AUSTRALIAN PRODUCT INFORMATION
ONUREG® (AZACITIDINE) FILM-COATED TABLETS

1 NAME OF THE MEDICINE

Azacitidine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 300 mg film-coated tablet contains 300 mg azacitidine.

Each 200 mg film-coated tablet contains 200 mg azacitidine.

Excipient with known effect: Lactose.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Oral azacitidine is available as the following formulations:

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

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ONUREG 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.

4.2 Dose and method of administration

ONUREG treatment should be initiated and monitored under the supervision of a physician experienced in the use of chemotherapeutic medicinal products.

Patients are to be treated with an anti-emetic 30 minutes prior to each dose of ONUREG for the first 2 treatment cycles.

Anti-emetic prophylaxis may be omitted after 2 cycles, if there has been no nausea and vomiting (see section 4.4).

ONUREG should not be used interchangeably with injectable azacitidine due to differences in the exposure, dose and schedule of treatment. Healthcare professionals are recommended to verify the drug name, dose and administration route.

The recommended dose is 300 mg azacitidine orally once daily. Each repeated cycle consists of a treatment period of 14 days followed by a treatment free period of 14 days (28-day treatment cycle).

Oral azacitidine treatment should be continued until no more than 15% blasts are observed in peripheral blood or bone marrow or until unacceptable toxicity occurs.

Laboratory tests

Complete blood counts should be performed prior to initiation of therapy. Complete blood count monitoring is also 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 the start of subsequent cycles of treatment (see section 4.4).

Special Instructions for use

Oral azacitidine can be taken with or without food. Do not split or crush oral azacitidine tablets (see Section 6.6). Administer a dose at about the same time each day. If a dose of oral azacitidine 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.

Dose schedule modification - AML disease relapse

In the case of disease relapse (5% to 15% blasts in the peripheral blood or bone marrow), in conjunction with clinical assessment, recommend considering an extension of the dosage schedule from 14 days to 21 days of repeated 28-day treatment cycles (see Section 5.1.3.1). Do not exceed 21 days of dosing during any 28-day period. Discontinue oral azacitidine if more than 15% blasts are observed in either the peripheral blood or bone marrow or at the physician's discretion.

Dose adjustment for adverse reactions

Dose modification guidelines for haematologic and non-haematologic adverse reactions are recommended based on clinical and laboratory findings if toxicities are judged related to oral azacitidine (see Table 1).

Table 1 Dose Adjustment for Haematologic and Nonhaematologic Adverse Reactions

Adverse Reaction	Recommended Action
Grade 4 Neutropenia **Grade 3 Neutropenia with Fever**	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 oral azacitidine. • The use of supportive care such as GCSF, as clinically indicated, may be considered.

Adverse Reaction	Recommended Action
Grade 4 Thrombocytopenia or Grade 3 Thrombocytopenia with Active Bleeding	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 oral azacitidine.
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 oral azacitidine.
Other Grade 3 or Higher Nonhaematologic 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 oral azacitidine.

Special Populations

Paediatric population

The safety and efficacy of oral azacitidine in children below 18 years has not been established.

Elderly population

No specific dose adjustments are recommended for the elderly (patients 65 years of age or older) (Sections 5.2.6 and 5.2.7).

Renal impairment

Oral azacitidine can be administered to patients with renal impairment without dose adjustment.

Hepatic impairment

No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin (BIL) ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN, or BIL 1 to 1.5 × ULN and any AST) (see section 5.2).

Patients with moderate (BIL > 1.5 to 3 × ULN) and severe hepatic impairment (BIL > 3 × ULN) should be monitored more frequently for adverse reactions and appropriate dose adjustment should be made (see Table 1).

4.3 Contraindications

Hypersensitivity to azacitidine or any excipients in the formulation (see Section 6.1).

Breast-feeding (see section 4.6).

Pregnancy

4.4 Special warnings and precautions for use

Haematological toxicity

Treatment with ONUREG can be associated with neutropenia, thrombocytopenia and febrile neutropenia (see section 4.8 for frequencies). Interruption, reduction or discontinuation of ONUREG may be necessary to manage haematological toxicities. Patients should be advised to promptly report febrile episodes. Patients with low platelet counts should be advised to report early signs or symptoms of bleeding. Supportive care such as antibiotics and/or antipyretics for management of infection/fever and GCSF for neutropenia should be provided based on individual patient characteristics, treatment response and according to the current clinical guidelines (see section 4.2 Table 1).

