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; first three months split fill for ivosidenib (Tibsovo)
- Renewal: 12 months

Quantity Limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>enasidenib</td>
<td>50 mg tablets</td>
<td>Acute myeloid leukemia, relapsed/refractory</td>
<td>30 tablets/30 days</td>
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<tr>
<td></td>
<td>100 mg tablets</td>
<td></td>
<td></td>
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<tr>
<td>(Idhifa)</td>
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<tr>
<td>ivosidenib</td>
<td>250 mg capsule</td>
<td>Acute myeloid leukemia, relapsed/refractory</td>
<td>60 capsules/30 days</td>
</tr>
<tr>
<td>(Tibsovo)</td>
<td></td>
<td>Acute myeloid leukemia, newly diagnosed</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cholangiocarcinoma, advanced/metastatic</td>
<td></td>
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Initial Evaluation

I. **Enasidenib (Idhifa) or ivosidenib (Tibsovo)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
   C. Will not be used in combination with other oncologic agents (i.e. as monotherapy); **AND**
   D. 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); **OR**

3. **Locally advanced or metastatic cholangiocarcinoma; AND**
   i. Request is for ivosidenib (Tibsovo); **AND**
   ii. Provider attests that the member is not a candidate for surgery (i.e., unresectable cholangiocarcinoma); **AND**
   iii. Presence of IDH-1 mutation as detected by an FDA-approved test; **AND**
   iv. Member has had disease progression on, or after, at least one systemic therapy (e.g., gemcitabine, or 5-fluorouracil).

II. Enasidenib (Idhifa) and/or ivosidenib (Tibsovo) is/are considered **investigational** when used for all other conditions, including but not limited to:
   A. Enasidenib (Idhifa) and/or ivosidenib (Tibsovo) used in combination with another oncology therapy
   B. Advanced cholangiocarcinoma without IDH-1 mutation
   C. Chondrosarcomas
   D. Myelodysplastic Syndrome (MDS)

**Renewal Evaluation**
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I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; AND

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, 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, or exhibited tumor response).

Supporting Evidence

I. Efficacy and safety of enasidenib (Idhifa) and ivosidenib (Tibsovo) has not been studied in the pediatric population. Current FDA approvals for these agents are limited to adult members.

II. Diagnosis and management of acute myeloid leukemia and cholangiocarcinoma require detailed clinical examination in combination with advanced testing such as MRI, EEG, and genetic screening (e.g., IDH-1 mutation). Given the complexities of diagnosis and treatment of these conditions, supervision of treatment by a hematologist or an oncologist is required.

III. *Enasidenib (Idhifa):*
   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.
   
   ii. 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.
   
   iii. NCCN Guidelines preferred therapies for the treatment of recurrent/relapse AML include the following: clinical trial, systemic chemotherapy, or allogenic hematopoietic stem cell transplant.

IV. *Ivosidenib (Tibsovo):*
   1. 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).

- 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 precluded 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.

- Efficacy and safety of ivosidenib (Tibsovo) for the treatment of cholangiocarcinoma was evaluated in a double-blind, placebo-controlled, phase 3 (ClarIDHy) clinical trial. Adult participants (N=185), who had advanced or metastatic unresectable cholangiocarcinoma with documented IDH-1 mutation, and who had progressed on or after at least one systemic therapy consisting of gemcitabine or 5-fluorouracil were included. This trial included a one-way crossover allowing the patients randomized to placebo arm to crossover to receive ivosidenib (Tibsovo) upon progression. Although the crossover population was included for the calculation of overall survival (OS) data, primary outcome (progression-free survival (PFS)) only included initially randomized population (ITT analysis). After a median follow-up of 6.9 months, ivosidenib (Tibsovo) exhibited statistically significant improvement in PFS: 2.7 months versus 1.4 months for placebo arm (HR 0.37; 95% CI 0.25 to 0.54; p<0.0001). Additionally median OS at data cut-off was 10.8 months (7.7, 17.6) with ivodesinib (Tibsovo) as compared to 9.7 months (4.8, 12.1) with placebo.
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(HR 0.69; 95% CI 0.44, 1.10; p 0.06). Although not statistically significant, in presence of significant primary outcome (PFS), the OS data provided indication of survival benefit with ivosidenib (Tibsovo). Additionally, treatment with ivosidenib (Tibsovo) also indicated improvement in quality of life parameters (QoL) upon comparing the patient answered questionnaires at cycle 2 of treatment versus cycle.

- During ClarIDHy clinical trial, 30% patients, who were on ivosidenib (Tibsovo), reported serious (≥ grade 3) adverse reactions, which included hyperbilirubinaemia, jaundice cholestatic, ECG QT prolonged, and pleural effusion. No additional concerning safety signals were noted during this clinical trial when compared to previous trials for AML. Treatment related dose reduction rates were 3%, treatment discontinuation rate 6%, and dose interruption rate 29%, respectively. Among the 78 deaths (49 in the treatment arm) reported during the trial, none were ascribed as treatment-emergent.

- NCCN Guideline preferred first-line systemic therapies for the treatment of hepatobiliary cancer include: surgical resection followed by adjuvant chemotherapy (e.g., capecitabine, 5-fluorouracil (5FU), cisplatin). For non-resectable metastatic biliary tract cancer, first-line gemcitabine in combination with cisplatin is preferred regimen (category 1). 5FU, FOLFOX, FOLFIRI may serve as subsequent-line therapies.

Investigational or Not Medically Necessary Uses

I. Enasidenib (Idhifa) and/or ivosidenib (Tibsovo) are used in combination with another oncology therapy
   A. Current clinical trial data leading to FDA approval are in the monotherapy setting. Safety and efficacy have not been established for specific combination regimens.

II. Advanced cholangiocarcinoma without IDH-1 mutation
   A. Ivosidenib (Tibsovo) has received FDA approval in the setting of advanced cholangiocarcinoma with IDH-1 mutations. Efficacy and safety of this drug has not been established in the absence of IDH-1 mutations. Additionally, enasidenib (Idhifa) has not been sufficiently studied and is not FDA-approved for the treatment of cholangiocarcinoma.

III. Chondrosarcomas
   A. Clinical trials currently ongoing and limited to proof-of-concept.

IV. 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.
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References


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Update to include expanded indication for ivosidenib (Tibsovo) for cholangiocarcinoma; updated supporting evidence; added split fill requirement for Tibsovo.</td>
<td>10/2021</td>
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<tr>
<td>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.</td>
<td>02/2020</td>
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<tr>
<td>Policy created. Tibsovo and Idhifa was combined into one policy.</td>
<td>12/2019</td>
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