179). Conventional treatment regimens consisted of supportive care alone (n=105), low-dose cytarabine plus supportive care (n=49), or standard induction chemotherapy plus supportive care (n=25). Patients were selected by their physicians for one of the three conventional treatment regimens prior to randomization. If a patient was not randomized to the azacitidine group, they received the pre-selected regimen. One of the criteria for inclusion in the study was an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2. Patients with secondary MDS were excluded from the study. The primary endpoint of the study was overall survival. Azacitidine was administered at a subcutaneous dose of 75 mg/m² daily for 7 days, with a median of 9 cycles (range 1-39 cycles) and a mean of 10.2 cycles, followed by a 21-day rest period (28-day treatment cycle). The mean age in the intention-to-treat (ITT) population was 69 years (range 38-88 years).

In the ITT analysis of 358 patients (179 on azacitidine and 179 on conventional treatment regimens), median survival was 24.46 months with azacitidine versus 15.02 months with conventional treatment. The difference was 9.4 months ($p<0.0001$). The two-year survival rate was 50.8% in patients receiving azacitidine, compared to 26.2% in patients receiving conventional treatment regimens ($p<0.0001$).



Number of patients at risk

AZA	179	152	130	85	52	30	10	1	0
KT	179	132	95	69	32	14	5	0	0

KEY: AZA = azacitidine; CT = conventional therapy; CI = confidence interval; HR = hazard ratio

The survival benefits of azacitidine are consistent regardless of the conventional treatment regimen option used in the control arm (best supportive care alone, low-dose cytarabine plus best supportive care, or standard induction chemotherapy plus best supportive care).

When analyzed by cytogenetic subgroup using the International Prognostic Scoring System (UPSS), similar results were observed across all groups (good, intermediate, poor cytogenetics, including monosomy 7) in terms of median overall survival. When analyzed by age subgroups, an increase in median overall survival was observed across all groups (<65 years, ≥65 years, and ≥75 years).

The median time to death or conversion to AML was 13 months in the azacitidine group, whereas it was 7.6 months in the group receiving conventional therapy. Azacitidine provided a 5.4-month advantage, with a p-value of 0.0025. Furthermore, azacitidine therapy was associated with a reduction in cytopenia and symptoms. Azacitidine treatment led to a decrease in the need for red blood cell (RBC) and platelet transfusions. Forty-five percent of patients in the azacitidine group who were initially dependent on RBC transfusions became independent of RBC transfusions during the treatment period, compared to 11.4% in the combined CCR groups ((33.6% (95% CI: 22.4, 44.6) statistically significant (p<0.0001) difference)), a difference of 33.6%. Among patients initially dependent on KKH transfusion who became independent, the median time to KKH transfusion independence was 13 months in the azacitidine group.

The overall response rate (complete remission [CR] + partial remission [PR]) achieved in the azacitidine group was 29%, compared to 12% in the combined conventional therapy regimens group (p=0.0001). The overall response (TR + PR) obtained by the Independent Review Committee in the AZA PH GL 2003 CL1 study was 7% (12/179) in the azacitidine group and 1% (2/179) in the combined conventional therapy groups (p=0.0113). The differences between the responses of the Independent Review Committee and the investigators' assessments are a result of the International Working Group (IWG) criteria, which require improvement in peripheral blood counts and maintenance of this improvement for at least 56 days. An advantage in survival was also observed in patients who did not achieve TR or PR following azacitidine treatment. According to the Independent Review Committee's assessment, hematologic improvement (major or minor) was detected in 49% of patients receiving azacitidine, compared to 29% of patients treated with combined conventional therapy regimens (p<0.0001).

In patients with one or more cytogenetic abnormalities at baseline, the rate of major cytogenetic response was similar in the azacitidine and combined conventional therapy groups. Minor cytogenetic response was statistically significantly higher in the azacitidine group (34%) compared to the combined conventional treatment regimen group (10%) (P=0.0015).

Patients aged 65 years and older with acute myeloid leukemia (AML) and more than 30% bone marrow blasts

Results for the treatment-intended patient population in the AZA-AML-001 clinical trial are presented below (see Section 4.1).