Gastrointestinal toxicity

Gastrointestinal toxicities were the most frequent adverse reactions in patients treated with ONUREG (see section 4.8). Patients should be administered prophylactic anti-emetic therapy for the first 2 cycles of ONUREG treatment (see section 4.2). Diarrhoea should be treated promptly at the onset of symptoms. Interruption, reduction or discontinuation of ONUREG may be necessary to manage gastrointestinal toxicities (see section 4.2).

Use in the elderly

No data available.

Paediatric use

No data are available.

Rare lactose/galactose metabolic conditions

ONUREG tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Effects on laboratory tests

No interactions identified.

4.5 Interactions with other medicines and other forms of interactions

No formal clinical drug-drug interaction studies with azacitidine have been conducted.

In case of concomitant administration with other antineoplastic agents, caution and monitoring is recommended as an antagonistic, additive, or synergistic pharmacodynamic effect cannot be excluded. These effects may be dependent on the dose, sequence and schedule of administration.

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

An in vitro study of azacitidine with human liver fractions indicated that azacitidine was not metabolized by cytochrome P450 isoforms (CYPs). Therefore, interactions with CYP inducers or inhibitors are considered unlikely.

Clinically relevant inhibitory or inductive effects of azacitidine on the metabolism of CYP substrates are unlikely. In vitro studies indicated that at concentrations up to 100 µM (approximately 30-fold higher than clinically achievable concentrations), azacitidine did not induce CYP isoforms 1A2, 2C19, 3A4 or 3A5. At concentrations up to 100 µM, azacitidine in vitro did not inhibit CYP isoforms 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4, and 2E1.

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. Azacitidine is not a substrate of P-gp. These data suggest that no clinically relevant drug-drug interactions would be expected when oral azacitidine is co-administered with transporter substrates or P-gp modulators.

Other forms of interactions

No other interactions identified.

4.6 Fertility, pregnancy and lactation

Effects on fertility

There are no human data on the effect of azacitidine on fertility. In animals, adverse effects of azacitidine on male fertility have been documented (see section 5.3).

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 oral azacitidine therapy.

Azacitidine had adverse effects on male fertility in rodents. Administration of azacitidine to male mice at 9.9 mg/m^2 IP (well below the recommended human daily dose on a mg/m^2 basis) daily for 3 days prior to mating with untreated female mice resulted in decreased fertility and increased pre- and post-implantation loss.

Treatment of male rats three times per week for 6 to 11 weeks at doses well below the recommended human daily dose on a mg/m^2 basis, resulted in decreased weight of the testes and epididymides, decreased sperm counts accompanied by decreased pregnancy rates and increased loss of embryos in mated females, and an increase in abnormal embryos in mated females when examined on day 2 of gestation (see Use in Male Patients). There have been no animal studies which have examined the effects of azacitidine on female fertility.

Use in pregnancy

Pregnancy Category: X

Azacitidine may cause fetal harm when administered to a pregnant woman. Studies in animals have shown reproductive toxicity including teratogenic effects at relatively low doses. Azacitidine must not be used during pregnancy.

Increased fetal resorptions were observed in mice treated with azacitidine (6 mg/m^2 IP, well below the recommended human daily dose) on single days during gestation (days 10-14). In pregnant rats given azacitidine on gestation days 4 8 at doses well below the recommended human dose, fetal survival and fetal weights were decreased.

Azacitidine caused multiple fetal abnormalities in rats after administration of a single IP dose of 3 to 12 mg/m^2 (well below the recommended human daily dose) on gestation day 9, 10, 11 or 12. Fetal abnormalities included CNS abnormalities (exencephaly/encephalocele), limb abnormalities (micromelia, club foot, syndactyly, oligodactyly) and others (microphthalmia, micrognathia, gastroschisis, oedema, and rib abnormalities). Azacitidine also caused multiple fetal abnormalities in mice after administration of a single IP dose of 6 mg/m^2 (well below the recommended human daily dose) on gestation day 10, 11 or 12. Fetal abnormalities included: CNS abnormalities (exencephaly), limb abnormalities (malformed limbs, polydactyly, syndactyly, oligodactyly) and others (cleft palate, skull bone defects and rib abnormalities).

