ivosidenib (Tibsovo®); enasidenib (Idhifa®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCCO123

Description

Ivosidenib (Tibsovo) and olutasidenib (Rezlidhia) inhibit the isocitrate dehydrogenase 1 (IDH-1) enzyme. It limits the proliferation of the 2-HG oncometabolite, a competitive inhibitor of the normal metabolite, and promotes cell differentiation. Enasidenib (Idhifa) inhibits isocitrate dehydrogenase 2 (IDH-2). It specifically targets IDH-2 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) and olutasidenib (Rezlidhia)
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
enasidenib (Idhifa)	Acute myeloid leukemia, relapsed/refractory	50 mg tablets 100 mg tablets	30 tablets/30 days
ivosidenib (Tibsovo)	Acute myeloid leukemia, relapsed/refractory Acute myeloid leukemia, newly diagnosed Cholangiocarcinoma, advanced/ metastatic	250 mg capsule	60 capsules/ 30 days
olutasidenib (Rezlidhia)	Acute myeloid leukemia, relapsed/refractory	150 mg capsule	60 capsules/ 30 days

Initial Evaluation

I. **Enasidenib (Idhifa)**, **ivosidenib (Tibsovo),** and **olutasidenib (Rezlidhia)** 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. The member has not previously progressed on or after an IDH inhibitor [e.g., ivosidenib (Tibsovo), olutasidenib (Rezlidhia), enasidenib (Idhifa)]; **AND**
D. A diagnosis of one of the following:
    1. **Relapsed or refractory acute myeloid leukemia (AML); AND**
        a. Medication will not be used in combination with other oncologic agents (i.e., as monotherapy); **AND**
        b. Treatment with one of the following has been ineffective, or not tolerated unless both are contraindicated:
            i. Systemic chemotherapy**; OR**
            ii. Allogenic hematopoietic stem cell transplant; **AND**
        c. Presence of IDH-1 mutation as detected by an FDA-approved test is documented; **AND**
            i. Request is for ivosidenib (Tibsovo) or olutasidenib (Rezlidhia); **OR**
        d. Presence of IDH-2 mutation as detected by an FDA-approved test is documented; **AND**
            i. Request is for enasidenib (Idhifa); **OR**
    2. **Newly diagnosed AML**; **AND**
        a. Presence of IDH-1 mutation as detected by an FDA-approved test; **AND**
        b. Member is 75 years of age or older; **OR**
        c. 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**
        d. Request is for ivosidenib (Tibsovo); **AND**
            i. Treatment will not be used in combination with other oncologic agents (i.e., as monotherapy); **OR**
            ii. Treatment will be used in combination with injectable azacitidine; **OR**
    3. **Locally advanced or metastatic cholangiocarcinoma; AND**
        a. Request is for ivosidenib (Tibsovo); **AND**
        b. Ivosidenib (Tibsovo) will not be used in combination with other oncologic agents (i.e., as monotherapy); **AND**
        c. Provider attests that the member is not a candidate for surgery (i.e., unresectable cholangiocarcinoma); **AND**

d. Presence of IDH-1 mutation as detected by an FDA-approved test; **AND**
e. 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) used in combination with another oncology therapy
   B. Ivosidenib (Tibsovo) used in combination with another oncology therapy for relapsed or refractory AML and locally advanced or metastatic cholangiocarcinoma
   C. olutasidenib (Rezlidhia) used in combination with another oncology therapy for relapsed or refractory AML
   D. olutasidenib (Rezlidhia) for newly diagnosed AML or cholangiocarcinoma
   E. Advanced cholangiocarcinoma without IDH-1 mutation
   F. Chondrosarcomas
   G. Myelodysplastic Syndrome (MDS)

Renewal Evaluation

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), olutasidenib (Rezlidhia), 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 IDH-1 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.

ii. 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).

iii. Ivosidenib (Tibsovo) was studied in an open-label, single-arm, multicenter clinical trial in 28 adult patients with newly diagnosed AML that have a IDH-1 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.

