CLINICAL GUIDELINES FOR MEDICAL NECESSITY

MEDICAL POLICY

Ivosidenib (Tibsovo®)

Version: 1.0

EFFECTIVE DATE: 1/1/2025

NantHealth® | Eviti®

Please note the following:

Ivosidenib (Tibsovo®)

Note: For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Please refer to the CMS website at http://www.cms.gov for additional information.

Note: For Medicaid members/enrollees, circumstances when state Medicaid coverage provisions conflict with the coverage provisions within this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Ivosidenib (Tibsovo): Discussion

Ivosidenib inhibits the mutated form of the isocitrate dehydrogenase 1 (IDH1) enzyme. Normal IDH1 is important for cell metabolism, converting isocitrate into α-ketoglutarate (α-KG) and CO_2. When IDH1 is mutated (mIDH1), it changes function and instead converts α-KG into a harmful substance called 2-hydroxyglutarate (2-HG), while also reducing NADPH (nicotinamide adenine dinucleotide phosphate hydrogen). 2-HG prevents cells from maturing properly and can lead to cancer.[1]

Ivosidenib has severe adverse reactions depending on the cancer type. The most common adverse reactions in patients with acute myeloid leukemia (AML) are leukocyte decrease diarrhea, hemoglobin decrease, platelet decrease, glucose increase, and fatigue. In patients with relapsed or refractory myelodysplastic syndromes (MDS), the most common adverse reactions are creatinine increase, hemoglobin decrease, arthralgia, albumin decrease, aspartate aminotransferase increase, fatigue, diarrhea, and cough. In patients with cholangiocarcinoma, the most common adverse reactions are fatigue, nausea, abdominal pain, diarrhea, cough, decreased appetite, ascites, vomiting, anemia, and rash.

Ivosidenib is approved by the Food and Drug Administration (FDA) for acute myeloid leukemia (AML), MDS, and cholangiocarcinoma.[2]

The National Comprehensive Cancer Network (NCCN) endorses ivosidenib for the following cancer types: biliary tract, bone, central nervous system, AML, and MDS.[3,4,5,6,7]

Ivosidenib: Definitions

- **National Comprehensive Cancer Network (NCCN)** - An alliance of more than 30 leading cancer centers devoted to patient care, research, and education. The NCCN guidelines are utilized for Radiation Therapy and Medical Oncology standards. NCCN consensus clinical standards are periodically updated and NantHealth, Inc. reviews these and updates its policies within a timely manner.
- **Food and Drug Administration (FDA)** - The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.

- **Revised-International Prognostic Scoring System (IPSS-R)** - An important standard for assessing the prognosis of primary untreated adult patients with myelodysplastic syndromes (MDS). To refine the IPSS, MDS patient databases from international institutions were merged to assemble a much larger combined database for analysis, hence the revised IPSS (IPSS-R).[8]

Ivosidenib: Policy

Note: Coverage of ivosidenib will be provided for an FDA-approved indication or National Comprehensive Cancer Network (NCCN) guidelines when it is a Category 1, 2A, or 2B recommendation or when all criteria are met.

Ivosidenib will be considered for coverage when the following criteria are met:

Acute Myeloid Leukemia (AML)

1. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

2. At least 75 years of age; AND
3. Monotherapy or in combination with azacitidine for newly diagnosed patients, or those with comorbidities that preclude the use of intensive induction chemotherapy; OR
4. Relapsed or refractory[2]; OR

For **NCCN** required criteria coverage:

5. At least 18 years of age; AND
6. Single agent or in combination with azacitidine in IDH1-mutation for one of the following:
   a) Lower intensity induction treatment when not a candidate for intensive induction therapy or if the patient declines treatment
   b) Post induction therapy after the response to previous lower intensity therapy with the same regimen
   c) Consolidation therapy as a continued low-intensity regimen used for induction for one of the following:
      i. Poor risk AML (with and without tp53-mutation or del17p abnormality),
      ii. Therapy-related AML other than core-binding factor acute myeloid leukemia (CBF-AML),
      iii. Antecedent myelodysplastic syndromes /chronic myelomonocytic leukemia (MDS/CMML), or
      iv. Cytogenetic changes consistent with MDS (AML-MRC); OR

Note: Patients with disease progression to AML from MDS after significant exposure to hypomethylating agents (HMAs) may be less likely to derive benefit from continued treatment with HMAs compared to patients who are HMA-naive. Alternative treatment strategies should be considered.

