Bristol Myers Squibb

ONUREG™ (azacitidine) FILM-COATED TABLETS 200 MG
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1 INDICATIONS

ONUREG™ (azacitidine film-coated tablets) is a nucleoside metabolic inhibitor indicated for:

- maintenance therapy in adult patients with acute myeloid leukemia (AML) who achieved complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following induction therapy with or without consolidation treatment, and who are not eligible for hematopoietic stem cell transplantation (HSCT).

Limitations of Use:

- ONUREG™ is not interchangeable with, and should not be substituted with or for, azacitidine for injection. See **DOSAGE AND ADMINISTRATION, Administration** and **WARNINGS AND PRECAUTIONS, General**.
- The safety and effectiveness of ONUREG for treatment of myelodysplastic syndromes have not been established. Treatment of patients with myelodysplastic syndromes with ONUREG is not recommended outside of controlled trials. See **WARNINGS AND PRECAUTIONS, General**.

1.1 Pediatrics

Pediatrics (**< 18 years of age)**:
No data are available on administration of ONUREG™ to pediatric or adolescent patients (< 18 years of age).

1.2 Geriatrics

Geriatrics (≥ 65 years of age): No dosage adjustment is required for ONUREG™ based on age, see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics.**

2 CONTRAINDICATIONS

ONUREG™ is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.**

ONUREG™ is contraindicated in patients with advanced malignant hepatic tumors.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- No specific dose adjustments are recommended for elderly patients (≥ 65 years of age), see **INDICATIONS**.

- Administer an antiemetic 30 minutes prior to each dose of ONUREG for the first 2 cycles. Antiemetic prophylaxis may be omitted after 2 cycles if there has been no nausea and vomiting.
- ONUREG™ can be administered to patients with renal impairment without initial dose adjustment, see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment** and **CLINICAL PHARMACOLOGY, Pharmacokinetics**.

4.2 Recommended Dose and Dosage Adjustment

Recommended Starting Dosage:

The recommended starting dose of ONUREG™ is 300 mg orally once daily on Day 1 through Day 14 of repeated 28-day treatment cycles.

If the absolute neutrophil count (ANC) is less than 500/mcL on Day 1 of a cycle, do not administer ONUREG™. Delay the start of the cycle until the ANC is 500/mcL or more.

ONUREG™ maintenance therapy should be initiated after achievement of a CR/CRi following completion of induction and consolidation therapy or following induction if consolidation therapy is not planned.

Dose Modifications During Treatment:

Dose Adjustment for Renal Impairment: No dose adjustment is required for patients with mild to moderate renal impairment.

ONUREG™ can be administered to patients with severe renal impairment without initial dose adjustment. 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 ONUREG dosage for adverse reactions, see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**.

Dose Adjustment for Hepatic Impairment: ONUREG™ has not been studied in patients with pre-existing severe hepatic impairment (total bilirubin > 3 × ULN).

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

No dose adjustment of ONUREG™ 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).

Dose Adjustment for Adverse Reactions: Dose modification guidelines for hematologic and non-hematologic adverse reactions are recommended based on clinical and laboratory findings if toxicities are judged related to ONUREG™ (see Table 1).

Table 1: Dose Adjustment for Hematological and Nonhematological Adverse Reactions

Adverse Reaction	Recommended Action
Grade 4 Neutropenia **(Absolute Neutrophil Count (ANC): < 500/mcL)** **or** **Grade 3 Neutropenia with Fever** **(ANC: 500 – 1000/mcL)**	First Occurrence • Interrupt dose. Resume at the same dose once neutrophils return to Grade 2 or lower. • The use of supportive care such as granulocyte colony stimulating factor (GCSF), as clinically indicated, may be considered. Occurrence in 2 Consecutive Cycles • Interrupt dose. After neutrophils return to Grade 2 or lower, reduce dose to 200 mg. • If a patient continues to experience the toxicity after dose reduction, reduce the treatment duration by 7 days. • If the toxicity continues or reoccurs after dose and schedule reduction, discontinue ONUREG™. • The use of supportive care such as GCSF, as clinically indicated, may be considered.
Grade 4 Thrombocytopenia **(Platelets: < 25,000/mcL)** **or** **Grade 3 Thrombocytopenia with Active Bleeding** **(Platelets: 25,000 – 50,000/mcL)**	First Occurrence • Interrupt dose. Resume at the same dose once platelets return to Grade 2 or lower. Occurrence in 2 Consecutive Cycles • Interrupt dose. After platelets return to Grade 2 or lower, reduce dose to 200 mg. • If a patient continues to experience the toxicity after dose reduction, reduce the treatment duration by 7 days. • If the toxicity continues or reoccurs after dose and schedule reduction, discontinue ONUREG™.
Grade 3 or Higher **Nausea, Vomiting or Diarrhea**	• Interrupt dose. Resume at the same dose once toxicity has resolved to Grade 1 or lower. • If event reoccurs, interrupt dose until resolved to Grade 1 or lower. Reduce the dose to 200 mg. • If a patient continues to experience the toxicity after dose reduction, reduce the treatment duration by 7 days. • If the toxicity continues or reoccurs after dose and schedule reduction, discontinue ONUREG™.

Adverse Reaction	Recommended Action
Other Grade 3 or Higher Nonhematologic Events	• Interrupt dose and provide medical support. Resume at the same dose once toxicity has resolved to Grade 1 or lower. • If event reoccurs, interrupt dose until resolved to Grade 1 or lower. Reduce the dose to 200 mg. • If a patient continues to experience the toxicity after dose reduction, reduce the treatment duration by 7 days. • If the toxicity continues or reoccurs after dose and schedule reduction, discontinue ONUREG™.

Continuation and Discontinuation Recommendations:

ONUREG™, given Day 1 through Day 14 of repeated 28-day treatment cycles, is intended for continuous use. ONUREG™ treatment should be continued until more than 15% blasts are observed in peripheral blood or bone marrow or until unacceptable toxicity occurs. Discontinue ONUREG™ if more than 15% blasts are observed in either the peripheral blood or bone marrow or at the physician's discretion.