Women 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 an effective method of contraception during treatment with oral azacitidine and for at least 6 months after the last dose.

Use in Male Patients

Males with female sexual partners of reproductive potential should not conceive a child and should use effective contraception during treatment with oral azacitidine, and for at least 3 months after the last dose. Before starting treatment, men are advised to seek counselling on sperm storage.

Use in lactation

It is not known whether azacitidine or its metabolites are excreted in human milk. The safety of azacitidine has not been investigated in lactating animals. Given the serious toxicity (severe target organ toxicity, genotoxicity and carcinogenicity) observed in other animal studies and the potential for serious adverse effects on the nursing child, breastfeeding must be discontinued during azacitidine therapy.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive or use machinery have been performed. Azacitidine has a minor influence on the ability to drive and use machines. Fatigue, asthenia, and gastrointestinal reactions such as nausea, vomiting, diarrhea and constipation have been reported with the use of azacitidine.

4.8 Adverse effects (Undesirable effects)

Most frequently reported adverse reactions (≥ 10%) are nausea (64.8%), vomiting (59.7%), diarrhoea (50.4%), neutropenia (44.5%), fatigue/asthenia (44.1%), constipation (38.6%), thrombocytopenia (33.5%), abdominal pain (21.6%), respiratory tract infection (17%), arthralgia (13.6%), decreased appetite (12.7%), febrile neutropenia (11.9%), back pain (11.9%), leucopenia (10.6%), pain in extremity (10.6%) and pneumonia (10.2%).

Serious adverse reactions occurred in 16.1% of patients receiving ONUREG. The most common serious adverse reactions are febrile neutropenia (6.8%) and pneumonia (5.1%). Permanent discontinuation of ONUREG due to an adverse reaction occurred in 6.8% of patients. The most common adverse reactions requiring permanent discontinuation are nausea (2.1%), diarrhoea (1.7%), and vomiting (1.3%).

Dose interruptions due to an adverse reaction occurred in 36.4% of patients who received ONUREG. Adverse reactions requiring dose interruption include neutropenia (19.9%), thrombocytopenia (8.5%), nausea (5.5%), diarrhoea (4.2%), vomiting (3.8%), pneumonia (3.4%), leucopenia (2.5%), febrile neutropenia (2.1%), and abdominal pain (2.1%). Dose reductions due to an adverse reaction period occurred in 14% of patients who received ONUREG. Adverse reactions requiring dose reduction included neutropenia (5.5%), diarrhoea (3.4%), thrombocytopenia (1.7%), and nausea (1.7%).

Tabulated list of adverse reactions

Table 2 presents the frequency category of ADRs reported in the pivotal Phase 3 study with ONUREG (QUAZAR AML-001 or CC-486-AML-001). A total of 236 patients received ONUREG. The median treatment duration was 11.6 months (range: 0.5 to 74.3 months) for ONUREG arm.

Frequencies are defined as: 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); not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Adverse reactions are presented in the table below according to the highest frequency observed.

Table 2 Adverse drug reactions (ADRs) in AML patients receiving ONUREG maintenance therapy.

System organ class	All grades[a] frequency
Infections and infestations	**Very common** Pneumonia[1,6], respiratory tract infection[2] **Common** Influenza, urinary tract infection[3], bronchitis, rhinitis
Blood and lymphatic system disorders	**Very common** Neutropenia, thrombocytopenia[6], febrile neutropenia[6], leucopenia
Metabolism and nutrition disorders	**Very common** Decreased appetite
Psychiatric disorders	**Common** Anxiety
Gastrointestinal disorders	**Very common** Nausea, vomiting, diarrhoea, constipation, abdominal pain[4]
Musculoskeletal and connective tissue disorders	**Very common** Arthralgia, back pain, pain in extremity
General disorders and administration	**Very common**

site conditions	Fatigue / asthenia[5]
Investigations	**Common** Weight decreased

[a] All AEs with at least 5.0% of patients in the ONUREG arm and at least 2.0% higher frequency than the placebo arm.

