ivosidenib (Tibsovo®); enasidenib (Idhifa®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCCO123

Description

Ivosidenib (Tibsovo) inhibits the isocitrate dehydrogenase 1 (IDH1) enzyme. It limits the proliferation of the 2-HG oncometabolite, a competitive inhibitor of the normal metabolite, and promotes cell differentiation.

Enasidenib (Idhifa) inhibits the isocitrate dehydrogenase 2 (IDH2) enzyme. It specifically targets IDH2 variants mutant R140Q, R172S, and R172K to decrease 2-hydroxyglutarate (2-HG) levels and induce myeloid differentiation; thereby, reducing blast counts and increasing mature myeloid cell percentage.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
enasidenib (Idhifa)	50 mg tablets 100 mg tablets	Acute myeloid leukemia, relapsed/refractory	30 tablets/30 days
ivosidenib (Tibsovo)	250 mg capsule	Acute myeloid leukemia, relapsed/refractory Acute myeloid leukemia, newly diagnosed	60 capsules/ 30 days

Initial Evaluation

I. Enasidenib (Idhifa) or ivosidenib (Tibsovo) may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
   B. Will not be used in combination with other oncologic agents (i.e. as monotherapy); **AND**
   C. A diagnosis of one of the following:
      1. **Relapsed or refractory acute myeloid leukemia (AML); AND**
         i. Treatment with the following has been ineffective, contraindicated, or not tolerated:
            a. Systemic chemotherapy**; OR**
            b. Allogenic hematopoietic stem cell transplant; **AND**
         ii. Presence of IDH-1 mutation as detected by an FDA-approved test; **AND**
            a. Request is for ivosidenib (Tibsovo); **OR**
         iii. Presence of IDH-2 mutation as detected by an FDA-approved test; **AND**

a. Request is for enasidenib (Idhifa); **OR**

2. **Newly diagnosed AML**; **AND**
   i. Presence of IDH-1 mutation as detected by an FDA-approved test; **AND**
   ii. Member is 75 years of age or older; **OR**
      a. Provider attests that the member has comorbidities that preclude intensive induction chemotherapy (e.g., baseline Eastern Cooperative Oncology Group performance status of ≥ 2, severe cardiac or pulmonary disease, hepatic impairment with bilirubin >1.5 times the upper limit of normal, or creatine clearance <45 mL/min); **AND**
   iii. Request is for ivosidenib (Tibsovo).

II. Enasidenib (Idhifa) and/or ivosidenib (Tibsovo) is/are considered investigational when used for all other conditions, including but not limited to:
   A. Advanced cholangiocarcinoma
   B. Chondrosarcomas
   C. Myelodysplastic Syndrome (MDS)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms (e.g., became independent of red blood cell and platelet transfusion).

Supporting Evidence

I. Enasidenib (Idhifa) was studied in a Phase I/II open-label, single-arm, multicenter, two-cohort clinical trial in patients who have a diagnosis of relapsed/refractory acute myeloid leukemia (AML) and IDH2 mutation. The study was conducted in 3 parts: (1) Phase 1 dose escalation, (2) Phase 1 expansion, and (3) Phase 2 expansion. Cohort 1 (dose-escalation): patients receiving enasidenib (Idhifa) 50mg to 650mg. Cohort 2 (Phase 1 & phase 2 expansion): patients receiving enasidenib (Idhifa) 100mg daily. The primary outcome measure of the study was to determine the safety and maximum tolerated dose (MTD) of enasidenib (Idhifa). In the phase I/II study,

enasidenib (Idhifa) demonstrated that the MTD was not reached at doses of up to 650mg daily; and 26.1% of all patients in the study had treatment-related serious adverse events. In the most recent Phase 2 expansion data, the secondary outcome measures were reported for patients who were taking enasidenib (Idhifa) 100mg daily, which included: a complete response (CR) of 20.1%, a median time to CR of 3.7 months, and the median duration of response for patients who achieved CR was 8.8 months.

II. NCCN Guideline preferred therapies for the treatment of recurrent/relapse AML include the following: clinical trial, systemic chemotherapy, or allogenic hematopoietic stem cell transplant.