4.3 Administration

ONUREG™ can be taken with or without food. Do not split, crush, dissolve or chew ONUREG™ tablets. Administer a dose at about the same time each day. Consider providing prophylactic anti-emetic therapy during ONUREG™ treatment.

ONUREG™ is not interchangeable with, and should not be substituted with or for, azacitidine for injection. Due to differences in exposure, the dose and schedule recommendations for ONUREG™ are different from those for injectable azacitidine. Verify drug name, dose, and administration route. See **INDICATIONS, Limitation of Use.**

4.5 Missed Dose

If a dose of ONUREG™ is missed, or not taken at the usual time, administer the dose as soon as possible on the same day, and return to the normal time of dose administration 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, but return to the normal time of dose administration the following day.

5 OVERDOSAGE

In the event of overdose, monitor the patient with appropriate blood counts and provide supportive treatment, as necessary. There is no known specific antidote for ONUREG™ overdose.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2: Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/ Composition	Non-medicinal Ingredients
Oral	Film-coated tablet 200 mg azacitidine	Tablet core: Croscarmellose sodium, Magnesium stearate, Mannitol and Silicified microcrystalline cellulose Tablet Coating: Opadry II Pink 33G94107 containing Hypromellose, Titanium dioxide, Lactose monohydrate, Polyethylene Glycol, Triacetin and Iron oxide red.
Oral	Film-coated tablet 300 mg azacitidine	Tablet core: Croscarmellose sodium, Magnesium stearate, Mannitol and Silicified microcrystalline cellulose Tablet Coating: Opadry II Brown 33G165005 containing Hypromellose, Titanium dioxide, Lactose monohydrate, Polyethylene Glycol, Triacetin, Iron oxide yellow, Iron oxide red and Black iron oxide.

ONUREG™ film-coated tablets 200mg are pink, oval tablet with debossed “200” on one side and “ONU” on the other side.

ONUREG™ film-coated tablets 300mg are brown, oval tablet with debossed “300” on one side and “ONU” on the other side.

ONUREG™ tablets are available in 7 count aluminum-aluminum blister packages.

7 WARNINGS AND PRECAUTIONS

General

Due to substantial differences in the pharmacokinetic parameters (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics***)*, the recommended dose and schedule for ONUREG are different from those for the intravenous or subcutaneous azacitidine products. Treatment of patients using intravenous or subcutaneous azacitidine at the recommended dosage of ONUREG™ may result in a fatal adverse reaction. Treatment of patients using ONUREG™ at the doses recommended for intravenous or subcutaneous azacitidine may not be effective. Do not substitute ONUREG™ for intravenous or subcutaneous azacitidine (see **DOSAGE AND ADMINISTRATION, Administration** and **INDICATIONS, Limitation of Uses**).

In AZA-MDS-003 (NCT01566695), 216 patients with red blood cell transfusion-dependent anemia and thrombocytopenia due to myelodysplastic syndromes were randomized to ONUREG™ or placebo. One-hundred and seven patients received a median of 5 cycles of ONUREG™ 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 ONUREG™ compared with placebo. The most frequent fatal adverse reaction was sepsis. Therefore, the safety and effectiveness of ONUREG™ for treatment of myelodysplastic

syndromes have not been established. Treatment of patients with myelodysplastic syndromes with ONUREG™ is not recommended outside of controlled trials. (See **INDICATIONS, Limitation of Uses)**

Carcinogenesis and Mutagenesis

In vitro studies demonstrated that azacitidine is mutagenic and clastogenic in bacterial and mammalian cell systems. Azacitidine induced neoplastic lesions and tumours in multiple tissues in rats and mice administered with azacitidine intraperitoneally (see **NON-CLINICAL TOXICOLOGY**).

Cardiovascular

Patients with a history of severe congestive heart failure, clinically unstable cardiac disease or pulmonary disease were excluded from the pivotal clinical study and therefore the safety and efficacy of ONUREG™ in these patients have not been established.

No thorough clinical QT/QTc study or *in vitro* studies (hERG, canine Purkinje fiber assay) were performed to rule out the effect of ONUREG™ on QT prolongation. An *in vivo* safety pharmacology study in dogs receiving azacitidine reported increased QTc interval, but interpretation of this study is limited by confounding effects associated with toxicity (see **NON-CLINICAL TOXICOLOGY**).

Driving and Operating Machinery

No studies on the effects on the ability to drive or use machinery have been performed. Patients should be advised that they may experience undesirable effects such as fatigue, asthenia, and gastrointestinal reactions such as nausea, vomiting, diarrhea and constipation, during treatment with ONUREG™. Therefore, caution should be exercised when driving or operating a vehicle or potentially dangerous machinery.

Gastrointestinal

Gastrointestinal toxicities were the most frequent adverse reactions in the ONUREG™ treatment group. Nausea (64.8%), vomiting (59.7%), and diarrhea (50.4%) were reported in patients treated with ONUREG™. Grade 3 or 4 diarrhea, vomiting, or nausea occurred in 5.1%, 3.0%, and 2.5%, respectively in patients treated with ONUREG™. The first occurrence of Grade 3 or 4 diarrhea, vomiting, or nausea occurred within the first 2 cycles in 1.3%, 3.0%, and 1.7%, respectively in patients treated with ONUREG™.

Consider providing prophylactic anti-emetic therapy during ONUREG™ treatment. Treat diarrhea with antidiarrheal medications promptly at the onset of symptoms.

Hematologic

New or worsening Grade 3 or higher neutropenia (41.1%), thrombocytopenia (22.5%), or febrile neutropenia (11.4%) were commonly reported (10% or more) adverse reactions in

patients treated with ONUREG™. The first occurrence of Grade 3 or 4 neutropenia, thrombocytopenia, or febrile neutropenia occurred within the first 2 cycles in 19.9%, 10.6%, and 1.7%, respectively in patients treated with ONUREG™.

Monitor complete blood counts and modify the dosage as recommended (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**). Consider the use of supportive care such as granulocyte colony stimulating factor (GCSF) as clinically indicated.