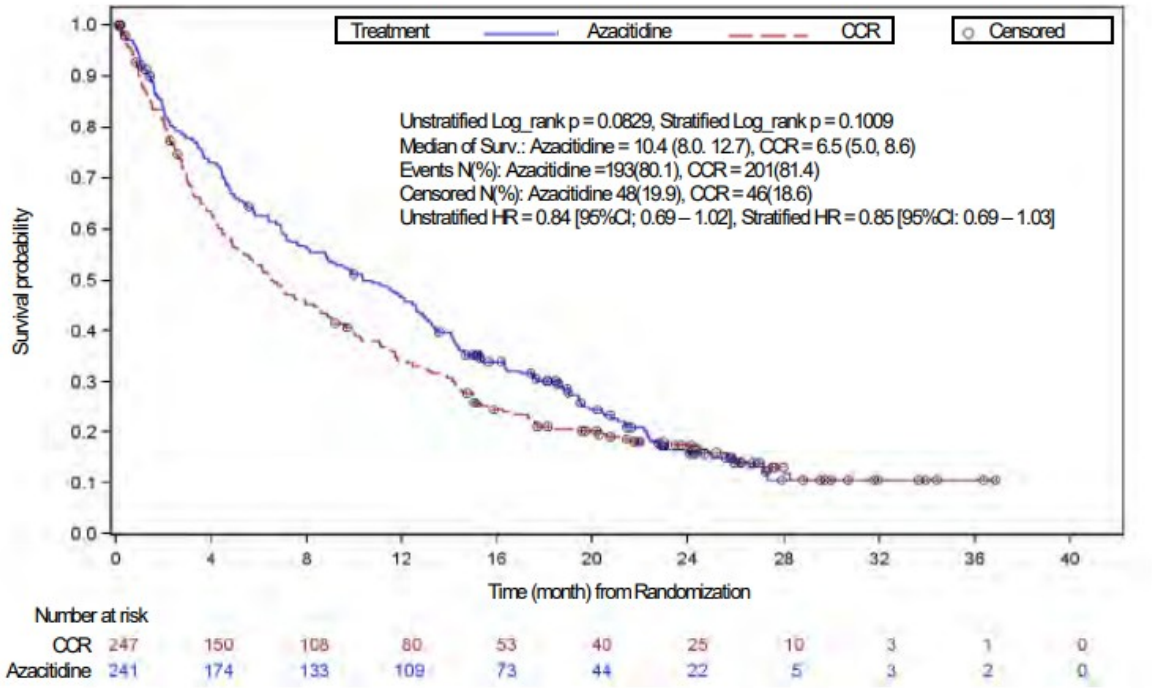
The efficacy and safety of azacitidine were evaluated in an international, multicenter, controlled, open-label, parallel-group Phase 3 study in patients aged 65 years and older with newly diagnosed or secondary AML with >30% bone marrow blasts, who were not eligible for hematopoietic stem cell transplantation, according to the World Health Organization classification. Best supportive care with azacitidine (n=241) was compared with conventional treatment regimens. Conventional treatment regimens consisted of supportive care alone (n=45), low-dose cytarabine plus supportive care (n=158), or standard intensive chemotherapy with cytarabine and anthracycline plus supportive care (n=44). One of the three patients who received a conventional treatment regimen prior to randomization was selected by their physicians. Patients continued to receive their pre-selected treatment regimen if they were not randomized to the azacitidine group. Inclusion criteria were an ECOG performance status of 0 to 2 and intermediate- or low-risk cytogenetic abnormalities. The primary endpoint of the study was overall survival.

For those receiving azacitidine, 75 mg/m^2 was administered subcutaneously for 7 days (28-day treatment cycle) following a 21-day rest period, with a median of 6 cycles (1-28 cycles).

while those receiving only best supportive care received a median of 3 cycles (1-20 cycles), those receiving low-dose cytarabine received a median of 4 cycles (1-25 cycles), and those receiving standard intensive chemotherapy received a median of 2 cycles (1-3 induction cycles plus 1 or 2 consolidation cycles).

