EXPRESS SCRIPTS®

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Tibsovo® (ivosidenib tablets – Agios)

TAC APPROVAL DATE: 02/06/2019

OVERVIEW

Tibsovo, an isocitrate dehydrogenase-1 (IDH1) inhibitor, is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible IDH1 mutation as detected by an FDA-approved test.[1] The recommended dose is 500 mg orally once daily (QD) with or without food until disease progression or unacceptable toxicity. Do not administer with a high-fat meal.

Disease Overview

AML is a heterogeneous hematologic malignancy hallmarked by clonal expansion of myeloid blasts in the peripheral blood, bone marrow, and/or other tissues.[2] 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).[2] 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.[3] 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.[3] Various gene mutations are present in adults with AML.[2,3] The incidence of IDH1 mutations have been reported in 6% to 9% of AML cases.[2]

Clinical Efficacy

The efficacy of Tibosovo was assessed in an open-label, single-arm, multicenter, clinical study involving 174 adult patients with relapsed or refractory AML that had an IDH1 mutation.[1,4] Patients were assigned to receive Tibosovo 500 mg QD. The median patient age was 67 years.[1,4] The most common types of IDH1 mutation were R132C and R132H.[1] Patients had received a median of two prior therapies (range, 1 to 6).[4] Approximately 70% and 64% of patients had received prior intensive chemotherapy and non-intensive chemotherapy, respectively.[4] Efficacy was based on the rate of complete remission (CR) plus complete remission with partial hematologic recovery (CRh), the duration of CR+CRh, and the rate of conversion from transfusion dependence to transfusion independence.[1] The median follow-up was 8.3 months (range, 0.2 to 39.5 months) and the median treatment duration was 4.1 months (range, 0.1 to 39.5 months). CR (defined as < 5% blasts in the bone marrow, no evidence of disease and full recovery of peripheral blood counts [platelets > 100,000/microliter and absolute neutrophil counts > 1,000/microliter]) was achieved by 24.7% of patients (n = 43/174). Approximately 8% of patients (n = 14/174) 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/microliter and absolute neutrophil count > 500/microliter]). For patients who obtained CR or CRh, the median time first response was 2 months (range, 0.6 to 5.6 months). For the 110 patients who

were dependent upon red blood cell (RBC) and/or platelet transfusions at baseline, 37.3% of patients (n = 41/110) became independent of RBC and platelet transfusions during any 56-day post-baseline period.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on AML (version 1.2019 – January 18, 2019), are extensive.[2] Tibsovo is recommended for patients who have relapsed or refractory disease who have the IDH1 mutation. Another clinical scenario is for treatment induction among patients ≥ 60 years of age who are not a candidate for intensive remission induction therapy or declines such therapy. In patients ≥ 60 years of age who had a response to previous lower intensity therapy, Tibsovo can be continued. Both clinical scenarios apply to patients who are IDH1 mutation positive.

Safety

Tibsovo has a Boxed Warning regarding differentiation syndrome.[1] Other more common adverse events (AEs) were fatigue (39%), leukocytosis (38%), arthralgia (36%), diarrhea (34%), dyspnea (33%), edema (32%), nausea (31%), mucositis (28%), electrocardiogram QT prolongation (26%), rash (26%), pyrexia (23%), cough (22%), and constipation (20%). Warnings and precautions include QTc interval prolongation and Guillain-Barre Syndrome.

POLICY STATEMENT

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

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tibsovo 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-1 (IDH1) mutation positive as detected by an approved test.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Tibsovo 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. Tibsovo® tablets [prescribing information]. Cambridge, MA: Agios; July 2018.
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.
4.   DiNardo CD, Stein EM, De Botton S, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. *N Engl J Med*. 2018;378(25):2386-2398.
5.   Idhifa® tablets [prescribing information]. Cambridge, MA and Summit, NJ: Agios and Celegene; August 2017.

HISTORY

Type of Revision	Summary of Changes[*]	TAC Approval Date
New policy	Not applicable	07/25/2018
Early annual revision	Added criteria to approve if the patient is IDH1 mutation-positive "as deleted 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.