Hepatic/Biliary/Pancreatic

Patients with extensive tumor burden due to metastatic disease have been rarely reported to experience progressive hepatic coma and death during injectable treatment with azacitidine, especially in such patients with baseline serum albumin < 30 g/L. ONUREG™ is contraindicated in patients with advanced malignant hepatic tumors (see **CONTRAINDICATIONS**).

Monitoring and Laboratory Tests
Complete blood count monitoring is recommended every other week for the first 2 cycles (56 days), every other week for the next 2 cycles after dose adjustment, and monthly thereafter, prior to start of next cycle.

Monitor patients with severe renal impairment (CLcr 15 to 29 mL/min) more frequently for adverse reactions and modify the ONUREG™ dosage for adverse reactions, see **DOSING AND ADMINISTRATION, Recommended Dose and Dosage Adjustment.** No dose adjustment of ONUREG™ is required for patients with mild to severe renal impairment (CLcr 15 to 89 mL/min), see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics.**

Sexual Health

Fertility

There are no human data on the effect of azacitidine on fertility. In animals, adverse effects of azacitidine on male and female fertility have been documented. See **NON-CLINICAL TOXICOLOGY**

Reproduction

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

If either a female of reproductive potential wishes to have a child or a male wishes to conceive a child, they should seek advice for reproductive counseling and cryo-conservation of either ovum or sperm prior to starting ONUREG™.

7.1 Special Populations

7.1.1 Pregnant Women

Azacitidine may cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. There are no available data on ONUREG™ use

in pregnant women. Azacitidine was teratogenic in animals and caused embryo-fetal lethality in animals at doses less than the recommended human daily dose of oral azacitidine, see **NON-CLINICAL TOXICOLOGY**.

Females of childbearing potential should be advised to avoid pregnancy during treatment with azacitidine. If this drug is used during pregnancy or if a patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Advise females of reproductive potential to use effective contraception during treatment with ONUREG™ and for at least 6 months after the last dose.

7.1.1.1 Males with Female Sexual Partners of Reproductive Potential

Males with female sexual partners of reproductive potential should not conceive a child and should use effective contraception during treatment with ONUREG™, and for at least 6 months after the last dose.

7.1.2 Breast-feeding

It is not known whether azacitidine or its metabolites are excreted in human milk or the effects on the nursing child or milk production. Due to the potential serious adverse reactions in the nursing child, breast-feeding must be discontinued during ONUREG™ therapy and for one week after the last dose.

7.1.3 Pediatrics

Pediatrics (**< 18 years of age)**: No data are available on administration of ONUREG™ to pediatric or adolescent patients (< 18 years of age).

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): No dosage adjustment is required for ONUREG™ based on age, see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

This section describes the safety data from the QUAZAR (CC-486-AML-001) trial (see **CLINICAL TRIALS**).

The most frequently reported adverse events (≥ 10%) were nausea, vomiting, diarrhea, neutropenia, fatigue/asthenia, anemia, constipation, thrombocytopenia, abdominal pain, respiratory tract infection, arthralgia, decreased appetite, febrile neutropenia, back pain, leukopenia, pain in extremity, dizziness and pneumonia. The most frequent serious adverse events to ONUREG™ that occurred in ≥ 2% of patients were febrile neutropenia (6.8%), pneumonia (5.1%) and pyrexia (2.1%).

Permanent discontinuation of ONUREG™ due to an adverse event occurred in 6.8% of patients. The most common adverse events to ONUREG™ requiring permanent

discontinuation in 1% or more of patients included nausea (2.1%), diarrhea (1.7%), and vomiting (1.3%).

Adverse events in the ONUREG™ arm requiring dosage interruption in 2% or more of patients included neutropenia (19.9%), thrombocytopenia (8.5%), nausea (5.5%), diarrhea (4.2%), vomiting (3.8%), pneumonia (3.4%), leukopenia (2.5%), febrile neutropenia (2.1%), and alanine aminotransferase increased (2.1%). Adverse events to ONUREG™ requiring dosage reduction in 1% or more of patients included neutropenia (5.5%), diarrhea (3.4%), thrombocytopenia (1.7%), and nausea (1.7%).

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Treatment emergent adverse events (TEAEs) observed in the QUAZAR (CC-486-AML-001) trial are listed in Table 3. Median treatment duration differed between the two groups: of 11.6 months (range: 0.5 to 74.3 months) for the ONUREG™ treated patients and 5.7 months (range: 0.7 to 68.5 months) for the placebo arm.

Table 3: All Treatment Emergent Adverse Events Reported in ≥ 5% and Grade 3/4 Treatment Emergent Adverse Events Reported in ≥ 1% of ONUREG™ Treated Patients (≥ 1% frequency versus placebo) from the CC-486-AML-001 trial (safety population)

System Organ Class Preferred Term	ONUREG™ n = 236		Placebo n = 233	
	All Grade N (%)	Grade 3-4 N (%)	All Grade N (%)	Grade 3-4 N (%)
Gastrointestinal Disorders				
Nausea	153 (65)	6 (3)	55 (24)	1 (0.4)
Vomiting	141 (60)	7 (3.0)	23 (10)	0 (0)
Diarrhea	119 (50)	12 (5)	50 (22)	3 (1)
Constipation	91 (39)	3 (1)	56 (24)	0 (0)
Abdominal pain*	51 (22)	4 (2)	30 (13)	1 (0.4)
Flatulence	13 (6)	0 (0)	4 (2)	0 (0)
Blood and lymphatic system disorders				
Neutropenia	105 (45)	97 (41)	61 (26)	55 (24)
Thrombocytopenia	79 (34)	53 (23)	63 (27)	50 (22)
Anemia	48 (20)	33 (14)	42 (18)	30 (13)
Febrile neutropenia	28 (12)	27 (11)	18 (8)	18 (8)