iv. The efficacy and safety of combination ivosidenib (Tibsovo) and azacitidine was studied in a double-blind, randomized, placebo controlled, phase 3 (AGILE) clinical trial. Adult participants (N=146) with newly diagnosed AML, confirmed IDH-1 mutations who were age 75 years or older or who had comorbidities that precluded the use of intensive induction chemotherapy were included in the study population. Patients were randomized 1:1 to ivosidenib (Tibsovo) plus azacitidine or placebo plus azacitidine. The trial ended early per an observation of the difference in number of deaths favoring ivosidenib (Tibsovo) and azacitidine arm – concluding the trial prior to enrolling the number needed for its power calculation. The primary outcome measure was progression event-survival reported as a hazard ratio of 0.33 (95% confidence interval [CI], 0.16 to 0.69; p= 0.002]. Median event-free survival was 0.03 months in both the treatment and placebo arms as more than half the patients in each arm did not have complete remission by week 24. Secondary endpoints included the rate of complete remission (CR) or complete remission with partial hematologic recovery (CRh) was 53% (95% CI, 41 to 65) in the treatment arm compared to 18% (95% CI, 10 to 28) in the placebo arm. CR was 47% (95% CI, 35 to 59) to 15% (95% CI, 8 to 25) respectively and the objective response rate was 62% (95% CI, 50 to 74) to 19% (95% CI, 11 to 30; p< 0.001). Median overall survival on the basis of 74 deaths was 24 months in the treatment arm (95% CI, 11.3 to 34.1) compared to 7.9 months (95% CI, 4.1 to 11.3) in the placebo arm HR 0.44; 95% CI, 0.27 to 0.73; P = 0.001). Together the combination ivosidenib (Tibsovo) + azacitidine provided a significantly better CR rate as compared to placebo + azacitidine. Additionally, combination therapy provided a favorable risk reduction in both PFS and OS indicating efficacy in the newly diagnosed AML population.

v. Though the AGILE study did not compare ivosidenib (Tibsovo) monotherapy to combination therapy with azacitidine indirect comparisons between ivosidenib (Tibsovo) monotherapy and ivosidenib (Tibsovo) + azacitidine combination therapy can be made. Combination therapy showed an increase in CR rates between the two trials [28.6% to 47% respectively]. CR is the first goal of AML induction chemotherapy**.** With a noted increase in reported CR rates in combination and monotherapy trials it can be assumed with moderate confidence

that combination ivosidenib (Tibsovo) + azacitidine provides a clinically meaningful benefit as compared to monotherapy alone.

vi. 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 (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.

vii. 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.

viii. 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.

III. **Olutasidenib (Rezlidhia):**

A. The clinical program for olutasidenib (Rezlidhia) studied this agent as a monotherapy for the treatment of R/R AML. Participants in the clinical trial did not have previous treatment exposure to another IDH1 inhibitor (e.g., ivosidenib (Tibsovo)). At this time, the efficacy of olutasidenib (Rezlidhia) for patients, who have progressed on or after ivosidenib (Tibsovo) is unknown.

B. FDA approval of olutasidenib (Rezlidhia) was based on an ongoing open-label, single-arm, phase 1/ 2 clinical trial (Study 2102-HEM-101). Subjects (N= 147) with R/R AML and confirmed IDH1 mutation were given olutasidenib (Rezlidhia) 150 mg twice daily. The majority of patients had intermediate to poor cytogenetic risk and were experiencing first or second relapse with 31% patients being primary refractory. Twelve percent of patients had a history of HSCT. The efficacy of olutasidenib (Rezlidhia) was assessed based on the rate of complete remission (CR), complete remission with partial hematological recovery (CRh), and the duration of CR+CRh after a median follow-up duration of 10.2 months. Thirty-fice percent of trial participants reported a combined CR + CRh with 32% achieving CR at the end of treatment exposure. Median duration of combined response was reported to be 25.9 months.
C. Additionally, among the 86 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 29 (34%) became independent of RBC and platelet transfusions during any time in the 56-day post-baseline period. Of the 61 patients who were transfusion independent at baseline, 39 (64%) remained transfusion independent during any 56-day post-baseline period. Given the exchange between transfusion dependence and independence, the direct effect upon conversion to transfusion independence as a result of olutasidenib (Rezlidhia) remains uncertain.
D. Limitations of the clinical trial for olutasidenib (Rezlidhia) include the lack of a comparator, open-label study design, and lack of clinically meaningful outcomes. Although CR is an objective measure and can indicate an effective response to therapy, it remains shy of accurately predicting long-term prognosis and survival outcomes in AML. For newly diagnosed AML, CR following induction therapy has been associated with overall survival (OS) benefits. However, in the setting of R/R AML, morphologic and hematologic thresholds that define CR may be only indirect predictors of adequate response depth. CR remains an imperfect proxy for key long-term mortality outcomes. The quality of evidence is considered low due to the observational nature of the trial. Additionally, the efficacy of olutasidenib (Rezlidhia) in comparison with, or after, progression on ivosidenib (Tibsovo), remains unknown.
E. During clinical trial, serious adverse events (AE) occurred in 25% of patients on therapy, which included differentiation syndrome (9%) and transaminitis (6%). The most common (≥20%) AE included nausea (38%), fatigue (36%), edema (18%), arthralgia (28%), and leukocytosis (25%). Olutasidenib (Rezlidhia) therapy led to 32% dose interruptions due to AE, 11% dose reductions, and 8% permanent discontinuation of the therapy. Differentiation syndrome is a unique adverse effect of IDH inhibitors, which affected 16% of trial subjects within day one or 18 months of therapy and accounted for one death. The prescribing information for olutasidenib (Rezlidhia) includes boxed warnings regarding the risk of fatal differentiation syndrome and additional warning of hepatotoxicity. At this time, the real-world safety profile of olutasidenib (Rezlidhia) remains largely unknown.