[1] Grouped terms include pneumonia, bronchopulmonary aspergillosis, lung infection, Pneumocystis jirovecii pneumonia, atypical pneumonia, pneumonia bacterial, and pneumonia fungal.

[2] Grouped terms include upper respiratory tract infection, respiratory tract infection, and respiratory tract infection viral.

[3] Grouped terms include urinary tract infection, urinary tract infection bacterial, Escherichia urinary tract infection, and cystitis.

[4] Grouped terms include abdominal pain, abdominal pain upper, abdominal discomfort, and gastrointestinal pain.

[5] Grouped terms include fatigue and asthenia.

[6] Adverse reactions in which at least one was considered to be life threatening (if the outcome of the reaction was death, it is included with death cases).

Description of selected adverse reactions

Haematological toxicity

New or worsening Grade 3 or higher neutropenia (41.1%), thrombocytopenia (22.5%), or febrile neutropenia (11.4%) were commonly reported 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.

Gastrointestinal toxicity

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

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

4.9 Overdose

In the event of overdose, monitor the patient with appropriate blood counts and provide supportive treatment, as necessary, according to local recommendations. There is no known specific antidote for azacitidine overdose.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Pharmacotherapeutic group: Antineoplastic agents, Antimetabolites, Pyrimidine analogues.

Azacitidine is a DNA methyltransferase inhibitor and epigenetic modifier. Azacitidine is a pyrimidine nucleoside analogue 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, including acute myeloid leukaemia cells, modified epigenetic pathways through the inhibition of DNA methyltransferases, reduction of DNA methylation, and alteration of gene expression, including genes that regulate tumour suppression, immune pathways, cell cycle, and cell differentiation.

Incorporation of azacitidine into the RNA of cancer cells, including leukaemic cells, inhibited RNA methyltransferase, reduced RNA methylation, decreased RNA stability, and decreased protein synthesis.

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

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.

Clinical trials

QUAZAR AML-001 (CC-486-AML-001) was an international, multicenter, placebo-controlled, Phase 3 study with a double-blind, randomized, parallel-group design which evaluated the safety and efficacy of oral azacitidine versus placebo as maintenance therapy in AML patients. Patients were enrolled with de novo acute myelogenous leukaemia, AML secondary to prior diagnosis of myelodysplastic syndromes (MDS), or chronic myelomonocytic leukaemia (CMML); the patients were aged ≥ 55 years, and had achieved first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) within 4 months (+/- 7 days) after intensive induction chemotherapy with or without consolidation therapy. Patients were not eligible for transplant at the time of randomization, which included patients who were not eligible for haematopoietic stem cell transplantation (HSCT), who did not have a transplant donor, or who chose not to proceed to HSCT.

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.

Patients who achieved a CR/CRi after completion of intensive induction therapy with or without consolidation were administered oral azacitidine 300 mg or placebo on Days 1 through 14 of each 28-day cycle. In the event of disease relapse (5% to 15% blasts in peripheral blood or bone marrow), the dose schedule was extended to 21 days of repeated 28-day treatment

cycles. Treatment continued until disease progression (more than 15% blasts were observed in peripheral blood or bone marrow) or until unacceptable toxicity.

Table 3 Baseline Demographics and Disease-Related Characteristics in QUAZAR AML-001 (CC-486-AML-001)

Parameter	Oral Azacitidine (N = 238)	Placebo (N = 234)
Age (years)		
Median (Min, Max)	68.0 (55, 86)	68.0 (55, 82)
Age Category, n (%)		
< 65 years	66 (27.7)	68 (29.1)
≥65 years to <75 years	144 (60.5)	142 (60.7)
≥75 years	28 (11.8)	24 (10.3)
Sex, n (%)		
Male	118 (49.6)	127 (54.3)
Female	120 (50.4)	107 (45.7)
Race, n (%)		
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 (0)
ECOG Performance Status, n (%)		
0	116 (48.7)	111 (47.4)
1	101 (42.4)	106 (45.3)
2	21 (8.8)	15 (6.4)
3	0 (0)	2 (0.9)
Cytogenetic Risk Status at Diagnosis, n (%)		
Intermediate Risk [1]	203 (85.3)	203 (86.6)
Poor Risk Status [2]	35 (14.7)	31 (13.2)
Initial AML Classification, n (%)		
AML with recurrent genetic abnormalities	39 (16.4)	46 (19.7)
AML with myelodysplasia-related changes	49 (20.6)	42 (17.9)
Therapy related myeloid neoplasms	2 (0.8)	0 (0)
AML not otherwise specified	148 (62.2)	145 (62.0)
Missing	0 (0)	1 (0.4)
Type of AML, n (%)		
Primary (de novo)	213 (89.5)	216 (92.3)
Secondary	25 (10.5)	18 (7.7)
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 Leukaemia, MDS=Myelodysplastic Syndrome, CMML=Chronic Myelomonocytic Leukaemia, 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). Source for Intermediate and Poor Risk: National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for Acute Myeloid Leukaemia. National Comprehensive Cancer Network website. Available at http://www.nccn.org/professionals/physician_gls/PDF/aml.pdf. Accessed 01 Mar 2011.

