PDL DRUG REVIEW

Proprietary Name: Onureg®
Common Name: azacitidine
PDL Category: Antineoplastics

Comparable Products	Preferred Drug List Status
Rydapt	Non-Recommended with Conditions
Venclexta	Non-Recommended with Conditions

Summary

Pharmacology/Usage: Azacitidine, the active ingredient of Onureg®, is a nucleoside metabolic inhibitor; it is a pyrimidine nucleoside analog of cytidine that inhibits DNA/RNA methyltransferases. Azacitidine is incorporated into DNA and RNA after cellular uptake and enzymatic biotransformation to nucleotide triphosphates. Incorporation of azacitidine into the DNA of cancer cells in vitro, including acute myeloid leukemia cells, inhibited DNA methyltransferases, reduced DNA methylation and altered gene expression, including re-expression of genes regulating tumor suppression and cell differentiation. Incorporation of azacitidine into the RNA of cancer cells, including leukemic cells, inhibited RNA methyltransferases, reduced RNA methylation, decreased RNA stability and decreased protein synthesis.

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

Indication: For continued treatment of adults 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.

There is no pregnancy category for this product; however, the risk summary indicates that based on its mechanism of action and findings in animals, Onureg® can cause fetal harm when administered to a pregnant woman. There are no available data on use in pregnant women to assess for a drug-associated risk. Advise pregnant women of the potential risk to the fetus. Pregnancy testing is recommended for females of reproductive potential before starting Onureg®. Advise females of reproductive potential to use effective contraception during treatment and for at least 6 months after the last dose. In addition, advise males with female partners of reproductive potential to use effective contraception during treatment and for at least 3 months after the last dose. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Film-Coated Tablets: 200mg, 300mg. Do not split, crush, or chew.

Onureg® is a hazardous drug. Follow applicable special handling and disposal procedures.

Recommended Dosage: *Do not substitute Onureg® for IV or SC azacitidine. The indications and dosing regimen for Onureg® differ from that of IV or SC azacitidine.*

Take 300mg PO QD with or without food on days 1 through 14 of each 28-day cycle and continue until disease progression or unacceptable toxicity.

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.

Monitor complete blood count every other week for the first 2 cycles and prior to the start of each cycle thereafter. Increase monitoring to every other week for the 2 cycles after any dose reduction for myelosuppression. If the absolute neutrophil count (ANC) is less than 0.5Gi/L on day 1 of a cycle, do not administer Onureg®. Delay the start of the cycle until the ANC is 0.5Gi/L or more. Dose modifications may be required for adverse reactions, such as myelosuppression, gastrointestinal toxicity, or other adverse reactions. Refer to the prescribing information for further information for further information.

Monitor patients with severe renal impairment more frequently for adverse reactions and modify the Onureg® dosage for adverse reactions. However, dose adjustments are not recommended for patients with mild to severe renal impairment. Onureg® has not been studies in patients with severe hepatic impairment. While dose adjustments are not required with mild hepatic impairment, a recommended dosage has not been established for patients with moderate hepatic impairment.

Drug Interactions: There are no drug interactions listed with this product.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Onureg®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included nausea (41%), vomiting (50%), diarrhea (29%), constipation (15%), abdominal pain (9%), fatigue/asthenia (19%), pneumonia (10%), arthralgia (4%), pain in extremity (6%), decreased appetite (7%), febrile neutropenia (4%), and dizziness (2%).

New or worsening Grade 3 or 4 neutropenia and thrombocytopenia occurred in 49% and 22% of patients who received Onureg®, respectively. Febrile neutropenia occurred in 12%. Less than 1% of patients discontinued Onureg® due to either neutropenia or thrombocytopenia. Monitor complete blood counts and modify the dosage as recommended. Provide standard supportive care, including hematopoietic growth factors, if myelosuppression occurs.

In a clinical study, 216 patients with red blood cell transfusion-dependent anemia and thrombocytopenia due to myelodysplastic syndromes were randomized to Onureg® or placebo. In addition, 107 patients received a median of 5 cycles of Onureg® 300mg QD 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. The safety and efficacy 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.

Contraindications: In patients with known severe hypersensitivity to azacitidine or any component of the product

Manufacturer: Celgene Corp, A wholly owned subsidiary of Bristol Myers Squibb

Analysis: The safety and efficacy of Onureg® were assessed in a multicenter, randomized, double-blind, placebo-controlled study (QUAZAR) that included adults 55 years of age or older who had AML and were within 4 months of achieving first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) with intensive induction chemotherapy. Candidates for hematopoietic stem cell transplantation at the time of screening were excluded. Adults (N=472) who completed induction with or without consolidation therapy were randomized to receive Onureg® or placebo on days 1 through 14 of each 28-day cycle. Baseline characteristics of patients in the Onureg® vs placebo group included a median age of 68 years vs 68 years and most were male (50% vs 54%) and

white (91% vs 84%). Furthermore, 78% vs 77% had a CR disease status at study baseline while 18% vs 16% had a CRi disease status at study baseline.

The efficacy of Onureg® was established based on overall survival (OS). Results demonstrated a statistically significant improvement in OS for the Onureg® group compared to the placebo group. In addition, a subgroup analysis demonstrated consistency in the OS benefit for patients in either CR or CRi. Results can be seen in the table below, which was adapted from the prescribing information.

Treatment	Onureg® (N=238)	Placebo (N=234)
Overall Survival Events, n (%)	158 (66%)	171 (73%)
Median OS, months	24.7	14.8
Hazard Ratio; p-value	0.69; p=0.0009	

Place in Therapy: Onureg® is an oral agent 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. Due to substantial differences in pharmacokinetic parameters, the recommended dose and schedule for Onureg® are different from those for the IV of SC azacitidine products. Treatment of patients using IV or SC azacitidine at the recommended dosage of Onureg® may result in a fatal adverse reaction. Do not substitute Onureg® for IV or SC azacitidine as the indications and dosage regimen for Onureg® differ from that of IV or SC azacitidine. In a phase 3, placebo-controlled trial, a statistically significant improvement in overall survival was established for patients randomized to Onureg® vs placebo.

It is recommended that Onureg® should be non-recommended with conditions in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Recommended**
☒ **Non-Recommended with Conditions**

References

[1] Onureg [package insert]. Summit, NJ: Celgene Corp, a wholly owned subsidiary of Bristol Myers Squibb; 2020.