Ivosidenib (TIBSOVO) 
National Drug Monograph Addendum (Draft) 
October 2021 
VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

• Ivosidenib is an isocitrate dehydrogenase (IDH1) inhibitor, targeting the IDH1 enzyme.
• Mutations in IDH1 are among the most common genetic alterations in cholangiocarcinoma.
• Preclinical trials have shown that inhibiting IDH1 mutations in cholangiocarcinoma blocks the conversion of α-ketoglutarate (αKG) to 2-hydroxyglutarate (2HG) which play a role in liver progenitor differentiation and proliferation.

Indication(s) Under Review in This Document

• Previously treated locally advanced or metastatic cholangiocarcinoma with the IDH1 mutation

Dosage Form(s) Under Review

• 250 mg tablets; Recommended dosage of ivosidenib is 500mg by mouth once daily until disease progression or unmanageable toxicity

Clinical Evidence Summary

Efficacy Considerations

• Efficacy data are summarized in Table 1

Table 1: Efficacy results from Abou-Alfa GK, et al.

<table>
<thead>
<tr>
<th>Study (Phase III)</th>
<th>Inclusion/Exclusion</th>
<th>Intervention/Patients</th>
<th>Outcomes</th>
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</table>
| Abou-Alfa GK, et al. Study AG120-C-005 NCT02989857 | **Inclusion**
  - Age ≥ 18 years old
  - Histopathological diagnosis of nonresectable or metastatic cholangiocarcinoma not eligible for curative resection, transplantation, or ablative therapies
  - Documented IDH1 gene mutated disease
  - ECOG PS 0 to 1
  - Subjects who have received prior local therapy (including but not limited to embolization, chemoembolization, radiofrequency ablation, or radiation therapy) are eligible provided measurable | **Intervention**
  - Ivosidenib 500 mg or placebo PO QD in continuous 28-day cycles
  - Total N=185, randomized 2:1 ivosidenib (N=124) vs placebo (N=61) | **Primary Outcome**
  - Median PFS: 2.7 months
  - HR 0.37; 95% CI 0.25-0.54; p<0.0001 |
| **Secondary Outcomes**
  - PFS at 6 months
  - 32% at 6 months
  - 22% at 12 months
  - Median OS: 10.8 months |

Funded by Agios Pharmaceuticals
### Key components of Phase III Study Abou-Alfa GK, et al.

- **Design**: Randomized, double-blind, placebo-controlled, phase 3 multicenter study
- **Patients**: Locally advanced or metastatic cholangiocarcinoma with the IDH1 mutation, age ≥ 18 years old, ECOG PS score of 0 to 1, previously received at least 1 gemcitabine- or 5-FU-containing treatment regimen
- **Intervention**: Ivosidenib 500 mg or placebo PO QD in continuous 28-day cycles until disease progression, development of unacceptable toxicity, confirmed pregnancy, death, until subject withdraws consent, is lost to follow-up, whichever occurs first

<table>
<thead>
<tr>
<th>ECOG PS</th>
<th>HR 0.69; 95% CI 0.44-1.10; p = 0.06</th>
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<td>0 (40%)</td>
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<td>1 (60%)</td>
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<tr>
<th>IHD1 mutation type</th>
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<td>R132C (68%)</td>
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<th>Extent of disease at screening</th>
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<td>Metastatic disease (93%)</td>
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<th>Cholangiocarcinoma type at diagnosis</th>
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<td>Intrahepatic (90%)</td>
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### Exclusion

- Received prior IDH1 inhibitor
- Known symptomatic brain metastases requiring steroids
- Pregnant or breastfeeding
- Taking known strong CYP450 CYP3A4 inducers or sensitive to CYP3A4 substrate medications with a narrow therapeutic window, unless they can be transferred to other medications within ≥ 5 half-lives prior to dosing
- Active infection requiring systemic anti-infective therapy or an unexplained fever > 38.5°C within 7 days of Day 1
- Significant active cardiac disease within 6 months prior to start of study treatment, a heart-rate corrected QT interval ≥450 msec or other factors that increase risk of QT prolongation or arrhythmic events
- Known active HBV or HCV, positive HIV antibody results, or AIDS-related illness; subjects with sustained viral response to HCV treatment or immunity to prior HBV infection permitted; subjects with chronic HBV that is adequately suppressed will be permitted