7. Relapsed or refractory disease with IDH1-mutation for one of the following:
   a) Component of repeating the initial successful induction regimen if ≥12 months have passed since the induction regimen, which was not administered continuously and did not stop due to the development of clinical resistance
   b) Single agent.[3]

Biliary Tract Cancers - Intrahepatic/Extrahepatic Cholangiocarcinoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. Locally advanced or metastatic disease who have been previously treated[2]; OR

For **NCCN** required criteria coverage:

4. Subsequent-line treatment as a single agent for progression on or after systemic treatment for unresectable or resected gross residual (R2) disease, or metastatic disease with an isocitrate dehydrogenase-1 (IDH1) mutation.[4]

Chondrosarcoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Conventional (grades 1-3) disease and a susceptible IDH1 mutation; OR
4. Dedifferentiated disease and a susceptible IDH1 mutation.[5]

Central Nervous System Cancers - Adult Glioma

Oligodendroglioma - IDH-mutant, 1p19q codeleted/IDH-mutant Astrocytoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Single agent as an adjuvant treatment of IDH1 mutant, 1p19q codeleted, WHO grade 2 oligodendroglioma for one of the following:
   a) Residual or recurrent tumor after resection or biopsy and upfront treatment with radiation therapy (RT) and chemotherapy is not preferred if a good Karnofsky Performance Status (KPS) ≥ 60
   b) If a poor KPS <60; OR

4. Single agent for recurrent or progressive IDH1 mutant, 1p19q codeleted oligodendroglioma if (KPS) ≥ 60 for one of the following:
   a) WHO grade 2 disease after RT + chemotherapy
   b) WHO grade 3 disease.[6]

Myelodysplastic Syndromes

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. Relapsed or refractory disease[2]; OR,

For **NCCN** required criteria coverage:

4. Lower risk disease if mIDH1 associated with clinically relevant thrombocytopenia or neutropenia following disease progression or no response to or relapse after, for one of the following:
   a) Azacitidine or decitabine
   b) Immunosuppressive therapy (+/- eltrombopag)
   c) Immunosuppressive therapy (+/- eltrombopag) followed by azacitidine or decitabine; OR
5. Lower risk disease if mIDH1 associated with symptomatic anemia with del (5q), with or without one other cytogenetic abnormality (except those involving chromosome 7) following no response to or relapse after either lenalidomide or an erythropoiesis-stimulating agent (ESA) followed by no response to or intolerance or relapse after one of the following:
   a) Either azacitidine, decitabine, imetelstat, or lenalidomide (if not already received) if poor probability to respond to immunosuppressive therapy (IST)
   b) IST followed by no response to or intolerance or relapse after either azacitidine, decitabine, imetelstat, or lenalidomide (if not already received); OR
6. Lower risk disease if mIDH1 associated with symptomatic anemia with no del(5q), with or without other cytogenetic abnormalities with ring sideroblasts <15% (or ring sideroblasts <5% with an SF3B1 mutation), with serum erythropoietin for one of the following:
   a) ≤500 mU/mL following no response to (despite adequate iron stores) or relapse after either an ESA alone or luspatercept-aamt, followed by no response to or relapse after either an ESA with or without either lenalidomide or a granulocyte-colony stimulating factor (G-CSF), or to imetelstat, or to luspatercept-aamt alone
   b) >500 mU/mL following no response to or intolerance or relapse after either azacitidine, decitabine, imetelstat, or lenalidomide
   c) ≤500 mU/mL following no response to (despite adequate irons stores) or relapse after either an ESA alone or luspatercept-aamt, followed by no response to or relapse after either an ESA with or without either lenalidomide or a G-CSF, or to imetelstat, or to luspatercept-aamt alone (if not previously used) followed by no response to or intolerance or relapse after either azacitidine, decitabine, imetelstat (if not previously used), or lenalidomide (if not already receiving)

d) >500 mU/mL following no response to or intolerance or relapse after immunosuppressive therapy followed by no response to or intolerance or relapse after either azacitidine, decitabine, imetelstat, or lenalidomide; OR

