IDH Inhibitors

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCCO123

Description

Ivosidenib (Tibsovo) and olutasidenib (Rezlidhia) inhibit the isocitrate dehydrogenase 1 (IDH-1) enzyme, limitingthe 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), 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. Vorasidenib (Voranigo) is a dual inhibitor of both IDH-1 and IDH-2.

Length of Authorization

- Initial:
  - enasidenib (Idhifa): Six months
  - ivosidenib (Tibsovo) and olutasidenib (Rezlidhia): Six months; Split fill first three months
  - vorasidenib (Voranigo): 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
enasidenib (Idhifa)	Acute myeloid leukemia, relapsed/refractory	50 mg tablets	30 tablets/30 days
		100 mg tablets	
ivosidenib (Tibsovo)	Acute myeloid leukemia, relapsed/refractory Acute myeloid leukemia, newly diagnosed Cholangiocarcinoma, advanced/ metastatic Myelodysplastic syndromes, relapsed/refractory	250 mg capsule	60 capsules/30 days
olutasidenib (Rezlidhia)	Acute myeloid leukemia, relapsed/refractory	150 mg capsule	60 capsules/30 days
vorasidenib (Voranigo)	Grade 2 IDH-mutant diffuse glioma (i.e., oligodendroglioma or astrocytoma)	40 mg tablet	30 tablets/30 days
		10 mg tablet	60 tablets/30 days

Initial Evaluation

I. **Enasidenib (Idhifa)**, **ivosidenib (Tibsovo), olutasidenib (Rezlidhia)**, and **vorasidenib (Voranigo)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **OR**
   B. Member is 12 years of age or older; **AND**
      1. Request is for vorasidenib (Voranigo); **AND**
   C. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
   D. The member has not previously progressed on or after an isocitrate dehydrogenase (IDH) inhibitor [e.g., ivosidenib (Tibsovo), olutasidenib (Rezlidhia), enasidenib (Idhifa), vorasidenib (Voranigo)]; **AND**
   E. 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 <u>one</u> 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. **<u>Newly</u> 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**
         iii. 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**
         iv. Request is for ivosidenib (Tibsovo); **AND**
            a. Treatment will <u>not</u> be used in combination with other oncologic agents (i.e., as monotherapy); **OR**
            b. Treatment will be used in combination with injectable azacitidine; **OR**
      3. **Locally advanced or metastatic cholangiocarcinoma; AND**
         i. Request is for ivosidenib (Tibsovo); **AND**
         ii. Ivosidenib (Tibsovo) will not be used in combination with other oncologic agents (i.e., as monotherapy); **AND**

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

4. Relapsed or refractory myelodysplastic syndromes (MDS); AND
i. Request is for ivosidenib (Tibsovo); **AND**
ii. Ivosidenib (Tibsovo) will not be used in combination with other oncologic agents (i.e., as monotherapy); **AND**
iii. Documentation 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., azacitidine, decitabine, cedazuridine, lenalidomide); **AND**
v. Attestation member is not eligible for currently enrolling clinical trials; **OR**

5. **IDH-mutant diffuse glioma; AND**
i. Request is for vorasidenib (Voranigo); **AND**
ii. Documentation of an *IDH1* or *IDH2* mutation; **AND**
iii. Documentation member has Grade 2 astrocytoma (without 1p/19q codeletion); **OR**
a. Documentation member has Grade 2 oligodendroglioma (1p/19q-codeleted); **AND**
iv. Member has residual or recurrent tumor after surgery including biopsy, sub-total resection, or gross total resection; **AND**
v. Provider attestation of a Karnofsky performance status (KPS) of greater than or equal to 60 (i.e., able to live at home and care for most personal needs with varying amounts of assistance); **AND**
vi. Member has <u>not</u> undergone treatments with prior anticancer therapies (e.g., radiation therapy, chemotherapy) for the treatment of glioma.