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**ECOG** = Eastern Cooperative Oncology Group; **PS** = performance status; **RECIST**: response evaluation criteria in solid tumor; **PFS** = progression free survival, **OS** = overall survival, **CV** = cardiovascular; **HR** = hazard ratio, **CI** = confidence interval, **SCR** = serum creatinine, **CrCl** = creatinine clearance, **ULN** = upper limit of normal, **ANC** = absolute neutrophil count, **Hgb** = hemoglobin, **AST/ALT** = aspartate transaminase/alanine transaminase, **Hepatitis B** = HBV, **hepatitis C** = HCV, **HIV** = human immunodeficiency virus, **AIDS** = acquired immunodeficiency syndrome, **PO** = by mouth, **QD** = once daily
Placebo to ivosidenib crossover was permitted on radiological progression per investigator assessment

- **Outcomes:**
  - Primary endpoint: PFS by the central IRC based on RECIST v1.1
    - Median PFS ivosidenib 2.7 months vs placebo 1.4 months [HR 0.37; 95% CI 0.25-0.54; one-sided p<0.0001]
      - Ivosidenib PFS: 6 months = 32%; 12 months = 22%
      - No patients in the placebo group were free from progression ≥ 6 months
  - Secondary endpoints:
    - Median OS ivosidenib 10.8 months vs placebo 9.7 months for placebo group [HR 0.69; 95% CI 0.44-1.1; p=0.06]
- **Limitations:** Treatment effect estimate on the primary analysis of OS was likely confounded by allowance of crossover
  - Despite limitation, median PFS was still significantly higher than placebo

### Safety Considerations

- Highlights of safety data can be found in Table 2

#### Table 2: Safety Results from Clinical Trial

<table>
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<th>Study (Phase III)</th>
<th>Safety Results</th>
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</table>
| NCT02989857, Study AG120-C-005 | N = 185  
Median duration of treatment 2.6 months (IQR 1.4-6.0)  
Most common AEs grade 1-2: nausea (33%), diarrhea (31%), fatigue (23%), cough (21%), abdominal pain (19%), decreased appetite (17%), vomiting (17%), ascites (13%), asthenia (12%), constipation (12%), pyrexia (12%)  
Most common AEs ≥ grade 3: ascites (7%), blood bilirubin (6%), aspartate aminotransferase increased (5%), anemia (3%), fatigue (3%), hyponatremia (3%)  
1 DC due generalized oedema; 1 DC due to hyperbilirubinemia |

AE = adverse events, DC = discontinuation

- **Key components of Phase III Study Abou-Alfa GK, et al.**
  - Overall ivosidenib was well tolerated with majority of AEs being Grade 1 or 2; most common AEs were nausea, low-grade diarrhea, and fatigue
  - AEs leading to death (not related to study-drug) 6 patients total, including 2 crossover patients; Included pneumonia, sepsis, intestinal obstruction, pulmonary embolism, hepatic cirrhosis, intestinal pseudo-obstruction
  - Dose reduction or discontinuation were uncommon secondary to AEs
    - Dose reduction 4 of 121 (3%) received ivosidenib versus none receiving placebo
    - Treatment discontinuation 7 of 121 patients receiving ivosidenib vs. 5 receiving placebo

- **Contraindications:** None

- **Other warnings/precautions:**
  QT-prolongation and ventricular arrhythmias – avoid populations at risk; monitor closely
  Guillain-Barré syndrome - rare occurrence
Projected Place in Therapy

- IDH1/2 mutations occur in 10% to 23% of intrahepatic cholangiocarcinomas.
- The prognostic effect of this mutation in intrahepatic cholangiocarcinoma is uncertain, but the IDH1 mutation which accounts for 0.8% of patients with extrahepatic cholangiocarcinoma is associated with poor prognosis.
- Treatment options for patients who have progressive disease on fluoropyrimidine- and gemcitabine-based regimens are limited. As such, ivosidenib would be a reasonable option for patients with the IDH1 mutation who have progressed after receiving these prior regimens.
- Overall, therapy appeared to be well-tolerated; AEs of interest include fatigue, ascites, and QT prolongation.
- Per NCCN v5.2021, ivosidenib is included as a subsequent-line treatment option “useful in certain circumstances” for unresectable or metastatic cholangiocarcinoma with IDH1 mutations following disease progression.4

References


