AZAREST

Azacitidine 300 mg tablets

Everest

COMPOSITION

AZAREST Tablet: Each film coated tablet contains Azacitidine INN 300 mg.

PHARMACOLOGY

Mechanism of Action:

Azacitidine is a pyrimidine nucleoside analog of cytidine that inhibits DNA/RNA methyltransferases. Azacitidine is incorporated into DNA and RNA following cellular uptake and enzymatic biotransformation to nucleotide triphosphates.

Incorporation of Azacitidine into the DNA of cancer cells in vitro, including acute myeloid leukemia cells, inhibited DNA methyltransferases, reduced DNA methylation and altered gene expression, including re-expression of genes regulating tumor suppression and cell differentiation. Incorporation of Azacitidine into the RNA of cancer cells, including leukemic cells, inhibited RNA methyltransferases, reduced RNA methylation, decreased RNA stability and decreased protein synthesis.

Antileukemic activity of Azacitidine was demonstrated by reduction of cell viability and induction of apoptosis in AML cell lines in vitro. Azacitidine decreased tumor burden and increased survival in leukemic tumor models in vivo.

Pharmacokinetic properties

Absorption:

The mean oral bioavailability is approximately 11% relative to subcutaneous administration. The median time to peak plasma concentration of Azacitidine is 1 hour.

Effect of food

A high-fat, high-calorie meal (approximately 800 to 1000 calories, 50% fat) did not affect AUC0-INF and decreased Cmax by 21%.

Distribution

The mean (CV%) apparent volume of distribution (Vz/F) of Azacitidine is 881 L (67%). The in vitro serum protein binding of Azacitidine is approximately 6% to 12%. The blood-to-plasma ratio is approximately 0.3.

Elimination

The mean (CV%) terminal half-life is approximately 0.5 hours (27%) and the apparent clearance (CL/F) is 1240 L/hour (64%).

Metabolism

Azacitidine undergoes spontaneous hydrolysis and deamination mediated by cytidine deaminase.

Excretion

Following the administration of Azacitidine 300 mg orally once daily, < 2% of the dose was recovered unchanged in the urine.

Specific Populations

Age (46 years to 93 years), sex, body weight (39.3 kg to 129 kg), mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin 1 to 1.5 × ULN and any AST), and mild to moderate renal impairment (CLcr 30 to 89 mL/min) have no clinically meaningful effect on the pharmacokinetics of oral Azacitidine. The effects of race/ethnicity, moderate to severe hepatic impairment (total bilirubin > 1.5 × ULN and any AST), and severe renal impairment (CLcr 15 to 29 mL/min) on the pharmacokinetics of oral Azacitidine is unknown.

Severe renal impairment increased Azacitidine exposure by approximately 70% after a single or 41% after multiple subcutaneous daily administration.

Drug Interaction Studies

Effect of Gastric Acid Reducing Agents on Azacitidine:

Coadministration of omeprazole (a proton pump inhibitor) with Azacitidine increased Azacitidine AUC0-INF by 19% and had no effect on Cmax.

In Vitro Studies

Cytochrome P450 (CYP) Enzymes: Azacitidine does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, or CYP2E1 at clinically relevant concentrations. Azacitidine is not an inducer of CYP1A2, CYP2C19 or CYP3A.

INDICATIONS

Azacitidine is indicated for continued treatment of adult patients with acute myeloid leukemia who achieved first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following intensive induction chemotherapy and are not able to complete intensive curative therapy.

DOSAGE AND ADMINISTRATION

Important Administration Information.

Do not substitute Azacitidine for intravenous or subcutaneous Azacitidine. The indications and dosing regimen for Azacitidine differ from that of intravenous or subcutaneous Azacitidine.

Recommended Dosage

The recommended dosage of Azacitidine is 300 mg orally once daily with or without food on Days 1 through 14 of each 28-day cycle. Continue Azacitidine until disease progression or unacceptable toxicity.

Administer an antiemetic 30 minutes prior to each dose of Azacitidine for the first 2 cycles. Antiemetic prophylaxis may be omitted after 2 cycles if there has been no nausea and vomiting.