[3] MRD status in bone marrow was measured during screening period by flow cytometric assay at a sensitivity level of 0.1%.

Most patients received consolidation therapy after induction therapy in both the oral azacitidine (78%) and placebo (82%) treatment groups; more than 90% of these patients in each treatment group received 1 or 2 cycles of consolidation therapy after induction therapy (Table 4).

Table 4 Consolidation Therapy - QUAZAR AML-001 (CC-486-AML-001)

Parameter	**Oral Azacitidine (N=238)**	**Placebo (N=234)**
Received Consolidation Therapy following Induction		
Yes, n (%)	186 (78.2)	192 (82.1)
1 Cycle, n (%)	110 (46.2)	102 (43.6)
2 Cycles, n (%)	70 (29.4)	77 (32.9)
3 Cycles, n (%)	6 (2.5)	13 (5.6)
No, n (%)	52 (21.8)	42 (17.9)
CR / CRi Status at Randomization		
CR, n (%)	183 (76.9)	177 (75.6)
CRi, n (%)	50 (21.0)	44 (18.8)
Not in CR/CRi [a], n (%)	5 (2.1)	11 (4.7)
Missing, n (%)	0 (0)	2 (0.9)

CR=Complete Remission; CRi=morphologic CR with incomplete blood count recovery.

[a] These patients had baseline bone marrow of less than 5% blasts and both ANC <1 x 109 and platelets <100 x 109.

A total of 472 patients were randomized 1:1 between the oral azacitidine and placebo treatment groups. Baseline demographic and disease characteristics for an AML patient population were balanced between treatment groups as shown in Table 4. The median treatment duration was 11.6 months (range: 0.5 to 74.3 months) for oral azacitidine versus 5.7 months (range: 0.7 to 68.5 months) for placebo. A total of 51 patients (21%) receiving oral azacitidine and 40 patients (17%) receiving placebo extended their dose schedule to 300 mg daily for 21 days due to AML disease relapse.

The efficacy of ONUREG in adult patients with AML was established based on overall survival (OS) and relapse-free survival (RFS). The efficacy results are summarized in the Table 5. The median overall survival was significantly longer with oral azacitidine 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 oral azacitidine arm. The median RFS was 10.2 months for oral azacitidine versus 4.8 months for placebo, HR 0.65 (95% CI: 0.52, 0.81; p=0.0001) indicating a 35% reduction in the risk of relapse or death for the oral azacitidine arm.

Table 5 QUAZAR AML-001 (CC-486-AML-001) Efficacy Results (ITT Population)

Endpoints	**Oral Azacitidine (N=238)**	**Placebo (N=234)**
Overall Survival		
OS Events, n (%)	158 (66.4)	171 (73.1)
Median OS (95% CI) Months	24.7 (18.7, 30.5)	14.8 (11.7, 17.6)
Hazard Ratio (95% CI) p value	0.69 (0.55, 0.86) 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)
Relapse-Free Survival		
Events, n (%)	164 (68.9)	181 (77.4)
Median RFS (95% CI) Months	10.2 (7.9, 12.9)	4.8 (4.6, 6.4)