II. Enasidenib (Idhifa), ivosidenib (Tibsovo), olutasidenib (Rezlidhia), and/or vorasidenib (Voranigo) are considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
A. When used in combination with oncology therapies not specifically detailed above
B. Advanced cholangiocarcinoma without IDH-1 mutation
C. Chondrosarcomas
D. Myelodysplastic Syndrome (MDS) (therapies other than ivosidenib (Tibsovo))
E. Vorasidenib (Voranigo) used in those with a poor performance status (Karnofsky PS <60)
F. Recurrent or Progressive Enhancing IDH-1 Mutant Glioma following treatment with other anti-cancer therapies (e.g., radiation therapy, chemotherapy)
G. Acute myeloid leukemia (newly diagnosed or relapsed/refractory)
H. IDH-mutant Grade 3 diffuse glioma

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, exhibited tumor response, no new T2 or FLAIR abnormalities, no new enhancement, stability of Karnofsky performance status)

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, myelodysplastic syndromes, cholangiocarcinomas, and gliomas 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.

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. The National Comprehensive Cancer Network (NCCN) Guidelines preferred therapies for the treatment of recurrent/relapse AML include the following: clinical trial, systemic chemotherapy, or allogenic hematopoietic stem cell transplant.

Ivosidenib (Tibsovo):

I. 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. 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 an 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.

II. 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. Complete response (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.

- 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]. Complete response (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.

III. 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.

- 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.

IV. Ivosidenib (Tibsovo) was studied in an ongoing Phase 1, open-label, single-arm, multicenter clinical trial of 18 adult patients with relapsed or refractory MDS with a susceptible IDH-1 mutation as detected by an FDA-approved test. Patients had a median age of 74 (range 61-84) and were treatment experienced, with chemotherapy (17% intensive chemotherapy vs 83% non-intensive chemotherapy). At the data cutoff, a CR of 38.9% was achieved with a median time to CR of 1.9 months (1.0 to 5.6 months). The median follow-up was 27.1 months (3.7 to 88.7 months) and median duration of exposure to ivosidenib (Tibsovo) was 8.3 months (3.3 to 78.8 months). Of the nine patients who were dependent on transfusions prior to initiation of therapy 6 (67%) became independent to RBC and platelet transfusions during the 56 days post-baseline.

- Fourteen patients (74%) were exposed to ivosidenib (Tibsovo for at least 6 months and 8 patients (42%) were exposed for at least 1 year. Serious adverse reactions in ≥ 5% included differentiation syndrome (11%), fatigue (5%), and rash (5%).
- NCCN guidelines currently recommend allo-HSCT, HMA-based therapies, high intensity chemo (induction), and clinical trial as standard therapies for MDS dependent on a patients IPSS-R score. For those who are progress or fail to respond Tibsovo (ivosidenib) is guideline recommended as a treatment option (Category 2A) for those with IDH1 mutation.

Olutasidenib (Rezlidhia):

I. 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.

II. Federal Drug Administration (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.

III. 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.

IV. 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. Complete response (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.

V. 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.

VI. 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.

Vorasidenib (Voranigo)

I. Efficacy and safety of vorasidenib (Voranigo) has not been studied in the pediatric population younger than 16 years old. However, there is access to vorasidenib (Voranigo) via an expanded access program for those aged 12 years and older. FDA approval for this agent is in patients ≥12 years old on the basis of additional population pharmacokinetic data demonstrating that age had no clinically meaningful effect on the pharmacokinetics of vorasidenib (Voranigo).

II. The INDIGO clinical program studied vorasidenib (Voranigo) as a monotherapy for the treatment of Grade 2 IDH-mutant diffuse glioma (i.e., oligodendroglioma or astrocytoma). Participants in the clinical trial did not have any prior exposure to other anticancer agents for glioma.

