## HIGHLIGHTS OF PRESCRIBING INFORMATION

**These highlights do not include all the information needed to use TIBSOVO safely and effectively. See full prescribing information for TIBSOVO.**

**TIBSOVO® (ivosidenib tablets), for oral use**
**Initial U.S. Approval: 2018**

**WARNING: DIFFERENTIATION SYNDROME IN AML**

***See full prescribing information for complete boxed warning.***

**Patients treated with TIBSOVO have experienced symptoms of differentiation syndrome, which can be fatal. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution (5.1, 6.1).**

**----------RECENT MAJOR CHANGES----------**

| | |
|---|---|
| Indications and Usage (1.1) | 5/2022 |
| Indications and Usage (1.3) | 8/2021 |
| Dosage and Administration (2.2) | 5/2022 |

**----------INDICATIONS AND USAGE----------**

TIBSOVO is an isocitrate dehydrogenase-1 (IDH1) inhibitor indicated for patients with a susceptible IDH1 mutation as detected by an FDA-approved test with:

Newly Diagnosed Acute Myeloid Leukemia (AML)

- In combination with azacitidine or as monotherapy for the treatment of newly diagnosed AML in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy (1.1).

Relapsed or refractory AML

- For the treatment of adult patients with relapsed or refractory AML (1.2).

Locally Advanced or Metastatic Cholangiocarcinoma

- For the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma who have been previously treated (1.3).

**----------DOSAGE AND ADMINISTRATION----------**

500 mg orally once daily with or without food until disease progression or unacceptable toxicity (2.2). Avoid a high-fat meal.

**----------DOSAGE FORMS AND STRENGTHS----------**

Tablets: 250 mg (3).

**----------CONTRAINDICATIONS----------**

None (4).

**----------WARNINGS AND PRECAUTIONS----------**

- QTc Interval Prolongation: Monitor electrocardiograms and electrolytes. If QTc interval prolongation occurs, dose reduce or withhold, then resume dose or permanently discontinue TIBSOVO (2.3, 5.2).
- Guillain-Barré Syndrome: Monitor patients for signs and symptoms of new motor and/or sensory findings. Permanently discontinue TIBSOVO in patients who are diagnosed with Guillain-Barré syndrome (2.3, 5.3).

**----------ADVERSE REACTIONS----------**

The most common adverse reactions including laboratory abnormalities (≥25%) in patients with AML are leukocytes decreased, diarrhea, hemoglobin decreased, platelets decreased, glucose increased, fatigue, alkaline phosphatase increased, edema, potassium decreased, nausea, vomiting, phosphate decreased, decreased appetite, sodium decreased, leukocytosis, magnesium decreased, aspartate aminotransferase increased, arthralgia, dyspnea, uric acid increased, abdominal pain, creatinine increased, mucositis, rash, electrocardiogram QT prolonged, differentiation syndrome, calcium decreased, neutrophils decreased, and myalgia (6.1).

The most common adverse reactions (≥15%) in patients with cholangiocarcinoma are fatigue, nausea, abdominal pain, diarrhea, cough, decreased appetite, ascites, vomiting, anemia, and rash (6.1).

The most common laboratory abnormalities (≥10%) in patients with cholangiocarcinoma are hemoglobin decreased, aspartate aminotransferase increased, and bilirubin increased (6.1).

**To report SUSPECTED ADVERSE REACTIONS, contact Servier Pharmaceuticals at 1-800-807-6124 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

**----------DRUG INTERACTIONS----------**

- Strong or Moderate CYP3A4 Inhibitors: Reduce TIBSOVO dose with strong CYP3A4 inhibitors. Monitor patients for increased risk of QTc interval prolongation (2.4, 5.2, 7.1, 12.3).
- Strong CYP3A4 Inducers: Avoid concomitant use with TIBSOVO (7.1, 12.3).
- Sensitive CYP3A4 substrates: Avoid concomitant use with TIBSOVO (7.2, 12.3).
- QTc Prolonging Drugs: Avoid concomitant use with TIBSOVO. If co-administration is unavoidable, monitor patients for increased risk of QTc interval prolongation (5.2, 7.1).