The groups receiving azacitidine and conventional treatment regimens are comparable in terms of individual baseline parameters. The median age of patients is 75 (range 64 to 91 years). 75.2% are Caucasian, and 59% are male. According to the World Health Organization classification, at baseline, 60.7% of patients had AML alone, 32.4% had AML with myelodysplastic changes, 4.1% had therapy-related myeloid neoplasms, and 2.9% had AML with recurrent genetic abnormalities.

In the ITT analysis of 488 patients (241 patients treated with azacitidine and 247 patients treated with the conventional treatment regimen), the median survival rates for patients receiving azacitidine treatment and those receiving the conventional treatment regimen were 10.4 months and 6.5 months, respectively. The difference was 3.8 months (p=0.1009). The hazard ratio for treatment effect was 0.85 (95% CI=0.69; 1.03). One-year survival rates were 46.5% in patients receiving azacitidine and 34.3% in patients receiving the conventional treatment regimen.



Using a Cox PH model adjusted for predefined baseline prognostic factors, the hazard ratio for azacitidine versus conventional treatment regimens was determined to be 0.8 (95% CI=0.66, 0.99; p=0.0355).

Furthermore, although the study did not show a statistically significant difference when comparing patients receiving azacitidine with those receiving pre-selected conventional treatment regimens, the survival rate of patients receiving azacitidine was longer than that of patients receiving conventional treatment options such as supportive care and low-dose cytarabine plus supportive care. When compared to patients receiving intensive chemotherapy with supportive care, the survival rate is similar.

In favor of azacitidine in terms of overall survival benefit, all pre-specified subgroups, including age (under 75 and 75 and older), gender, race, ECOG performance status (0 or 1 and 2), baseline cytogenetic risk (intermediate or low), geographic region, and WHO classification of AML (including AML with myelodysplastic features), baseline white blood cell count (≤ 5 x10^9/L and >5x10^9/L), baseline bone marrow blast count ($\leq$50% and >50%), and prior history of MDS. Only a very small group achieved statistical significance in overall survival risk ratio. These groups included patients with poor cytogenetic risk, AML patients with myelodysplastic changes, patients under 75 years of age, female patients, and Caucasian patients.

Hematologic and cytogenetic responses were evaluated by investigators and the IRC with similar results. The IRC determined the rate of complete responses (complete remission [CR] and complete remission without blood count recovery [CRi]) to be 27.8% for the azacitidine group and 25.1% for the combined conventional treatment regimen (p=0.5384). Among patients who achieved CR and Cri, the median time to remission was 10.4 months (95% CI=7.5; 15.2) in patients receiving azacitidine and 12.3 months (95% CI=9; 17) in patients receiving the conventional treatment regimen. Patients treated with azacitidine who did not achieve a complete response showed a survival advantage compared to conventional treatment regimens.

Azacitidine therapy improved peripheral blood counts and reduced the need for erythrocyte and platelet transfusions. If the patient received one or more erythrocyte or platelet transfusions for 56 days (8 weeks) or more prior to randomization, they were considered erythrocyte or platelet transfusion-dependent at baseline. If the patient did not receive red blood cell or platelet transfusions for any consecutive 56 days during the treatment period and reporting period, they were considered not to be dependent on red blood cell or platelet transfusions.

At baseline, 38.5% of patients in the azacitidine group who were dependent on erythrocyte transfusion (95% CI=31.1; 46.2) no longer required erythrocyte transfusion during the treatment period. This rate was 27.6% in patients receiving the combined conventional treatment regimen (95% CI=20.9; 35.1). For patients initially dependent on erythrocyte transfusion who became transfusion-independent with treatment, the median time to transfusion independence was 13.9 months in the azacitidine group, while this time could not be reached in patients receiving the conventional treatment regimen.

Of the patients in the azacitidine group who were dependent on platelet transfusions at the start of the study, 40.6% (95% CI=30.9; 50.8) remained free of platelet transfusion dependency during the treatment period. This rate was 29.3% in patients receiving the combined conventional treatment regimen (95% CI=19.7; 40.4). For patients who were initially dependent on platelet transfusions and became transfusion- e with treatment, the median time to transfusion- e status was 10.8 months in the azacitidine group and 19.2 months in patients receiving the conventional treatment regimen.