Hazard Ratio (95% CI) p value	0.65 (0.52, 0.81) 0.0001	
Time to Relapse		
Relapsed, n (%)	154 (64.7)	179 (76.5)
Died without Documented Relapse, n (%)	10 (4.2)	2 (0.9)
Median Time to Relapse Months, (95% CI)	10.2 (8.3, 13.4)	4.9 (4.6, 6.4)
Time to Discontinuation from Treatment		
Treatment Discontinued, n (%)	193 (81.1)	208 (88.9)
Median Time to Treatment Discontinuation, Months (95% CI)	11.4 (9.8, 13.6)	6.1 (5.1, 7.4)
Treatment Discontinued – Disease Relapse, n (%)	143 (60.1)	180 (76.9)

Prespecified subgroup analyses of OS and RFS showed a consistent treatment effect for oral azacitidine across demographic and disease-related subgroups including baseline cytogenetic risk, the number of prior consolidation cycles received, and CR/CRi status. The Kaplan-Meier curves display the OS (see Figure 1) and RFS (see Figure 2) results.

Figure 1 Kaplan-Meier Curve for Overall Survival: Oral Azacitidine versus Placebo (ITT Population)

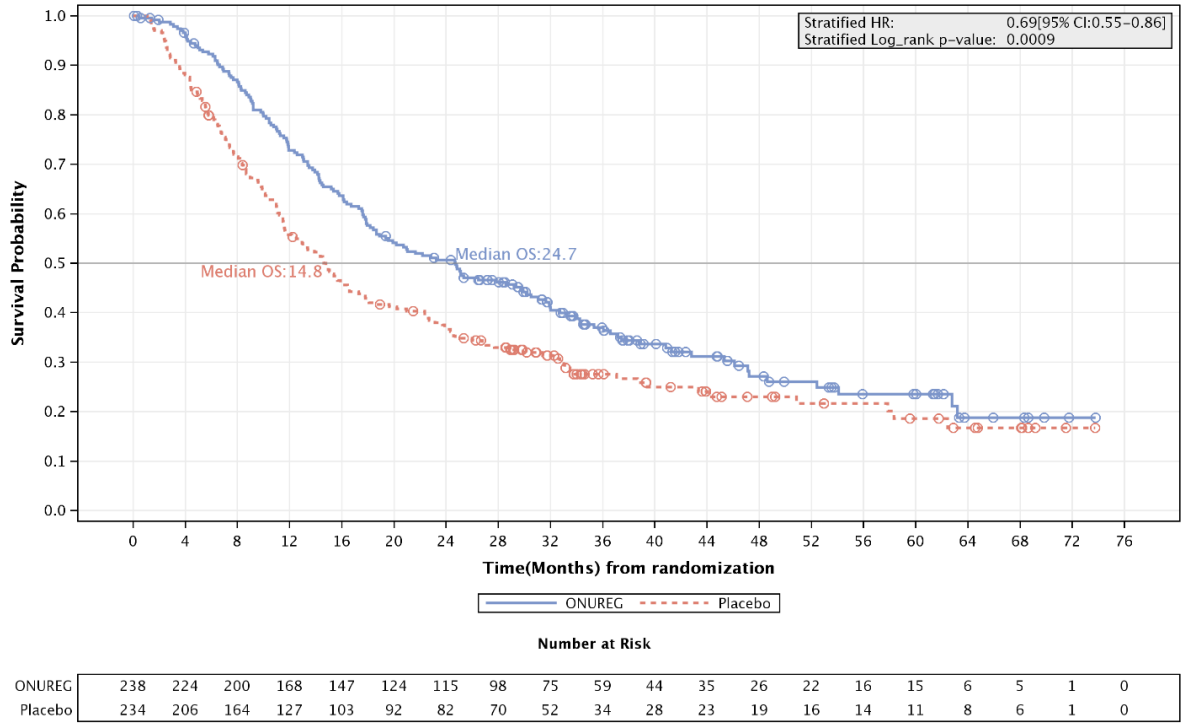
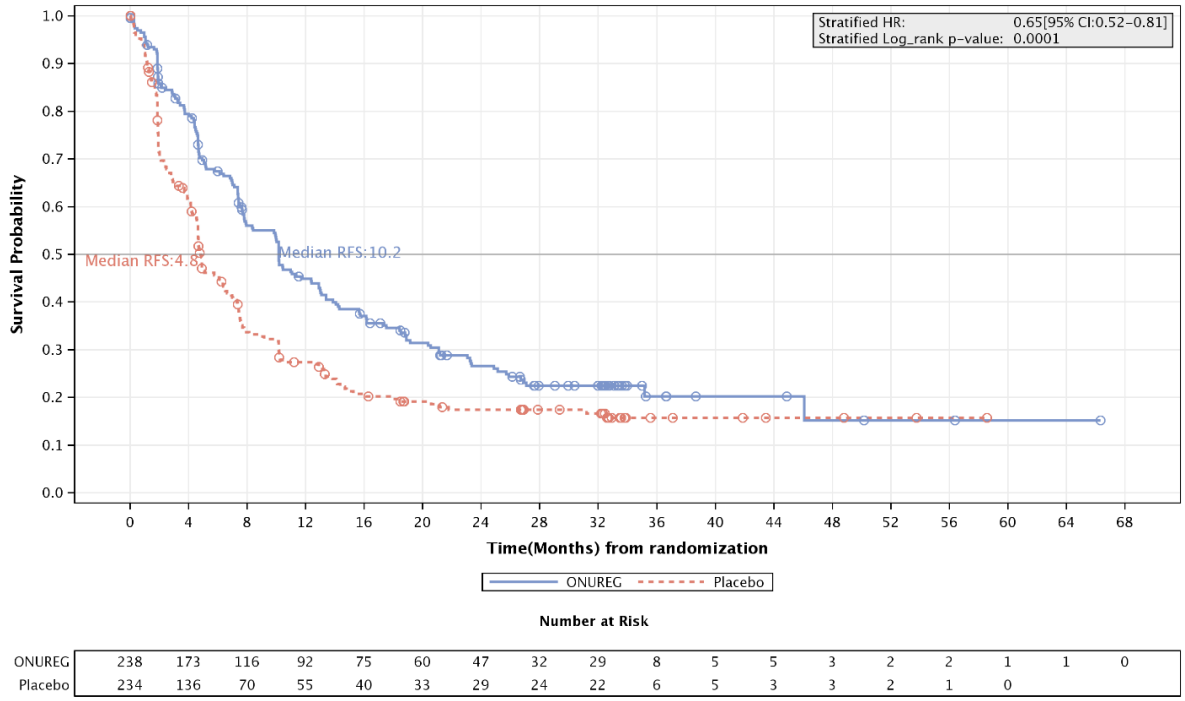