III. Vorasidenib (Voranigo) was studied in a Phase 3, double-blind, placebo-controlled trial of 331 patients with IDH mutated residual or recurrent histologically confirmed Grade 2 oligodendroglioma or astrocytoma. All patients underwent surgery and had a measurable non-enhancing target lesion. Those with other prior anti-cancer treatments, including corticosteroids, were excluded.
    - Gliomas that have a mutation in *IDH1* or *IDH2* and an unbalanced translocation between chromosomes 1 and 19 (1p/19q-codeleted) are defined as oligodendrogliomas, whereas IDH-mutant gliomas without 1p/19q codeletion are defined as astrocytomas.

IV. All participants in the INDIGO trial were required to have a Karnofsky performance status (KPS) score of at least 80 (0-100 with lower scores indicating greater disability). NCCN guidelines recommend those with a score greater than, or equal to, 60 as eligible for watchful waiting. A score of less than 60 indicates poor performance status where watchful waiting is not indicated. Use of vorasidenib (Voranigo) outside of a population with good performance status has not been evaluated in clinical trials.

V. The trial population had a slight male majority (1.3:1), with age ranging from 16 to 71 years (median ~40 years). More than half of patients (53%) had Karnofsky performance status of 100 at baseline, indicating no signs or symptoms of disease. Most patients were IDH1 positive (95%), while a minority were IDH2 positive (5%), and the most common IDH1 mutation was R132H (86%), oligodendroglioma (52%), and astrocytoma (48%). All patients had undergone brain tumor surgery previously, with 21.5% of the patients having undergone two or more tumor surgeries before enrollment. The median interval between the last glioma surgery and randomization was 2.4 years.

VI. Patients were randomized 1:1 to vorasidenib (Voranigo) or placebo. The trial ended early per an observation of vorasidenib (Voranigo) demonstrating a benefit compared to placebo. The primary outcome measure was progression free survival (PFS) 27.7 months (17.0 to NE) vorasidenib (Voranigo) compared to placebo 11.1 months (11.0 to 13.7) [HR 0.39 (95% CI, 0.27 to 0.56; P<0.001)]. Key secondary endpoints included time to next intervention (TTNI) which was not reached for the vorasidenib (Voranigo) arm as compared to 17.8 months for placebo [HR 0.26 (95% CI, 0.15 to 0.43; P<0.001)].

VII. The results of the INDIGO clinical trial showed vorasidenib (Voranigo) significantly improved both imaging-based PFS, as compared with placebo, among patients who were considered to be candidates for watchful waiting. Progression free survival (PFS) and TTNI endpoints reported statistically significant differences in favor of vorasidenib (Voranigo). Time to next intervention (TTNI) has not been reached for the vorasidenib (Voranigo) group, though the proportion of patients not requiring next intervention at 24 months showed a stark difference between the treatment groups with 83.4% of patients in the vorasidenib (Voranigo) arm not requiring next therapy as compared to 27% of the placebo arm. Additionally, overall response was also in favor of vorasidenib (Voranigo). However, the number of patients achieving a partial or minor

response were low and those achieving stable disease were comparable, 82.7% vs 88.3% in the vorasidineb (Voranigo) and placebo groups respectively.

VIII. Patients with diffuse LGG may have image-based progression (<25% increase of the lesion) but choose to continue therapy in the absence of symptoms of clinical deterioration. Continued use of vorasidineb (Voranigo) in the presence of imaged-based progression may be clinically appropriate when clinical symptoms are stabilized. Clinical judgement should be exercised.

- Progression per RANO-LGG is defined as any of the following: (1) development of new lesions or increase of enhancement (radiological evidence of malignant transformation); (2) a 25% increase of the T2 or FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy, not attributable to radiation effect or to comorbid events; (3) definite clinical deterioration not attributable to other causes apart from the tumor, or decrease in corticosteroid dose; or (4) failure to return for evaluation because of death or deteriorating condition, unless caused by documented non-related disorders.
- The present RANO criteria for high-grade glioma that are recommended for a definition of clinical deterioration are a decrease in the Karnofsky performance score (KPS) from 100 or 90 to 70 or less, a decrease in KPS of at least 20 from 80 or less, or a decrease in KPS from any baseline to 50 or less, for at least 7 days. These definitions may be extrapolated to low-grade gliomas to assess the efficacy of therapy and progression to clinical deterioration.