Health-Related Quality of Life (HRQoL) was assessed using the European Organization for Research and Treatment of Cancer Core Quality of Life (EORTC QLQ-C30) questionnaire. HRQoL data were analyzable for the entire population subset in the test study. Despite some limitations in the analysis, the available data indicate that patients did not experience a significant loss in quality of life during azacitidine treatment.

Pediatric population
The AZA-JMML-001 study was conducted to evaluate the pharmacokinetics, pharmacodynamics, safety, and activity of azacitidine prior to HSCT in pediatric patients with newly diagnosed advanced MDS or JMML; it is a Phase 2, international, multicenter, open-label study. The primary objective of the clinical trial was to evaluate the effect of azacitidine on the response rate at day 28 of the third cycle.

Patients (MDS, n=10; JMML, n=18, aged 3 months–15 years; 71% male) were treated with a daily dose of 75 mg/m^{2}intravenous azacitidine for the first 7 days of a 28-day cycle for a minimum of 3 cycles and a maximum of 6 cycles.

Patient enrollment in the MDS arm was discontinued after 10 MDS patients due to lack of observed efficacy: no confirmed response was recorded in these 10 patients.

In the JMML arm, 18 patients (13 PTPN11, 3 NRAS, 1 KRAS somatic mutation, and 1 neurofibromatosis type 1 clinically diagnosed [NF 1]) were enrolled. Sixteen patients completed 3 cycles, and 5 patients completed 6 cycles of treatment. A clinical response was observed on day 28 of the third cycle in a total of 11 JMML patients. A confirmed clinical response was observed in 9 of these 11 patients (50%) (3 patients with cCR - confirmed complete response and 6 patients with cPR - confirmed partial response). In the cohort of patients treated with azacitidine, a sustained platelet response (counts $\geq 100\times10^9$/L) was observed in 7 (43.8%) patients, and 7 (43.8%) patients required transfusion at HSCT. Seventeen of the 18 patients proceeded to HSCT.

Due to the study design (small number of patients and confounding factors), it cannot be concluded from this clinical trial whether azacitidine before HSCT improves or does not improve survival in patients with JMML.

The AZA-AML-004 study is a Phase 2, multicenter, open-label study evaluating the safety, pharmacodynamics, and efficacy of azacitidine compared to anti-cancer therapy in pediatric patients with AML who developed molecular relapse after initial complete remission and in children and young adults with AML in molecular relapse.

Azacitidine was administered in a maximum of 3 cycles, with 100 $^{mg/m^2}$administered on the first 7 days of each 28-day cycle, in 7 patients (aged 2 to 12 years, median age 6.7 years, 71.4% male).

On day 84, minimal residual disease (MRD) assessment was performed in 5 patients, and molecular stabilization (n=3) or molecular remission (n=1) was detected in 4 patients, while clinical relapse was observed in one patient. Six of the seven patients treated with azacitidine (90% [95% CI = 0.4; 1]) underwent HSCT.

Due to this small sample size, the efficacy of azacitidine in pediatric AML cannot be determined.

For safety information, see Section 4.8.

5.2. Pharmacokinetic properties

General characteristics

Absorption:

Following a single 75 mg/m^{2}subcutaneous dose of azacitidine, azacitidine was rapidly absorbed, with peak plasma concentrations of 750±403 ng/mL occurring at 0.5 hours (first sampling point).

Based on the area under the curve (AUC), the bioavailability of azacitidine after subcutaneous administration compared to IV azacitidine (single 75 mg/m²dose) is approximately 89% as measured by the area under the curve (AUC).

The area under the curve and maximum plasma concentration (C_{max}) of subcutaneous azacitidine are proportional within a dose range of approximately 25-100 mg/m².

Distribution:

Following IV administration, the mean volume of distribution is 76±26 L and the systemic clearance is 147±47 L/hour.

Biotransformation:

In vitro data indicate that cytochrome P450 isoenzymes (CYPs), UDP-glucuronosyltransferases (UGTs), sulfotransferases (SULTs), and glutathione transferases (GSTs) are not involved in azacitidine metabolism.