Figure 2 Kaplan-Meier Curve for Relapse Free Survival: Oral Azacitidine Versus Placebo (ITT Population)



In patients who had their dose schedule extended to 300 mg for 21 days due to disease relapse, the median OS (22.8 months for oral azacitidine and 14.6 months for placebo) and median RFS (7.4 months for ONUREG and 4.6 months for placebo) were comparable to the overall study results.

Oral azacitidine demonstrated a favorable treatment effect for OS compared with placebo in both minimal residual disease (MRD)-positive and MRD-negative patients. The treatment effect for OS was more pronounced in MRD-positive patients (HR=0.69; 95% CI: 0.51, 0.93) than in MRD-negative patients (HR=0.81; 95% CI: 0.59, 1.12).

5.2 Pharmacokinetic properties

Absorption

Exposure was generally linear with dose-proportional increases in systemic exposure; high intersubject variability was observed. 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. Multiple dosing at the recommended dose regimen did not result in drug accumulation. Absorption of azacitidine was rapid, with a median T_{max} of 1 hour postdose. Mean oral bioavailability relative to subcutaneous (SC) administration was approximately 11%.

Effect of Food

The impact of food on the exposure of oral azacitidine was minimal. Therefore, oral azacitidine can be administered either with or without food.

Distribution

After oral administration, the geometric mean apparent volume of distribution was 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). Azacitidine undergoes spontaneous hydrolysis and deamination mediated by cytidine deaminase.

Excretion

The geometric mean apparent clearance was 1242 L/hour and the geometric mean half-life was approximately 0.5 hours. Following intravenous administration of 14C 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 14C-azacitidine was 50%. The amount of unchanged azacitidine recovered in urine relative to dose was <2% following either SC or oral administration.

Special populations

Age and gender

A population PK analysis determined that intrinsic factors of gender and body weight (39.3 kg to 129 kg) did not have clinically meaningful effects on the pharmacokinetics of azacitidine.