System Organ Class Preferred Term	ONUREG™ n = 236		Placebo n = 233	
	All Grade N (%)	Grade 3-4 N (%)	All Grade N (%)	Grade 3-4 N (%)
Leukopenia	25 (11)	18 (8)	19 (8)	14 (6)
Infections and infestations				
Influenza	18 (8)	3 (1)	7 (3)	0 (0)
Pneumonia†	24 (10)	2 (1)	13 (6)	1 (0.4)
Urinary tract infection‡	22 (9)	4 (2)	17 (7)	2 (1)
Bronchitis	13 (6)	0 (0)	9 (4)	0 (0)
Rhinitis	12 (5)	0 (0)	4 (2)	0 (0)
Cellulitis	9 (4)	4 (2)	3 (1)	1 (0.4)
Lung Infection	4 (2)	4 (2)	2 (1)	1 (0.4)
General disorders and administrative site conditions				
Fatigue / asthenia	104 (44)	9 (4)	58 (25)	3 (1)
Metabolism and nutrition disorders				
Decreased appetite	30 (13)	2 (1)	15 (6)	2 (1)
Musculoskeletal and connective tissue disorders				
Arthralgia	32 (14)	2 (1)	24 (10)	1 (0.4)
Back pain	28 (12)	3 (1)	23 (10)	2 (1)
Pain in extremity	25 (11)	1 (0.4)	12 (5)	0 (0.0)
Nervous System Disorders				
Dizziness	25 (11)	0 (0.0)	21 (9)	0 (0.0)
Syncope	5 (2)	5 (2)	1 (0.4)	1 (0.4)
Psychiatric Disorders				
Anxiety	16 (7)	0 (0.0)	8 (3)	1 (0.4)
Investigations				
Alanine aminotransferase increased	12 (5)	3 (1)	4 (2)	2 (1)
Blood Uric Acid Increased	5 (2)	5 (2)	2 (1)	2 (1)
Injury, Poisoning and Procedural Complications				

System Organ Class Preferred Term	ONUREG™ n = 236		Placebo n = 233	
	All Grade N (%)	Grade 3-4 N (%)	All Grade N (%)	Grade 3-4 N (%)
Fall	12 (5)	1 (0.4)	4 (2)	0 (0.0)
Cardiac Disorders				
Atrial Fibrillation	4 (2)	4 (2)	4 (2)	0 (0.0)

Treatment-emergent adverse events include adverse events that started between the first dose date and the date 28 days after the last dose date of study treatment.
A subject is counted only once for multiple events within preferred term/system organ class.
* Grouped terms included abdominal pain, abdominal pain upper, abdominal discomfort, and gastrointestinal pain.
† Grouped terms included pneumonia, bronchopulmonary aspergillosis, lung infection, Pneumocystis jirovecii pneumonia, atypical pneumonia, pneumonia bacterial, and pneumonia fungal.
‡ Grouped terms included urinary tract infection, urinary tract infection bacterial, Escherichia urinary tract infection, and cystitis.
Data cut-off date: 15 Jul 2019

8.3 Less Common Clinical Trial Adverse Reactions

Other adverse reactions that did not meet criteria for inclusion in Table 3 were respiratory tract infections (RTI; 18%) and weight decreased (4%) in patients treated with ONUREG™. RTI was a grouped term which included upper respiratory tract infection, respiratory tract infection, and respiratory tract infection viral.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Changes in selected laboratory abnormalities that have worsened from baseline in ≥20% of patients receiving ONUREG™ with a difference versus placebo of >10% is listed in Table 4.

Table 4: Selected Laboratory Abnormalities that Worsened from Baseline Reported in ≥20% of ONUREG™ Treated Patients (> 10% frequency versus placebo) from the CC-486-AML-001 trial

Laboratory Parameter[1]	ONUREG™ N = 236 n (%)		Placebo N = 233 n (%)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Decrease in neutrophils	203 (86)	152 (64)	176 (76)	111 (48)
Decrease in white blood cells	201 (85)	127 (54)	165 (71)	75 (32)
Decrease in red blood cells	103 (44)	27 (11)	67 (29)	14 (6)

[1]Not all lab shifts were reported as Treatment Emergent Adverse Events (TEAEs)

8.5 Post-Market Adverse Drug Reactions

The following adverse reactions have been identified during post-approval use of intravenous or subcutaneous azacitidine.

Blood and lymphatic system disorders:
- Hemorrhagic diathesis

Cardiac disorders:
- Atrial fibrillation, cardiac failure congestive, cardiac failure, pericardial effusion

Gastrointestinal disorders:
- Colitis, intestinal perforation, pancreatitis acute, subileus

Hepatobiliary disorders:
- Hepatic failure, hepatitis, ascites, hyperbilirubinemia, jaundice

Infections and infestations:
- Sepsis, septic shock, infection, bacterial sepsis, abscess intestinal, cellulitis, pseudomonal sepsis, lower respiratory tract infection, bronchopulmonary aspergillosis, Clostridium difficile colitis, lobar pneumonia, lung infection pseudomonal

Injury, poisoning and procedural complications:
- Splenic rupture

Investigations:
- Blood creatinine increased, blood bilirubin increased, AST increased, ALT increased

Metabolism and nutrition disorders:
- Dehydration, hyperglycemia, hyponatremia, tumor lysis syndrome

Nervous system disorders:
- Grand mal convulsion

Renal and urinary disorders:
- Renal failure acute, renal failure

Respiratory, thoracic, and mediastinal disorders:
- Interstitial lung disease, pulmonary embolism, acute respiratory distress syndrome

Skin and subcutaneous tissue disorders:
Leukocytoclastic vasculitis, pyoderma gangrenosum, Sweet's syndrome (acute febrile neutrophilic dermatosis), necrotizing fasciitis

9 DRUG INTERACTIONS

9.2 Overview

Based on *in vitro* data, azacitidine metabolism does not appear to be mediated by cytochrome P450 isoforms (CYPs). Therefore, interactions with CYP inhibitors and inducers are unlikely to have any impact on the metabolism of ONUREG™.

ONUREG™ is not a substrate of P-glycoprotein (P-gp).

Multiple nucleoside transporters are involved in azacitidine transport, therefore azacitidine uptake is unlikely to be altered by single nucleotide polymorphisms in individual nucleoside transporters or nucleoside modulators.

9.3 Drug-Drug Interactions

Oral azacitidine exposure was minimally affected when co-administered with a proton pump inhibitor (omeprazole). Therefore, a dose modification is not required when ONUREG™ is co-administered with proton pump inhibitors or other pH modifiers.