The metabolism of azacitidine occurs through deamination mediated by cytidine deaminase and spontaneous hydrolysis. It has been observed that metabolite formation in human liver S9 fractions is independent of NADPH, indicating that the metabolic steps are catalyzed by cytosolic enzymes. *In vitro* studies on human hepatocyte cultures show that azacitidine concentrations of 1-100 µM (approximately 30 times higher than clinically achievable concentrations) do not induce cytochrome P450 isoenzymes (CYP) "1A2, 2C19, 3A4, or 3A5. Inhibition did not occur in a series of P450 isoenzymes (CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4) incubated with 100 µM azacitidine . Therefore, enzyme inhibition is not considered likely at clinically achievable azacitidine plasma concentrations.

Elimination:
After SC administration, azacitidine is rapidly eliminated from plasma with a mean elimination half-life of 41±8 minutes. No accumulation occurs after subcutaneous administration of 75 mg/m^{2}azacitidine once daily for 7 days.
Azacitidine and/or its metabolites are primarily excreted in the urine.

^{14}Following SC and IV administration of C-azacitidine, <1% of the administered radioactivity is excreted in feces, while 50-85% is excreted in urine.

Characteristic features in patients
Special populations:
The effects of hepatic impairment (see Section 4.2), gender, age, or race on the pharmacokinetics of azacitidine have not been studied.

Pediatric population
In the AZA-JMML-001 study, pharmacokinetic analysis was performed on 10 MDS and 18 JMML pediatric patients on day 7 of the first cycle. (See Section 5.1). The mean age was 13.3 (age range 1.9-15) for MDS patients and 2.1 (age range 0.2-6.9) for JMML patients.

Following intravenous administration of a 75 mg/m² dose, azacitidine rapidly reached a C_{max} value within 0.083 hours in both the MDS and JMML populations. The geometric mean C_{max} for MDS and JMML patients was 1797.5 and 1066.3 ng/mL, respectively, while the geometric mean $AUC_{0-\infty}$ was 606.9 and 240.2 ng-hr/mL, respectively. The geometric mean distribution volume in MDS and JMML patients was 103.9 and 61.1 L, respectively. Total plasma exposure to azacitidine was higher in MDS patients; however, moderate to high variability was observed between patients for both AUC and C_{max}values.

The geometric mean $t_{½}$for MDS and JMML is 0.4 and 0.3 hours, respectively, and the geometric mean clearance is 166.4 and 148.3 L/hour, respectively.

Pharmacokinetic data obtained from the AZA-JMML-001 study were pooled and compared with pharmacokinetic data obtained from 6 adult patients with MDS who received azacitidine 75 mg/m² intravenously in the AZA-2002-BA-002 study. The mean C_{maks} and AUC_{0-t} of azacitidine were similar between adult and pediatric patients after intravenous administration (2750 ng/mL vs. 2841 ng/mL and 1025 ng·h/mL vs. 882.1 ng·h/mL, respectively).

Pharmacokinetic analysis in the AZA-AML-004 study was performed using data from six of the seven patients in whom at least one measurable post-dose pharmacokinetic concentration was detected (see Section 5.1). The median age of AML patients was 6.7 years, with an age range of 2–12 years.

Following multiple doses of 100 $^{mg/m^2}$administered multiple times, the geometric means of C_{max} and AUC_{0-tau} on day 7 of cycle 1 were 1557 ng/mL and 899.6 ng-hr/mL, respectively. High variability in C_{max} and AUC_{0-tau} values between patients was observed (CV percentage for C_{max} and AUC_{0-tau} was 201.6% and 87.8%, respectively). After intravenous administration, azacitidine rapidly reached C_{max} in a median time of 0.09 hours and declined with a geometric mean half-life ($t_{1/2}$) of 0.38 hours. The geometric mean clearance and volume of distribution were 127.2 L/h and 70.2 L, respectively.

