

# Onureg<sup>®</sup> (azacitidine tablets)

## Mechanism of Action

### What is Onureg? How does Onureg work?



*Onureg* is a DNA methyltransferase inhibitor and epigenetic modifier that works by preventing cancer cells from growing. Azacitidine is a pyrimidine nucleoside analog of cytidine that is incorporated into DNA and RNA following cellular uptake and enzymatic biotransformation to nucleotide triphosphates. This is thought to interfere with the production of new DNA and RNA and help kill cancer cells in leukemia.<sup>1</sup>



The main mechanism of action of *Onureg* is thought to be the incorporation of azacitidine into the DNA and RNA of cancerous cells. 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.<sup>1</sup>

### *Onureg* is Incorporated Into Both DNA and RNA Where it Exerts Multiple Antileukemic Effects

Incorporation of *Onureg* 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.<sup>1</sup>

Incorporation of *Onureg* into the RNA of cancer cells, including leukemic cells, inhibited RNA methyltransferase, reduced RNA methylation, decreased RNA stability, and decreased protein synthesis.<sup>1</sup>



**DNA**  
incorporation



**RNA**  
incorporation

### What does *Onureg* treat?



AML is one of the most common acute leukemias in adults. While many patients will achieve remission, up to 50% will relapse within one year, and long-term survival averages at six months.<sup>2,3</sup> *Onureg* is used for the treatment of adult patients with AML who achieved first complete remission (CR) or CR 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).<sup>1</sup>

## How is Onureg administered?



The recommended dosage of *Onureg* is 300 mg orally once daily with or without food on Day 1 through 14 of repeated 28-day treatment cycles. *Onureg* 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.<sup>1</sup>

### IMPORTANT SAFETY INFORMATION

#### CONTRAINDICATIONS

- ONUREG® is contraindicated in patients who are hypersensitive to azacitidine or to any ingredient in the formulation, including any non-medical ingredient, or component of the container.

#### LIMITATIONS OF USE

- ONUREG® is not interchangeable with, and should not be substituted with or for, azacitidine for injection.
- 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.

#### WARNINGS AND PRECAUTIONS

- **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.
- **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.
- **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 anti-diarrheal 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. Consider the use of supportive care such as granulocyte colony stimulating factor (G-CSF) 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.

#### ADVERSE REACTIONS

- 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%).

#### 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.

#### 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.

**PLEASE SEE [ACCOMPANYING OR ENCLOSED, ETC.] FULL PRESCRIBING INFORMATION FOR ONUREG®.**

#### REFERENCES

<sup>1</sup>Onureg Product Monograph. Last updated: January, 2021.

<sup>2</sup>SEER Cancer Statistics, 2007-2013

<sup>3</sup>Xu J, et al. *Medicine* (Baltimore) 2018;97:e12102.