No clinically relevant drug-drug interactions would be expected when ONUREG™ is co-administered with CYP or transporter substrates. In vitro, azacitidine did not inhibit P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporters (OAT) OAT1 and OAT3, organic anion transporting polypeptides (OATP) OATP1B1 and OATP1B3, or organic cation transporter (OCT) OCT2.

In vitro studies indicated that at concentrations up to 100 µM (approximately 30-fold higher than clinically achievable concentrations), azacitidine did not induce cytochrome P450 isoenzymes (CYPs) 1A2, 2C19, or 3A4 or 3A5. Using in vitro studies at concentrations up to 100 µM, azacitidine did not inhibit P450 isoenzymes CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4, and 2E1. Therefore, CYP induction or inhibition by azacitidine at clinically achievable plasma concentrations is unlikely.

9.4 Drug-Food Interactions

The impact of food on the exposure of ONUREG™ was minimal. Therefore, ONUREG™ can be administered either with or without food. See **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**.

9.5 Drug-Herb Interactions

No formal drug-herb interaction studies have been conducted.

9.6 Drug-Laboratory Test Interactions

No interactions identified.

9.7 Drug-Lifestyle Interactions

No formal drug-lifestyle (i.e. smoking) studies have been conducted.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Azacitidine is a DNA methyltransferase inhibitor and epigenetic modifier. Azacitidine is a pyrimidine nucleoside analog of cytidine that 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 of 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 methyltransferase, reduced RNA methylation, decreased RNA stability, and decreased protein synthesis.

Anti-leukemic activity of azacitidine was demonstrated by reduction of cell viability and induction of apoptosis in AML cell lines *in vitro. In vivo*, azacitidine decreased tumor burden and increased survival in leukemic tumor models.

ATC code: L01BC07

10.2 Pharmacodynamics

The epigenetic regulatory effect of oral azacitidine on DNA global methylation reduction in the blood was sustained with prolonged exposure of 300 mg daily administered for 14 or 21 days of a 28-day cycle in myeloid cancers including AML patients from a Phase 1/2 study. A positive correlation was observed between azacitidine plasma exposure and the pharmacodynamic effect of reduction in global DNA methylation in blood.

10.3 Pharmacokinetics

Table 5: Summary of ONUREG™ Pharmacokinetic Parameters in Adult Cancer Patients after 300 mg dose

	C_{max} (ng/mL)	T_{max} (h)	$t_{½}$ (h)	$AUC_{0-\infty}$ (ng·h/mL)	CL/F (L/h)	Vz/F (L)
Single dose mean*	145.1	1.0	0.5	241.6	1242	881.1

*The geometric mean value is shown for all parameters except for T_{max} which is the median.
N = 30

$AUC_{0-\infty}$ = area under the concentration-time curve from time zero to infinity; C_{max} = maximum concentration for the first dose; CL/F = apparent clearance; $t_{1/2}$ = elimination half-life; T_{max} = time to reach C_{max}; Vz/F = apparent volume of distribution

Absorption: The geometric mean (coefficient of variation [%CV]) C_{max} and AUC values after oral administration of a 300 mg single dose were 145.1 ng/mL (63.7) and 241.6 ng h/mL (64.5), respectively. Exposure was generally linear with dose-proportional increases in systemic exposure; high intersubject variability was observed. Absorption of azacitidine was rapid, with a median T_{max} of 1-hour post-dose.

Multiple dosing at the recommended dose regimen did not result in drug accumulation.

Mean oral bioavailability relative to subcutaneous (SC) administration was approximately 11%.

Food Effect: Co-administration of a high-fat, high-calorie meal (approximately 800 to 1000 calories with 150 calories from protein, 250 calories from carbohydrate, and 500 to 600 calories from fat) with a single 300mg dose of azacitidine in adult cancer patients delayed T_{max} by approximately 1 hour and decreased C_{max} by 21%. There was no significant impact of a high-fat, high-calorie meal on azacitidine exposure (AUC_T) when compared to administrations under fasting conditions. ONUREG™ may be administered with or without food.

Distribution: Following oral administration, the geometric mean apparent volume of distribution is 881 L. The plasma protein binding of azacitidine was approximately 6 to 12%.

Metabolism: Based on *in vitro* data, azacitidine metabolism does not appear to be mediated by cytochrome P450 isoenzymes (CYPs).

Metabolism of azacitidine is by spontaneous hydrolysis and deamination mediated by cytidine deaminase.

Elimination: The geometric mean apparent clearance of azacitidine was 1242 L/hour and the geometric mean half-life was approximately 0.5 hours.

Following intravenous administration of ^{14}C azacitidine to 5 cancer patients, the cumulative urinary excretion was 85% of the radioactive dose. Fecal excretion accounted for <1% of administered radioactivity over 3 days. Mean excretion of radioactivity in urine following subcutaneous administration of ^{14}C-azacitidine was 50%. The amount of unchanged azacitidine recovered in urine relative to dose was <2% following either SC or oral administration.

Special Populations and Conditions

Pediatrics: No data are available on administration of ONUREG™ to pediatric or adolescent patients (< 18 years of age).

Geriatrics: Age (46 to 93 years) did not have clinically meaningful effects on the pharmacokinetics of oral azacitidine. Therefore, dose modification for ONUREG™ is not required based on age.

Sex: Gender did not have clinically meaningful effects on the pharmacokinetics of azacitidine.

Ethnic origin: The effects of race (White [92%]) on the pharmacokinetics of azacitidine were not conclusive due to the small number of nonwhite patients enrolled.

Hepatic Insufficiency: The effects of moderate to severe hepatic impairment on the pharmacokinetics of azacitidine have not been studied.

Mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin 1 to 1.5 x ULN and any AST) had no clinically meaningful effect on the pharmacokinetics of azacitidine.

Renal Insufficiency: In patients with cancer, the pharmacokinetics of azacitidine in 6 patients with normal renal function (CLcr >80 mL/min) and 6 patients with severe renal impairment (CLcr <30 mL/min) were compared following daily subcutaneous dosing (Days 1 through 5) at 75 mg/m2/day. Severe renal impairment increased azacitidine exposure by approximately 70% after single and 41% after multiple subcutaneous administrations.