The pharmacokinetics observed in molecular relapse after first complete remission (CR1) in children with AML (azasididine) exposure is comparable to the exposure obtained from pooled data of 10 children with MDS and 18 children with JMML, and is also comparable to the azasididine exposure in adults with MDS.

Renal impairment

There is no significant effect of renal insufficiency on the pharmacokinetic exposure of azacitidine following single and multiple subcutaneous administrations. Following a single 75 mg/m² subcutaneous dose, the mean exposure values (AUC and C_{max}) in patients with mild, moderate, and severe renal impairment increased by 11-21%, 15-27%, and 41-66%, respectively, compared to patients with normal renal function. However, exposure is within the same overall exposure range observed in patients with normal renal function. Since azacitidine and/or its metabolites are primarily excreted by the kidneys, azacitidine can be administered to patients with renal impairment without initial dose adjustment, provided that these patients are closely monitored.

Pharmacogenomics:

The effect of known cytidine deaminase polymorphisms on azacitidine metabolism has not been investigated.

5.3. Preclinical safety data

Azacitidine induces both gene mutations and chromosomal abnormalities in *in vitro* bacterial and mammalian cell systems. The potential carcinogenicity of azacitidine has been

investigated in mice and rats. When azacitidine was administered intraperitoneally (i.p.) three times a week for 52 weeks, it induced hematopoietic system tumors in female mice. An increased incidence of tumors of the lymphoreticular system, lung, mammary gland, and skin was observed in mice treated with azacitidine administered i.p. for 50 weeks. In a tumor formation study in rats, the incidence of testicular tumors was increased.

In initial embryotoxicity studies in mice, intrauterine embryonic death was observed at a frequency of 44% (increased resorption) after a single i.p. injection of azacitidine during organogenesis.

In mice given azacitidine, developmental abnormalities were observed in the brain during or before closure of the hard palate. When given to rats during the preimplantation period, azacitidine showed no adverse reactions; however, when given during organogenesis, it was clearly embryotoxic. Fetal anomalies occurring in rats during organogenesis include: CNS anomalies (exencephaly, encephalocele), limb anomalies (micromelia, clubfoot, syndactyly, oligodactyly), and others (microphthalmia, micrognathia, gastroschisis, edema, and rib abnormalities).

Administration of azacitidine to male mice prior to mating with untreated female mice resulted in reduced fertility and loss of offspring during embryonic and postnatal development. Administration to male rats resulted in decreased testicular and epididymal weights, decreased sperm count, decreased pregnancy rates, loss of embryos in mated females, and an increase in abnormal embryos (see Section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol injectable (E421)

6.2 Incompatibilities

This product should not be mixed with products other than those specified in Section 6.6.

6.3 Shelf life

Unopened powder vial: 24 months.
VIZADIS should be used immediately after preparation. If not used immediately, it should be used within 45 minutes when stored at room temperature below 25°C in the original vial and/or syringe.

When prepared with injection water not stored in a refrigerator, VIZADIS should be used within 8 hours if placed in a refrigerator (2°C-8°C) immediately after preparation.

When VIZADIS is prepared with injection water stored in the refrigerator (2°C-8°C), it must be used within 22 hours if placed in the refrigerator (2°C-8°C) immediately after preparation.

6.4 Special precautions for storage

Store at a room temperature below 25°C.
Refer to section 6.3 for storage conditions of the prepared medicinal product.

6.5 Nature and contents of container

VIZADIS is packaged in a 30 mL Type I glass vial with a gray butyl stopper, aluminum safety seal, and white flip-off cap. One leak-proof vial is supplied in a cardboard box with a package leaflet.

6.6 Special precautions for disposal and other handling

Instruction for use:

Safety recommendations: VIZADIS is a cytotoxic drug and, as with other potentially toxic compounds, care should be taken when preparing and handling azacitidine suspensions.

Anti-cancer drug disposal and proper storage procedures should be followed. If the prepared azacitidine suspension comes into contact with the skin, it should be washed off immediately and thoroughly with soap and water. If it comes into contact with mucous membranes, it should be washed off thoroughly with water.