If the absolute neutrophil count (ANC) is less than 0.5 Gi/L on Day 1 of a cycle, do not administer Azacitidine (Azacitidine). Delay the start of the cycle until the ANC is 0.5 Gi/L or more.

Instruct patients on the following:

- Do not split, crush, or chew Azacitidine tablets.
- Take a dose about the same time each day.
- If a dose of Azacitidine is missed, or not taken at the usual time, take the dose as soon as possible on the same day, and resume the normal schedule the following day. Do not take 2 doses on the same day.
- If a dose is vomited, do not take another dose on the same day. Resume the normal schedule the following day. Azacitidine is a hazardous drug. Follow applicable special handling and disposal procedures.

Monitoring and Dosage Modifications for Adverse Reactions

Monitor complete blood count every other week for the first 2 cycles and prior to the start of each cycle thereafter. Increase monitoring to every other week for the 2 cycles after any dose reduction for myelosuppression.

CONTRAINDICATIONS

Azacitidine is contraindicated in patients with known severe hypersensitivity to Azacitidine.

WARNINGS AND PRECAUTIONS

Risks of Substitution with Other Azacitidine Products

Due to substantial differences in the pharmacokinetic parameters [see Clinical Pharmacology (12.3)], the recommended dose and schedule for Azacitidine are different from those for the intravenous or subcutaneous Azacitidine products. Treatment of patients using intravenous or subcutaneous Azacitidine at the recommended dosage of Azacitidinemay result in a fatal adverse reaction. Treatment of patients using Azacitidine at the doses recommended for intravenous or subcutaneous Azacitidine may not be effective.

Do not substitute Azacitidine for intravenous or subcutaneous Azacitidine.

Myelosuppression

New or worsening Grade 3 or 4 neutropenia and thrombocytopenia occurred in 49% and 22% of patients who received Azacitidine, respectively. Febrile neutropenia occurred in 12%. A dose reduction was required for 7% and 2% of patients due to neutropenia and thrombocytopenia, respectively. Less than 1% of patients discontinued Azacitidine due to either neutropenia or thrombocytopenia.

Monitor complete blood counts and modify the dosage as recommended. Provide standard supportive care, including hematopoietic growth factors, if myelosuppression occurs.

Increased Early Mortality in Patients with Myelodysplastic Syndromes

In AZA-MDS-003 (NCT01566695), 216 patients with red blood cell transfusion-dependent anemia and thrombocytopenia due to myelodysplastic syndromes were randomized to Azacitidine or placebo. One hundred and seven patients received a median of 5 cycles of Azacitidine 300 mg daily for 21 days of a 28-day cycle. Enrollment was discontinued early due to a higher incidence of early fatal and/or serious adverse reactions in patients who received Azacitidine compared with placebo. The most frequent fatal adverse reaction was sepsis. The safety and effectiveness of Azacitidine for treatment of myelodysplastic syndromes have not been established. Treatment of patients with myelodysplastic syndromes with Azacitidine is not recommended outside of controlled trials.

Embryo-Fetal Toxicity

Based on the mechanism of action and findings in animals, Azacitidine can cause fetal harm when administered to a pregnant woman. Azacitidine administered to pregnant rats via a single intraperitoneal dose less than the recommended human daily dose of oral Azacitidine on a mg/m2 basis caused fetal death and anomalies.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Azacitidine and for at least 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with Azacitidine and for at least 3 months after the last dose.

SIDE EFFECTS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Myelosuppression

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Acute Myeloid Leukemia

The safety of Azacitidine was evaluated in QUAZAR [see Clinical Studies (14)]. Patients received Azacitidine 300 mg (N=236) or placebo (N=233) orally once daily on Days 1 through 14 of each 28-day cycle. Among patients who received Azacitidine, 71% were exposed for 6 months or longer, and 49% were exposed for greater than one year. The median duration of exposure to Azacitidine was 11.6 months (range: 0.5 to 74.3 months) and the median number of cycles was 12 (range: 1 to 82 cycles).