III. Ivosidenib (Tibsovo) was studied in an open-label, single-arm, multicenter clinical trial in 174 adult patients with relapsed or refractory AML with an IDH1 mutation. In this trial, the primary objectives were to assess the safety, maximum tolerated dose, and the recommended phase 2 dose of ivosidenib (Tibsovo) in patients with secondary or later relapse. Patients included in the trial had a relapse after stem-cell transplantation, had disease that was refractory to induction or reinduction chemotherapy, or had a relapse less than 12 months after initial therapy. Ivosidenib (Tibsovo) was approved in the setting of relapsed and refractory AML based on the following results: the rate of complete remission or complete remission with partial hematologic recovery was 30.4% (95% confidence interval [CI], 22.5 to 39.3), the rate of complete remission was 21.6% (95% CI, 14.7 to 29.8), and the overall response rate was 41.6% (95% CI, 32.9 to 50.8). Of note, 12% of the patients went on to stem cell transplantation following ivosidenib (Tibsovo) treatment; and 15.1% of the patients died due to disease progression and complication of underlying disease (e.g., infection, respiratory failure, hemorrhage).

IV. Ivosidenib (Tibsovo) was studied in an open-label, single-arm, multicenter clinical trial in 28 adult patients with newly diagnosed AML that have a IDH1 mutation. In this trial, the eligible population included patients who were age 75 years or older or who had comorbidities that preclude the use of intensive induction chemotherapy (ECOG performance ≥2, severe cardiac or pulmonary disease, hepatic impairment with bilirubin > 1.5 times the upper limit of normal, or CrCL <45 mL/min). In this trial, the efficacy was determined by the rate of complete remission (CR) or complete remission with partial hematologic recovery (CRh), the duration of CR+CRh, and the rate of conversion from transfusion dependence to transfusion independence. Ivosidenib (Tibsovo) was granted FDA-approval as first-line therapy for AML patients with IDH-1 mutation, aged 75 years or above, or whose present comorbidities preclude the use of intensive induction chemotherapy. This approval was based on the following results: CR + CRh rate was 42.4% (95% confidence interval [CI], 25.5-60.8%) and 41.2% became independent of red blood cell (RBC) and platelet transfusion during any 56-day post-baseline period. Of note, 7% of the patients went on to stem cell transplantation following ivosidenib (Tibsovo) treatment.

Investigational or Not Medically Necessary Uses

I. Advanced cholangiocarcinoma
   A. Limited to proof-of-concept
   B. Mutations of isocitrate dehydrogenase have been identified only.
II. Chondrosarcomas
   A. Clinical trials currently ongoing and limited to proof-of-concept.
III. Myelodysplastic Syndrome (MDS)
   A. Current clinical trials are being conducted in patients with myelodysplastic syndrome (MDS). There is currently insufficient evidence to support the safety and efficacy of ivosidenib (Tibsovo) and enasidenib (Idhifa) for the treatment of MDS.

References

1. Tibsovo [prescribing information]. Cambridge, MA: Agios Pharmaceuticals, Inc.; July 2018.
2. Idhifa [package insert]. Cambridge, MA: Agios Pharmaceuticals & Celgene Corporation; August 2017.
3. DiNardo C, Stein EM, Botton S, et al. Durable Remssions with Ivosidenib in *IDH1*-mutated Relapsed or Refractory AML. *N Engl J Med.* 2018 June: 378:2386-2398. DOI: 10.1056/NEJMoa1716984
4. Roboz GJ, DiNardo CD, Stein EM, et al. Ivosidenib induces deep durable remission in patients with newly diagnosed *IDH1*-mutant acute myeloid leukemia. Blood. 2019; blood.2019002140. DOI:10.1182/blood.2019002140
5. NCCN Clinical Practice Guidelines in Oncology™. Acute Myeloid Leukemia v.3.2020. [cited 02/05/2020]; Available from: https://www.nccn.org/professionals/physician_gls/pdf/aml_blocks.pdf

Policy Implementation/Update:

Action and Summary of Changes	Date
Criteria update: To improve the clinical flow of the policy, the indication of relapse/refractory AML was separated from newly diagnosed AML. For clinical appropriateness and standard of practice, the requirement for both chemotherapy "AND" allogenic stem cell transplant for relapsed or refractory AML, was changed to an "OR;" therefore, either one prior regimen would satisfy that requirement. For the newly diagnosed AML diagnosis, additional information around comorbidities has been included in the policy to help better determine the comorbidities that may preclude newly diagnosed AML patients from intensive induction chemotherapy. Based on current clinical trials that are being conducted, myelodysplastic syndrome (MDS) has been added to the investigation/experimental section of this policy and supporting evidence has been updated to reflect the rationale for the addition. The supporting evidence in this whole policy has been updated to reflect the pivotal trials. The references section has been updated to include the pivotal trials and NCCN guideline for AML.	02/2020
Policy created. Tibsovo and Idhifa was combined into one policy.	12/2019