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

Renal impairment

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. This increase in exposure was not correlated with an increase in adverse events.

Patients with mild (CLcr: ≥60 to <90 mL/min), moderate (CLcr: ≥30 to <60 mL/min), and severe (CLcr: <30 mL/min) renal impairment had 19%, 25%, and 38% increases in azacitidine plasma AUC, respectively.

A population PK analysis following a 300 mg dose of oral azacitidine determined that the effect of severe renal impairment on oral azacitidine was similar to the above referenced clinical renal impairment study with injectable azacitidine (~40% increase in AUC). 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. Thus, no dose adjustment of ONUREG is recommended in patients with mild, moderate, or severe renal impairment.

Hepatic impairment

The effects of hepatic impairment on the pharmacokinetics of azacitidine have not been studied. A population PK analysis determined that mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin 1 to 1.5 × ULN and any AST)) did not have clinically meaningful effects on the pharmacokinetics of azacitidine. The effects of moderate to severe hepatic impairment (total bilirubin > 1.5 × ULN and any AST) on the pharmacokinetics of oral azacitidine is unknown.

5.3 Preclinical safety data

Genotoxicity

Azacitidine was mutagenic, as assessed in Salmonella typhimurium, Escherichia coli, L5178Y mouse lymphoma cells and human lymphoblast TK6 cells. Azacitidine was clastogenic in the in vitro micronucleus assays in Syrian hamster embryo fibroblasts and L5178Y mouse lymphoma cells. Azacitidine induced morphological transformation in Syrian hamster kidney and embryo fibroblasts. No in vivo tests have been conducted with azacitidine.

Carcinogenicity

Azacitidine has been shown to be carcinogenic when administered by the intraperitoneal route 2 or 3 times weekly for 50-52 weeks in mice at doses of 6 or 6.6 mg/m^2 and for 8-36 weeks in rats at doses of 15 or 60 mg/m^2. These doses are well below the recommended human daily dose (when compared on a mg/m^2 basis). Tumour types included lung, testicular, mammary gland, and skin tumours, lymphomas and tumours of the haematopoietic system.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each tablet contains:

Croscarmellose sodium, magnesium stearate, mannitol, silicified microcrystalline cellulose, and Opadry II, either pink (200 mg) or brown (300 mg).

The Opadry II tablet coating contains:

The 200 and 300 mg tablet coating contains hypromellose, titanium dioxide, lactose monohydrate, polyethylene glycol/macrogol, and triacetin.

The 200 mg tablet coating has iron oxide red.

The 300 mg tablet coating has iron oxide yellow, iron oxide red, and black iron oxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25°C. Store in the original container.

6.5 Nature and contents of container

Nylon (OPA) / polyvinyl chloride (PVC) / aluminum with aluminum push-through foil.

Onureg 200 mg and 300 mg film-coated tablets.

Pack size of 7 film-coated tablets.

6.6 Special precautions for disposal and other handling

Do not crush tablets when disposing.

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.

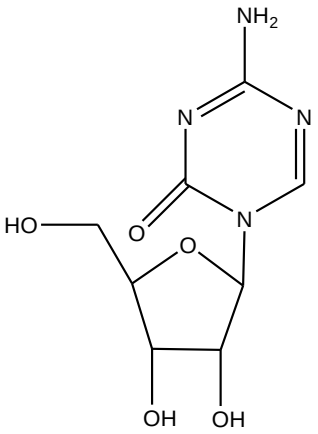
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Chemical Name

4-amino-1-β-D-ribofuranosyl-s-triazin-2(1*H*)-one.

Chemical Structure



CAS number

320-67-2

Molecular Formula

$C_8H_{12}N_4O_5$

Molecular Weight

244 g/mol

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine.

8. SPONSOR

Bristol-Myers Squibb Australia Pty Ltd

4 Nexus Court, Mulgrave

Victoria 3170, Australia

Toll free number: 1800 067 567

Email: MedInfo.Australia@bms.com

DATE OF FIRST APPROVAL (ARTG ENTRY)

8 April 2022

DATE OF REVISION OF THE TEXT

22 January 2025

Summary table of changes

Section Changed	Summary of new information
8	Update sponsor details

ONUREG® is a trademark of Celgene Corporation, a Bristol Myers Squibb Company.