

## PRIOR AUTHORIZATION POLICY

**POLICY:** Oncology – Idhifa® (enasidenib tablets – Celgene/Agios)

**TAC APPROVAL DATE:** 02/06/2019

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### OVERVIEW

Idhifa, an isocitrate dehydrogenase-2 (IDH2) inhibitor, is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with an IDH2 mutation as detected by an FDA-approved test.<sup>1</sup> The recommended dose is 100 mg orally once daily (QD) until disease progression or unacceptable toxicity. Inhibition of the mutant IDH2 enzyme by Idhifa led to decreased 2-hydroxyglutarate (2-HG) levels and induced myeloid differentiation.

### Disease Overview

AML is a heterogeneous hematologic malignancy characterized by clonal expansion of myeloid blasts in the peripheral blood, bone marrow, and/or other tissues.<sup>2</sup> Undifferentiated blast cells proliferate in bone marrow instead of maturing into normal blood cells. Among adults, it is the most common form of acute leukemia and accounts for the largest number of annual deaths from leukemias in the US. An estimated 21,380 individuals will be diagnosed with AML in 2017 and 10,590 are projected to die from the condition. The median age at diagnosis is 67 years. Diagnosis occurs at  $\geq 65$  years of age for 54% of patients with around one-third of patients diagnosed at  $\geq 75$  years of age. The incidence of AML increases as the population ages. Environmental factors such as prolonged exposure to petrochemicals, solvents such as benzene, pesticides, and ionizing radiation have been established to increase the risks for AML, as well as myelodysplastic syndrome (MDS).<sup>2</sup> The cure rates of AML have improved with this outcome noted in 35% to 40% of adult patients who are  $\leq 60$  years of age and 5% to 15% for patients who are  $> 60$  years of age.<sup>3</sup> However, among patients who are older and unable to receive intensive chemotherapy the survival rates are dismal with a median survival of only 5 to 10 months. Various gene mutations are present in adults with AML. The incidence of IDH2 mutations increase with advancing age.<sup>3</sup> IDH2 mutations have been reported in up to 12% of patients with AML.<sup>2</sup> Mutations have been identified in R172 and R140 of the IDH2 gene with the R140 mutation more frequently occurring.

### Clinical Efficacy

The efficacy of Idhifa was assessed in an open-label, single-arm, multicenter, two-cohort clinical study involving 199 adult patients with relapsed or refractory AML that had an IDH2 mutation.<sup>1</sup> Patients were assigned to receive Idhifa 100 mg QD. The median patient age was 68 years and patients had received a median of two prior therapies. Approximately 79% of patients were transfusion dependent at baseline. Of the IDH2 mutations, 78% of patients had R140 and 22% of patients had R172. The median follow-up was 6.6 months. In total, 19% of patient attained complete remission (defined as  $< 5\%$  blasts in the bone marrow, no evidence of disease and full recovery of peripheral blood counts [platelets  $> 100,000/\text{microliter}$  and absolute neutrophil counts  $> 1,000/\text{microliter}$ ]). Approximately 4% of patients obtained complete remission with partial hematological recovery (defined as  $< 5\%$  of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts [platelets  $> 50,000/\text{microliter}$  and absolute neutrophil count  $> 500/\text{microliter}$ ]). For patients who obtained complete remission or complete remission with partial hematologic recovery, the median time to first response was 1.9 months (range, 0.5 to 7.5 months); the median time to best response among these patients was 3.7 months (range, 0.6 to 11.2 months). For the 157 patients who were dependent upon red blood cell (RBC)

and/or platelet transfusions at baseline, 34% of patients (n = 53/157) became independent of RBC and platelet transfusions.

### **Guidelines**

The National Comprehensive Cancer Network (NCCN) guidelines on AML (version 1.2019 – January 18, 2019) note Idhifa as an alternative for IDH2 mutated AML in a variety of clinical scenarios. Idhifa is recommended for patients who have relapsed or refractory disease who have the IDH2 mutation. Another clinical scenario is for treatment induction among patients  $\geq 60$  years of age who are not a candidate for intensive remission induction therapy or declines such therapy. In patients  $\geq 60$  years of age who had a response to previous lower intensity therapy, Idhifa can be continued. Both clinical scenarios apply to patients who are IDH2 mutation positive.

### **Safety**

Idhifa has a Boxed Warning regarding differentiation syndrome.<sup>1</sup> Other more common adverse events (AEs) include nausea (50%), diarrhea (43%), vomiting (34%), and decreased appetite (34%). Elevated bilirubin levels were reported in 81% of patients, of which 15% were Grade  $\geq 3$  in severity.

### **POLICY STATEMENT**

Prior authorization is recommended for prescription benefit coverage of Idhifa. All approvals are provided for the duration noted below.

**Automation:** None.

### **RECOMMENDED AUTHORIZATION CRITERIA**

Coverage of Idhifa is recommended in those who meet the following criteria:

#### **FDA-Approved Indications**

1. **Acute Myeloid Leukemia (AML).** Approve for 3 years if the disease is isocitrate dehydrogenase-2 (IDH2)-mutation positive as detected by an approved test.

#### **CONDITIONS NOT RECOMMENDED FOR APPROVAL**

Idhifa has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

### **REFERENCES**

1. Idhifa® tablets [prescribing information]. Summit, NJ: Celgene; August 2017.
2. The NCCN Acute Myeloid Leukemia Clinical Practice Guidelines in Oncology (Version 1.2019 – January 18, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on January 23, 2019.
3. Dohner H, Weisdorf DJ, Bloomfield CD. Acute myeloid leukemia. *N Engl J Med.* 2015;373(12):1136-1152.

**OTHER REFERENCES UTILIZED**

- Stein EM, DiNardo CD, Pollyea DA, et al. Enasidenib in mutant-IDH2 relapsed or refractory acute myeloid leukemia. *Blood*. 2017;130(6):722-731.

**HISTORY**

Type of Revision	Summary of Changes*	TAC Approval Date
New Policy	Not applicable	08/16/2017
Annual revision	Removed the word “adults” in the indication for acute myeloid leukemia. Also, the wording was removed that the isocitrate dehydrogenase-2 (IDH2) mutation-positive confirmation had to be “detected by an FDA-approved test”.	08/22/2018
Early annual revision	Added criteria to approve if the patient is IDH2 mutation-positive “as detected by an approved test”.	02/06/2019

\* For a further summary of criteria changes, refer to respective TAC minutes available at: <http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx>; TAC – Therapeutic Assessment Committee; AML – Acute myeloid leukemia.