The exposure of azacitidine (AUC) is approximately 75% lower after oral administration relative to the exposure achieved following SC administration; therefore, an increase in exposure of approximately 40% following oral administration is still considered safe and tolerable. ONUREG™ can be administered to patients with renal impairment without initial dose adjustment. Patients with severe renal impairment should be closely monitored for toxicity

since ONUREG™ and/or its metabolites are primarily excreted through the kidney (see **DOSAGE AND ADMINISTRATION**, **Dose Modifications During Treatment)**.

Obesity: Body weight (39.3 kg to 129 kg) did not have clinically meaningful effects on the pharmacokinetics of azacitidine.

11 STORAGE, STABILITY AND DISPOSAL

Store below 30ºC. Store in the original aluminum-aluminum blisters.

12 SPECIAL HANDLING INSTRUCTIONS

Do not crush tablets.

If powder comes in contact with skin, immediately and thoroughly wash with soap and water. If powder comes in contact with mucous membranes, immediately flush the area with water.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

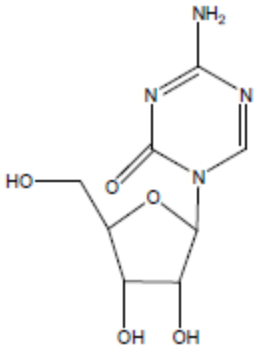
Drug Substance

Proper/Common name: azacitidine

Chemical name: 4-amino-1-β-D-ribofuranosyl-1,3,5-triazin-2(1H)-one

Molecular formula and molecular mass: $C_8H_{12}N_4O_5$, 244 g/mol

Structural formula:



Physicochemical properties: Azacitidine is a white to off-white solid. It is insoluble in acetone, ethanol, and methyl ethyl ketone; slightly soluble in ethanol/water (50/50), propylene glycol, and polyethylene glycol; sparingly soluble in water, water saturated octanol, 5% dextrose in water, N-methyl-2- pyrrolidone, normal saline and 5% Tween 80 in water; and soluble in dimethylsulfoxide (DMSO).

14 CLINICAL TRIALS

The clinical efficacy and safety of ONUREG™ were evaluated in adult patients in AML remission in the CC-486-AML-001 trial.

14.1 Trial Design and Study Demographics

Table 6: Summary of Clinical Trials in Patients in AML Remission

Study # Trial Design	Dosage, route of administration and duration	Number of Subjects
CC-486-AML-001 (QUAZAR) Phase 3, double-blind, randomized, placebo-controlled, multicenter study to compare the efficacy and safety of ONUREG™ plus BSC to placebo plus BSC as maintenance therapy in subjects with AML who have achieved CR or CRi following induction therapy with or without consolidation therapy.	300 mg ONUREG™ or matching placebo QD for 14 days of each 28-day treatment cycle [a].	ONUREG™ arm = 238 Placebo arm = 234

AML=Acute Myelogenous Leukemia, BSC = best supportive care CR=Morphologic Complete Remission, CRi=Morphologic complete remission with incomplete blood count recovery, QD = once daily
[a] Dose modification was permitted for adverse events. In the event of disease relapse (5% to 15% blasts in peripheral blood or bone marrow) dose schedule extension was permitted at investigator discretion.

CC-486-AML-001 Trial:

Adult patients aged ≥ 55 years with de novo AML, AML secondary to prior diagnosis of myelodysplastic syndromes (MDS), or chronic myelomonocytic leukemia (CMML), who had achieved first CR /CRi within 4 months +/- 7days after intensive induction chemotherapy with or without consolidation prior to randomization, were enrolled. Patients were not eligible for transplant at the time of randomization. Ineligibility to HSCT was due to age, comorbidities, performance status, no available donor, unfavourable cytogenetics or patient choice.

Patients in both treatment arms received best supportive care as deemed necessary by the investigator. Best supportive care included but was not limited to, treatment with red blood cell (RBC) transfusions; platelet transfusions; use of erythropoiesis stimulating agent; antibiotic, antiviral and/or antifungal therapy; granulocyte colony stimulating factors; anti-emetic therapy; and nutritional support.

The median treatment duration in the CC-486-AML-001 trial was 11.6 months (range: 0.5 to 74.3 months) for ONUREG™ versus 5.7 months (range: 0.7 to 68.5 months) for placebo.

Table 7 summarizes the patients baseline demographic and disease-related characteristics.

Table 7: Summary of Baseline Demographics and Disease-Related Characteristics of Patients in the Phase 3 CC-486-AML-001 trial

Parameter	ONUREG™ (N=238)	Placebo (N = 234)
Age (years)		
Median (Min, Max)	68.0 (55, 86)	68.0 (55, 82)
Race, n (%)		

Parameter	ONUREG™ (N=238)	Placebo (N = 234)
White	216 (90.8)	197 (84.2)
Black or African American	2 (0.8)	6 (2.6)
Asian	6 (2.5)	20 (8.5)
Other	12 (5.0)	11 (4.7)
Not Collected or Reported	2 (0.8)	0
Type of AML, n (%)		
Primary (de novo)	213 (89.5)	216 (92.3)
Secondary	25 (10.5)	18 (7.7)
ECOG Performance Status, n (%)		
Grade 0	116 (48.7)	111 (47.4)
Grade 1	101 (42.4)	106 (45.3)
Grade 2	21 (8.8)	15 (6.4)
Grade 3	0	2 (0.9)
Cytogenetic Risk Status at Diagnosis, n (%)		
Intermediate[1]	203 (85.3)	203 (86.8)
Poor[2]	35 (14.7)	31 (13.2)
Received Consolidation Therapy following Induction Therapy, n (%)		
Yes	186 (78.2)	192 (82.1)
1 Cycle	110 (46.2)	102 (43.6)
2 Cycles	70 (29.4)	77 (32.9)
3 Cycles	6 (2.5)	13 (5.6)
No	52 (21.8)	42 (17.9)
MRD Status at Randomization,[3] n (%)		
Negative	133 (55.9)	111 (47.4)
Positive	103 (43.3)	116 (49.6)
Missing	2 (0.8)	7 (3.0)

AML=Acute Myelogenous Leukemia, ECOG=Eastern Cooperative Oncology Group, CR=Morphologic Complete Remission, CRi=Morphologic complete remission with incomplete blood count recovery

[1] Intermediate risk was defined as normal cytogenetics +8, t(9;11), or Other undefined.
[2] Poor risk was defined as Complex (≥ 3 abnormalities): -5; 5q-; -7; 7q-; 11q23 - non t(9;11); inv(3); t(3;3); t(6;9); or t(9;22).
[3] MRD status in bone marrow was measured during screening period by flow cytometric assay at a sensitivity level of 0.1%.