F. The NCCN guidelines for the treatment of AML recommend olutasidenib (Rezlidhia) for the treatment of R/R AML (Category 2A recommendation). Olutasidenib (Rezlidhia) may be considered an alternative to ivosidenib (Tibsovo). The current clinical data for olutasidenib (Rezlidhia) does not provide evidence of the superiority of this drug as compared to ivosidenib (Tibsovo). At this time, weighing in the evidence of efficacy, safety, cost and net health benefits, ivosidenib (Tibsovo) and olutasidenib (Rezlidhia) may be considered comparable treatment options for R/R AML.

Investigational or Not Medically Necessary Uses

I. Enasidenib (Idhifa) 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. Ivosidenib (Tibsovo) used in combination with another oncology therapy for relapsed or refractory AML and locally advanced or metastatic cholangiocarcinoma
   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.
III. 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.
IV. olutasidenib (Rezlidhia) used in combination with another oncology therapy for relapsed or refractory AML or for newly diagnosed AML
   A. olutasidenib (Rezlidhia) is currently FDA-approved for the treatment of R/R AML. Safety and efficacy of this drug for the treatment of newly diagnosed AML is not established
V. Olutasidenib (Rezlidhia) is currently being investigated in ongoing clinical trials in the settings of newly diagnosed AML, for the treatment of R/R AML in combination with hypomethylating agents (e.g., azacitidine), and for the treatment of myelodysplastic syndrome (MDS). However, clinical data from these trials are not available as of February 2023, and robust conclusions cannot be drawn with respect to potential of olutasidenib (Rezlidhia) as a treatment for these conditions.
VI. Chondrosarcomas
   A. Clinical trials currently ongoing and limited to proof-of-concept.
VII. 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

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11. National Comprehensive Cancer Network. Acute Myeloid Leukemia. NCCN. V 3.2022; January 12, 2023. Accessed February 6, 2023. https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy

Policy Name	Disease state
venetoclax (Venclexta®)	Newly diagnosed acute myeloid leukemia (AML)
azacitidine (Onureg®)	Acute Myeloid Leukemia (AML), maintenance treatment after first complete remission
glasdegib (DAURISMO®)	Newly diagnosed acute myeloid leukemia (AML)

Policy Implementation/Update:

Action and Summary of Changes	Date
Removed the requirement of contraindication/intolerance to Tibsovo prior to coverage of Rezlidhia for R/R AML. Current evidence of efficacy, safety, cost, and net health benefits indicates Tibsovo and Rezlidhia may be considered comparable treatment options for R/R AML.	03/2023
Update to include olutasidenib (Rezlidhia) for the new indication of R/R AML;	02/2023

Update to include expanded indication for ivosidenib (Tibsovo) plus azacitidine in newly diagnosed AML; updated supporting evidence; added related policies table.	11/2022
Update to include expanded indication for ivosidenib (Tibsovo) for cholangiocarcinoma; updated supporting evidence; added split fill requirement for Tibsovo.	10/2021
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