Serious adverse reactions occurred in 15% of patients who received Azacitidine. Serious adverse reactions in ≥ 2% of patients who received Azacitidine were pneumonia (8%) and febrile neutropenia (7%). One fatal adverse reaction (sepsis) occurred in a patient who received Azacitidine.

Permanent discontinuation of Azacitidine due to an adverse reaction occurred in 8% of patients. Adverse reactions which resulted in permanent discontinuation of Azacitidine in > 1% of patients included nausea (2.1%), diarrhea (1.7%), and vomiting (1.3%).

Interruptions of Azacitidine due to an adverse reaction occurred in 35% of patients. Adverse reactions which required an interruption of Azacitidine in > 5% of patients included neutropenia (20%), thrombocytopenia (8%), and nausea (6%).

Dose reductions of Azacitidine due to an adverse reaction occurred in 14% of patients. Adverse reactions which required a dose reduction in > 1% of patients included neutropenia (6%), diarrhea (3.4%), thrombocytopenia (1.7%), and nausea (1.7%).

The most common (≥ 10%) adverse reactions were nausea, vomiting, diarrhea, fatigue/ asthenia, constipation, pneumonia, abdominal pain, arthralgia, decreased appetite, febrile neutropenia, dizziness, and pain in extremity.

Post-marketing Experience

The following adverse reactions have been identified during postapproval use of intravenous or subcutaneous Azacitidine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hypersensitivity reaction
- Interstitial lung disease
- Tumor lysis syndrome
- Sweet's syndrome (acute febrile neutrophilic dermatosis)
- Necrotizing fasciitis (including fatal cases)
- Differentiation syndrome

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on its mechanism of action and findings in animals, Azacitidine can cause fetal harm when administered to a pregnant woman. There are no available data on Azacitidine use in pregnant women to evaluate for a drugassociated risk. Azacitidine was teratogenic and caused embryo-fetal lethality in animals at doses less than the recommended human daily dose of oral Azacitidine on a mg/m2 basis. Advise pregnant women of the potential risk to the fetus.

The estimated background of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Lactation

Risk Summary

There are no data regarding the presence of Azacitidine in human milk or the effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with Azacitidine and for 1 week after the last dose.

Females and Males of Reproductive Potential

Azacitidine can cause embryo-fetal harm when administered to pregnant women.

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential before starting Azacitidine.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with Azacitidine and for at least 6 months after the last dose.

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with Azacitidine and for at least 3 months after the last dose.

Infertility

Based on animal data, Azacitidine may impair male or female fertility.

Pediatric Use

The safety and effectiveness of Azacitidine in pediatric patients have not been established

Geriatric Use

Of the 238 patients in QUAZAR who received Azacitidine, 72% were 65 years of age or older, while 12% were 75 years of age or older. No overall differences in safety or effectiveness of Azacitidine were observed between these patients and younger patients

Renal Impairment

Monitor patients with severe renal impairment (creatinine clearance [CLcr] 15 to 29 mL/min calculated by Cockcroft-Gault formula) more frequently for adverse reactions and modify the Azacitidine dosage for adverse reactions.

No dose adjustment of Azacitidine is recommended for patients with mild to severe renal impairment (CLcr 15 to 89 mL/min).

Hepatic Impairment

Azacitidine has not been studied in patients with pre-existing severe hepatic impairment (total bilirubin > 3 × ULN).

A recommended dosage of Azacitidine has not been established for patients with moderate hepatic impairment (total bilirubin > 1.5 to 3 × ULN).

No dose adjustment of Azacitidine is recommended for patients with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin 1 to 1.5 × ULN and any AST).

OVERDOSE

No Information provided.

STORAGE CONDITION

Store below 25°C, in a cool and dry place. Keep away from light. Keep out of the reach of children.

HOW SUPPLIED

AZAREST Tablet: Each HDPE container contains 14 film-coated tablets (each tablet contains 300 mg Azacitidine), a silica gel desiccant and polyester coil with a child-resistant closure.

Manufactured by
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