14.2 Study Results

The efficacy of ONUREG™ in adult patients in AML remission was established based on the primary endpoint of overall survival (OS).

The efficacy results are summarized in Table 8. The median OS was significantly longer with ONUREG™ versus placebo: 24.7 months versus 14.8 months [HR 0.69 (95% CI: 0.55, 0.86); p=0.0009], indicating a 31% reduction in the risk of death for the ONUREG™ arm. The Kaplan-Meier curve displays the OS (Figure 1) results.

Table 8: Efficacy Results of the CC-486-AML-001 Trial in Patients in AML Remission

Efficacy Endpoint Statistic	**ONUREG™ N = 238[d]**	**Placebo N = 234[d]**
Overall Survival (primary endpoint)		
Number of deaths, n (%)	158 (66.4)	171 (73.1)
Median overall survival (95% CI)[a] months	24.7 (18.7, 30.5)	14.8 (11.7, 17.6)
Hazard ratio$_{C/P}$ (95% CI)[b]	0.69 (0.55, 0.86)	
Stratified log-rank test: p-value [c]	0.0009	
Survival Estimates		
1-year (95% CI)	0.73 (0.67, 0.78)	0.56 (0.49, 0.62)
2-year (95% CI)	0.51 (0.44, 0.57)	0.37 (0.31, 0.43)

CI = confidence interval

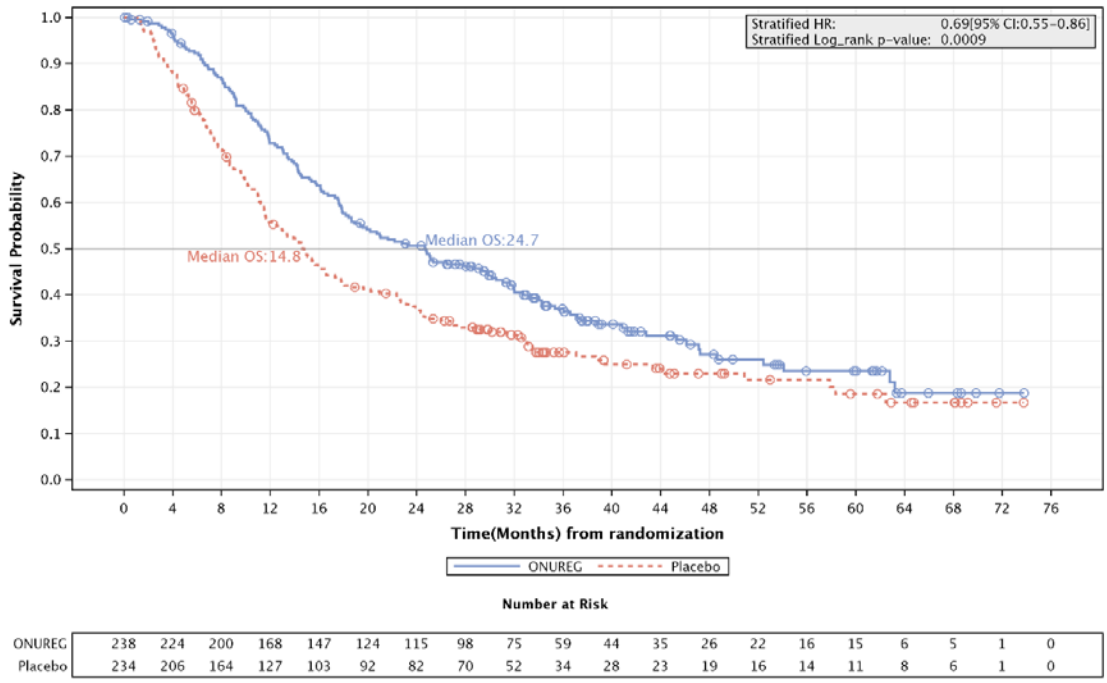
[a] Median estimate of OS is from an unstratified Kaplan-Meier analysis.

[b] The hazard ratio is from a Cox proportional hazards model stratified by age, cytogenetic risk category, and received consolidation therapy or not.

[c] The p-value is 2-sided from a log-rank test stratified by age, cytogenetic risk category, and received consolidation therapy or not.

[d] Includes patients who had dose schedule extension due to disease relapse (5% to 15% blasts in peripheral blood or bone marrow) at investigator discretion.

Figure 1: Kaplan-Meier Plot of Overall Survival for ONUREG™ (CC-486) vs. Placebo



CI = confidence interval; HR = hazard ratio; OS = overall survival.

Relapse-free survival (RFS), the key secondary endpoint in the QUAZAR trial, supports the OS results. The median RFS was 10.2 months for ONUREG™ versus 4.8 months for placebo [HR 0.65 (95% CI: 0.52, 0.81); p=0.0001].

Prespecified subgroup analyses of OS and RFS showed a consistent treatment effect for ONUREG™ across demographic and disease-related subgroups including baseline cytogenetic risk, the number of prior consolidation cycles received, and CR/CRi status at randomization.

Using the FACIT-fatigue scale and the EQ-5D-3L health-related quality of life (HRQoL) measurements, there were no clinically meaningful differences in QoL observed between the ONUREG™ + BSC and placebo + BSC treatment arms.