Preparation procedure

1. The following materials should be prepared:
   - Azacitidine vial: injection water vial(s); non-sterile surgical gloves;
   - Alcohol swabs; 5 mL syringe(s) with needle.
2. Draw 4 mL of water for injection into the syringe; there should be no air in the syringe.
3. The needle of the syringe containing 4 mL of water for injection should be inserted into the plastic-capped azacitidine vial and the water for injection should be injected into the vial.
4. After removing the needle and syringe from the azacitidine vial, the azacitidine vial should be vigorously shaken to obtain a cloudy, homogeneous suspension. At this point, each mL of the suspension contains 25 mg of azacitidine (100 mg/4 mL). The resulting drug is a homogeneous, cloudy suspension and should not contain any lumps. If large particles or lumps are present, the product should be discarded. Do not filter the suspension as this may remove the active ingredient. It should be noted that some adapters, syringes, and dosing systems contain filters. Therefore, these types of systems should not be used for administration after the drug has been prepared.
5. The plastic cap of the azacitidine vial should be cleaned, and a new syringe should be inserted. The vial should be inverted, ensuring that the needle tip is below the liquid level. Pull the syringe plunger to draw the required amount of medication for the dose, taking care to ensure there is no air in the syringe. Then remove the syringe and needle from the vial and discard the syringe needle.

6. A new subcutaneous needle tip (25 gauge is recommended) is attached to the syringe. To reduce the incidence of local reactions at the injection site, the needle tip should not be cleaned before injection.
7. When more than 1 vial is required, a new drug suspension is prepared by following the steps above. When more than 1 vial is required, the dose should be divided equally (e.g., if the dose is 150 mg = 6 mL, each of the 2 syringes should contain 3 mL of suspension). Due to delays in the vial and needle, it may not be possible to draw all of the suspension from the vial.
8. The contents of the syringe used for dosing should be shaken again before administration to the patient. During injection, the temperature of the suspension should be approximately 20°C-25°C. The suspension is shaken vigorously between two hands until a cloudy appearance is obtained. If large particles or lumps are present, the product should be discarded.

VIZADIS suspension should be prepared immediately before use, and the resulting suspension should be used within 45 minutes. If more than 45 minutes have passed since the suspension was prepared, the medication should be discarded appropriately and a new dose should be prepared. Alternatively, if the suspension must be prepared before administration to the patient, the prepared medication should be placed in the refrigerator (2°C-8°C) immediately after preparation. The suspension can be stored in the refrigerator for up to 8 hours. If the medication remains in the refrigerator for longer than 8 hours, the suspension should be discarded appropriately and a new dose prepared.

When prepared with water for injection stored in the refrigerator (2°C-8°C), it should be placed in the refrigerator (2°C-8°C) immediately after preparation. The suspension can be stored in the refrigerator for up to 22 hours. If the suspension remains in the refrigerator for more than 22 hours, it should be discarded and a new dose prepared.

Before administering the syringe containing the suspension to the patient, it should be left outside the refrigerator for up to 30 minutes to allow its temperature to reach approximately 20°C-25°C. If the time spent outside the refrigerator exceeds 30 minutes, the suspension should be disposed of appropriately and a new dose should be prepared.

Calculating the single dose
The total dose based on body surface area (BSA) can be calculated as follows:
Total dose (mg) = Dose (mg/m^2) x BSA (m^2)

Below is an example table showing how azacitidine doses should be calculated based on an average BSA of 1.8 m^2.

Dose mg/m²(percentage of	Total dose based on a VYA value of 1.8 m^2	Number of vials required	Required total suspension volume

recommended starting dose)			
75 mg/m² (100%)	135 mg	2 vials	5.4 mL
37.5 mg/m² (50%)	67.5 mg	1 vial	2.7 mL
25 mg/m² (33%)	45 mg	1 vial	1.8 mL

Administration method:
Do not filter the suspension after preparation!

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

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

The injection site should be changed. New injections should be administered at least 2.5 cm away from the previous injection site and should never be administered into soft, bruised, red, or hard areas.

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

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

7. MARKETING AUTHORISATION HOLDER
DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. 34303 No:1
Küçükçekmece / İSTANBUL / TÜRKİYE

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Date of first authorization: 06.09.2018
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