7. Lower risk disease if mIDH1 associated with symptomatic anemia with no del (5q), with or without other cytogenetic abnormalities with ring sideroblasts ≥15% (or ring sideroblasts ≥5% with an SF3B1 mutation), with serum erythropoietin for one of the following:
   a) ≤500 mU/mL following no response to or relapse after luspatercept-aamt, followed by no response to or relapse after either imetelstat or an ESA with or without G-CSF
   b) >500 mU/mL following no response to or relapse after luspatercept-aamt followed by no response to or relapse after either imetelstat or lenalidomide
   c) ≤500 mU/mL following no response to or relapse after luspatercept-aamt, followed by no response to or relapse after either imetelstat or an ESA with or without a G-CSF followed by no response to or intolerance or relapse after either azacitidine, decitabine, imetelstat (if not previously used), or lenalidomide
   d) >500 mU/mL following no response to or relapse after luspatercept-aamt followed by no response to or relapse after either imetelstat or lenalidomide followed by no response to or intolerance or relapse after either azacitidine, decitabine, imetelstat (if not previously used), or lenalidomide (if not previously used)
   e) After no response to or relapse after imetelstat followed by no response to or relapse after either lenalidomide or luspatercept-aamt
   f) After no response to or relapse after imetelstat followed by no response to or relapse after either lenalidomide or luspatercept-aamt, followed by no response to or intolerance or relapse after either azacitidine, decitabine, or lenalidomide (if not previously used); OR
8. Higher risk disease if mIDH1 in transplant candidates for one of the following:
   a) Initial treatment in combination with azacitidine followed by allogeneic hematopoietic cell transplant (allo-HCT)
   b) Single agent followed by allo-HCT and no response to initial treatment with either azacitidine +/- venetoclax, decitabine +/- venetoclax, or high-intensity chemotherapy; OR
9. Higher risk disease in nontransplant candidates if mIDH1 for one of the following:
   a) Initial treatment as a single agent or in combination with azacitidine
   b) Single agent if no response to or intolerance or relapse after initial treatment if an IDH1 inhibitor not previously used.[7]

Authorization Period and Renewal Criteria

1. Initial Authorization Period: 12 months
2. Renewal Criteria: No evidence of disease progression or unacceptable toxicity
3. Renewal Authorization Period: 12 months

Ivosidenib: References

1. Watts, J.M. Looking Beyond the Surface: Olutasidenib and Ivosidenib for Treatment of mIDH1 Acute Myeloid Leukemia. https://link.springer.com/article/10.1007/s11864-024-01264-7#citeas. Accessed December 12, 2024.
2. Ivosidenib Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/211192s011lbl.pdf. Accessed January 16, 2025.
3. National Comprehensive Cancer Network. Acute Myeloid Leukemia. https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf. Accessed December 12, 2024.
4. National Comprehensive Cancer Network. Biliary Tract Cancers. https://www.nccn.org/professionals/physician_gls/pdf/btc.pdf. Accessed December 12, 2024.
5. National Comprehensive Cancer Network. Bone Cancer. https://www.nccn.org/professionals/physician_gls/pdf/bone.pdf. Accessed December 12, 2024.
6. National Comprehensive Cancer Network. Central Nervous Cancers. https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed December 12, 2024.
7. National Comprehensive Cancer Network. Myelodysplastic Syndromes. https://www.nccn.org/professionals/physician_gls/pdf/mds.pdf. Accessed December 12, 2024.
8. Greenberg PL et al. Revised international prognostic scoring system for myelodysplastic syndromes. https://pmc.ncbi.nlm.nih.gov/articles/PMC4425443/. Accessed January 16, 2025.

Ivosidenib: Coding (CPT®, ICD 10, and HCPCS) *

*Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all-inclusive and is subject to updates. In addition, the codes listed are not a guarantee of payment. CPT codes are available through the AMA.

Code	Description
C22.1	Intrahepatic cholangiocarcinoma
C24.0	Extrahepatic cholangiocarcinoma
C41.9	Chondrosarcoma
C71.1	Oligodendroglioma
C71.9	Astrocytoma

C92.9	Acute myeloid leukemia
D46.9	Myelodysplastic syndromes
J8999, C9399	Ivosidenib

Ivosidenib: Revision and Review History

No.	Description	Date(s)
1	Original Effective Date:	1/1/2025
2	Policy Review Dates:	
3	Policy Revision Dates:	
4	Department Owner:	Medical Affairs
5	NH Advisory Committee:	1/24/2025
6	Revision Changes:	