16 NON-CLINICAL TOXICOLOGY

Toxicology data were collected from *in vitro* studies and studies conducted in mice, rats, dogs, and rhesus monkeys. Toxicity including effects on carcinogenicity, reproductive and developmental toxicity occurred in animals at doses lower than the maximum recommended clinical dose of 300 mg of ONUREG™ (equivalent to 185 mg/m^2 for a 60 kg person).

General Toxicology

Carcinogenicity:

Carcinogenicity studies have shown that azacitidine is a carcinogen in mice and rats after IP administration. The interpretation of study results is compromised by high toxicity and early mortality in mice and rats at high doses. In Sprague-Dawley rats administered 2.6 mg/kg or 5.2 mg/kg (15.6 mg/m^2 or 31.2 mg/m^2; approximately 8 to 32% of the recommended human daily dose of ONUREG) of azacitidine for approximately 9 months (34 weeks), neoplastic lesions were noted in multiple tissues, including an increased incidence of testicular tumours compared with controls. Azacitidine induced tumors of the hematopoietic system in female mice at 2.2 mg/kg (6.6 mg/m^2, approximately 4% of the recommended human daily dose of oral azacitidine on a mg/m^2 basis) administered intraperitoneally 3 times per week for 52 weeks and tumours in the lymphoreticular system, lung, mammary gland, and skin in mice treated with intraperitoneal azacitidine at 2 mg/kg (6 mg/m^2, approximately 3% of the recommended human daily dose of oral azacitidine on a mg/m^2 basis) once a week for 50 weeks.

Genotoxicity:

Genotoxicity studies conducted *in vitro* have consistently shown that azacitidine is both mutagenic and clastogenic and induces chromosome aberrations *in vitro*. Azacitidine caused a mutagenic response in bacterial systems at 1-10 µg/plate, and induced an increased number of micronuclei in mammalian cells at 0.1 to 5 µM.

Repeat-Dose:

In a 14-day oral toxicity study in dogs, mortality occurred at doses of 0.4 and 0.8 mg/kg/day (8 and 16 mg/m^2/day). Dose-related findings were present at ≥ 0.2 mg/kg/day (4 mg/m^2/day), including pancytopenia correlated with bone marrow hypoplasia, lymphoid depletion in the

thymus, spleen, and lymph nodes, gland/lumen dilation and single cell necrosis in mucosal crypts of small and large intestines and/or centrilobular hepatocellular vacuolation were observed. At 0.2 mg/kg/day, these findings were partially or completely resolved after 3 weeks of recovery period. Following parenteral azacitidine administrations at comparable dose ranges, mortality and similar target organ toxicities were observed in rodents, dogs and monkeys.

Reproductive and Developmental Toxicology:

In fertility studies in male rats, azacitidine treatment resulted in reduced fertility after IP administration of 5 mg/kg (30 mg/m^2) 3 times per week for 11 weeks before mating. Males treated with 2.5 mg/kg (15 mg/m^2) were fertile but mating with untreated females resulted in increases in preimplantation embryo loss and increases in the average number of abnormal embryos.

In mice, a 44% frequency of intrauterine embryonal death (increased absorption) were observed after a single intraperitoneal (IP) injection of 6mg/m^2 azacitidine (approximately 3.2% of the recommended human daily dose of ONUREG™ on a mg/m^2 basis) on gestation day 10. Developmental abnormalities in the brain have been detected in mice given azacitidine on or before gestation day 15.

In rats, azacitidine was embryotoxic when given IP on gestation days 4-8 (postimplantation) at 6.0 mg/m^2 (1.0 mg/kg; doses less than the recommended human daily dose of ONUREG) although treatment during the preimplantation period (on gestation days 1-3) had no adverse effect on the embryos at this dose.

Azacitidine caused an increase in fetal death and resorptions when administered as a single IP dose of 3 to 12 mg/m^2 on gestation days 9 or 10; average live animals per litter was reduced to 9% of control at the highest dose on gestation day 9. Multiple-statistically significant fetal anomalies were observed in rats following IP dosing of ≥ 1.8 mg/m^2 (0.3 mg/kg) on gestation day 1 to 8, or after a single IP dose of 3 to 12 mg/m^2 (0.5 to 2 mg/kg, respectively) on gestation day 9, 10, 11 or 12. Findings included: CNS anomalies (exencephaly/encephalocele), limb anomalies (micromelia, club foot, syndactyly, oligodactyly) and others (microphthalmia, micrognathia, gastroschisis, oedema, and rib abnormalities). Doses in these studies ranged from 1.0 to 6.5% of the recommended human daily dose of ONUREG™ on a mg/m^2 basis.

Safety Pharmacology:

An *in vivo* safety pharmacology study in dogs receiving azacitidine at single intravenous doses of ≥ 2 mg/kg (≥ 40mg/m^2) reported increased heart rate, decreased blood pressure and increased QTc interval. The interpretations of this study are limited by concurrent confounding effects associated with toxicity including severe clinical signs (e.g., vomiting, flushed skin, decreased food consumption, and decreased spontaneous locomotor activity as well as fecal changes such as watery, mucous, or loose stool) in dogs. Additionally, large excursions in heart rate, decreases in potassium, and concurrent elevated autonomic nervous system tone as indicated by a spectrum of clinical signs and tachycardia limit the interpretation of the measurements. Results from *in vitro* tissue studies support the conclusion that azacitidine had no direct effects on vasodilatory parameters in the isolated rat aorta, no positive chronotropic effect was observed on the pacemaker activity of the guinea pig right atria, and there was no effect on heart rate and contractility in the isolated perfused guinea pig hearts; therefore, suggesting that blood pressure and heart rate changes in the cardiovascular dog study were

also due to indirect effects of azacitidine-related toxicity.

In single-dose safety pharmacology studies in rats, azacitidine affected different central nervous system (CNS)-functional parameters including decreases in locomotor activity and muscle tone as well as altered several respiratory functional parameters including reductions in respiratory rate and tidal/minute volumes at an intravenous dose range of 10 to 40 mg/kg (60 to 240 mg/m^2).

17 SHELF LIFE

3 years

18 MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb (Singapore) Pte Ltd
80 Marine Parade Road
#20-01/09 Parkway Parade
Singapore 449269

19 DATE OF REVISION OF THE TEXT

August 2022