**----------USE IN SPECIFIC POPULATIONS----------**

Lactation: Advise women not to breastfeed (8.2).

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**

**Revised: 5/2022**

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**FULL PRESCRIBING INFORMATION: CONTENTS***



*Sections or subsections omitted from the full prescribing information are not listed

**FULL PRESCRIBING INFORMATION**

**WARNING: DIFFERENTIATION SYNDROME IN AML**

**Patients treated with TIBSOVO have experienced symptoms of differentiation syndrome, which can be fatal. Symptoms may include fever, dyspnea, hypoxia, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, hypotension, and hepatic, renal, or multi-organ dysfunction. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.**

# 1. INDICATIONS AND USAGE

## 1.1 Newly Diagnosed Acute Myeloid Leukemia

TIBSOVO is indicated in combination with azacitidine or as monotherapy for the treatment of newly diagnosed acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy *[see Dosage and Administration (2.1), Clinical Pharmacology (12.1) and Clinical Studies (14.1)]*.

## 1.2 Relapsed or Refractory Acute Myeloid Leukemia

TIBSOVO is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test *[see Dosage and Administration (2.1), Clinical Pharmacology (12.1) and Clinical Studies (14.2)]*.

## 1.3 Locally Advanced or Metastatic Cholangiocarcinoma

TIBSOVO is indicated for the treatment of adult patients with previously treated, locally advanced or metastatic cholangiocarcinoma with an isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test *[see Dosage and Administration (2.1), Clinical Pharmacology (12.1), and Clinical Studies (14.3)]*.

# 2 DOSAGE AND ADMINISTRATION

## 2.1 Patient Selection

Acute Myeloid Leukemia

Select patients for the treatment of AML with TIBSOVO based on the presence of IDH1 mutations in the blood or bone marrow *[see Clinical Studies (14.1)]*. Patients with AML without IDH1 mutations at diagnosis should be retested at relapse because a mutation in IDH1 may emerge during treatment and at relapse.

Locally Advanced or Metastatic Cholangiocarcinoma

Select patients for the treatment of locally advanced or metastatic cholangiocarcinoma with

TIBSOVO based on the presence of IDH1 mutations *[see Clinical Studies (14.3)]*.

Information on FDA-approved tests for the detection of IDH1 mutations in AML and cholangiocarcinoma is available at http://www.fda.gov/CompanionDiagnostics.

### 2.2 Recommended Dosage

Newly Diagnosed AML (Combination Regimen)

The recommended dosage of TIBSOVO is 500 mg taken orally once daily until disease progression or unacceptable toxicity. Start TIBSOVO administration on Cycle 1 Day 1 in combination with azacitidine 75 mg/m$^2$ subcutaneously or intravenously once daily on Days 1-7 (or Days 1-5 and 8-9) of each 28-day cycle *[see Clinical Studies (14.1)]*. Refer to the Prescribing Information for azacitidine for additional dosing information.

For patients without disease progression or unacceptable toxicity, continue TIBSOVO, in combination with azacitidine, for a minimum of 6 months to allow time for clinical response.

Newly Diagnosed AML and Relapsed or Refractory AML (Monotherapy Regimen)

The recommended dosage of TIBSOVO is 500 mg taken orally once daily until disease progression or unacceptable toxicity *[see Clinical Studies (14.1 and 14.2)]*.

For patients without disease progression or unacceptable toxicity, continue TIBSOVO for a minimum of 6 months to allow time for clinical response.

Cholangiocarcinoma

The recommended dosage of TIBSOVO is 500 mg taken orally once daily until disease progression or unacceptable toxicity [see Clinical Studies (14.3)].