Investigational or Not Medically Necessary Uses

I. Enasidenib (Idhifa), ivosidenib (Tibsovo), olutasidenib (Rezlidhia), or vorasidenib (Voranigo) used in combination with oncology therapies not specifically detailed above
   A. Current clinical trial data leading to FDA approval are in the monotherapy setting [with the exception of ivosidenib (Tibsovo) in combination with azacitidine]. Safety and efficacy have not been established for specific combination regimens.
   B. 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.
   C. Vorasidenib (Voranigo) is currently being investigated in ongoing clinical trials in combination with pembrolizumab (Keytruda) for the treatment of recurrent or progressive Grade 2 or Grade 3 IDHm gliomas following prior treatment with chemotherapy, radiation or both. Additionally, vorasidenib (Voranigo) in combination with temozolomide is under investigation for the treatment of Grade 2, 3 or 4 IDHm gliomas. However, trial results are not available as of October 2024 and safety and efficacy has not been established for use in these 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) (therapies other than ivosidenib (Tibsovo))
    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 enasidenib (Idhifa) and olutasidenib (Rezlidhia) for the treatment of MDS.
V. Vorasidenib (Voranigo) used in those with a poor performance status (Karnofsky PS <60)
    A. All participants in the INDIGO trial were required to have a Karnofsky performance status score of at least 80 (0-100 with lower scores indicating greater disability). NCCN guidelines recommend those with a score greater than or equal to 60 as eligible for watchful waiting. A score of less than 60 indicates poor performance status where watchful waiting is not indicated per NCCN recommendations. Use of vorasidenib (Voranigo) outside of a population with good performance status has not been evaluated in clinical trials.
VI. Recurrent or Progressive Enhancing IDH-1 Mutant Glioma following treatment with other anti-cancer therapies
    A. Clinical trials are being conducted in patients with grade 2 or 3 astrocytoma having received prior treatment with chemotherapy, radiation, or both. There is currently insufficient evidence to support the safety and efficacy of Vorasidenib (Voranigo) for the treatment of recurrent or progressive disease following treatment with other anti-cancer therapies.
VII. Acute myeloid leukemia (newly diagnosed or relapsed/refractory)
    A. Clinical trials are being conducted in patients with newly diagnosed AML and R/R AML. There is currently insufficient evidence to support the safety and efficacy of Vorasidenib (Voranigo) for the treatment of AML.
VIII. IDH-mutant Grade 3 diffuse glioma
    A. There is currently insufficient evidence to support the safety and efficacy of Vorasidenib (Voranigo) for the treatment of Grade 3 diffuse gliomas. Use of vorasidenib (Voranigo) outside of a population with Grade 2 disease has not been studied.

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

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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)
decitabine/cedazuridine (Inqovi™)	Myelodysplastic Syndrome (MDS)
	Chronic myelomonocytic leukemia (CMML)
lenalidomide (Revlimid®), pomalidomide (Pomalyst®), thalidomide (Thalomid®)	Follicular lymphoma
	Marginal zone lymphoma
	Multiple myeloma
	Myelodysplastic syndromes
	Mantle cell lymphoma
	Erythema Nodosum Leprosum

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated to include vorasidenib (Voranigo) for the treatment of Grade 2 IDH-mutant oligodendrogliomas or astraocytomas. Updated E/I criteria to incorporate new to market medication.	11/2024
Update to include expanded indication for ivosidenib (Tibsovo) in R/R MDS and updated formatting of supporting evidence.	03/2024
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