Administer TIBSOVO with or without food. Do not administer TIBSOVO with a high-fat meal because of an increase in ivosidenib concentration *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*. Do not split, crush, or chew TIBSOVO tablets. Administer TIBSOVO tablets orally about the same time each day. If a dose of TIBSOVO is vomited, do not administer a replacement dose; wait until the next scheduled dose is due. If a dose of TIBSOVO is missed or not taken at the usual time, administer the dose as soon as possible and at least 12 hours prior to the next scheduled dose. Return to the normal schedule the following day. Do not administer 2 doses within 12 hours.

### 2.3 Monitoring and Dosage Modifications for Toxicities

Obtain an electrocardiogram (ECG) prior to treatment initiation. Monitor ECGs at least once weekly for the first 3 weeks of therapy and then at least once monthly for the duration of therapy. Manage any abnormalities promptly *[see Adverse Reactions (6.1)]*.

Interrupt dosing or reduce dose for toxicities. See Table 1 for dose modification guidelines.

**Table 1: Recommended Dosage Modifications for TIBSOVO**

| Adverse Reactions | Recommended Action |
|---|---|
| • Differentiation syndrome | • If differentiation syndrome is suspected, administer systemic corticosteroids and initiate hemodynamic monitoring until symptom resolution and for a |

| Adverse Reactions | Recommended Action |
|---|---|
| | minimum of 3 days *[see Warnings and Precautions (5.1)]*.<br>• Interrupt TIBSOVO if severe signs and/or symptoms persist for more than 48 hours after initiation of systemic corticosteroids *[see Warnings and Precautions (5.1)]*.<br>• Resume TIBSOVO when signs and symptoms improve to Grade 2* or lower. |
| • Noninfectious leukocytosis (white blood cell [WBC] count greater than 25 x $10^9$/L or an absolute increase in total WBC of greater than 15 x $10^9$/L from baseline) | • Initiate treatment with hydroxyurea, as per standard institutional practices, and leukapheresis if clinically indicated.<br>• Taper hydroxyurea only after leukocytosis improves or resolves.<br>• Interrupt TIBSOVO if leukocytosis is not improved with hydroxyurea, and then resume TIBSOVO at 500 mg daily when leukocytosis has resolved. |
| • QTc interval greater than 480 msec to 500 msec | • Monitor and supplement electrolyte levels as clinically indicated *[see Warnings and Precautions (5.2)]*.<br>• Review and adjust concomitant medications with known QTc interval-prolonging effects *[see Drug Interactions (7.1)]*.<br>• Interrupt TIBSOVO.<br>• Restart TIBSOVO at 500 mg once daily after the QTc interval returns to less than or equal to 480 msec.<br>• Monitor ECGs at least weekly for 2 weeks following resolution of QTc prolongation. |
| • QTc interval greater than 500 msec | • Monitor and supplement electrolyte levels as clinically indicated *[see Warnings and Precautions (5.2)]*.<br>• Review and adjust concomitant medications with known QTc interval-prolonging effects *[see Drug Interactions (7.1)]*.<br>• Interrupt TIBSOVO.<br>• Resume TIBSOVO at a reduced dose of 250 mg once daily when QTc interval returns to within 30 msec of baseline or less than or equal to 480 msec.<br>• Monitor ECGs at least weekly for 2 weeks following resolution of QTc prolongation.<br>• Consider re-escalating the dose of TIBSOVO to 500 mg daily if an alternative etiology for QTc prolongation can be identified. |

| Adverse Reactions | Recommended Action |
|---|---|
| • QTc interval prolongation with signs/symptoms of life-threatening arrhythmia | • Discontinue TIBSOVO permanently *[see Warnings and Precautions (5.2)]*. |
| • Guillain-Barré syndrome | • Discontinue TIBSOVO permanently *[see Warnings and Precautions (5.3)]*. |
| • Other Grade 3* adverse reactions | *AML monotherapy*:<br>• Interrupt TIBSOVO until toxicity resolves to Grade 2* or lower.<br>• Resume TIBSOVO at 250 mg once daily; may increase to 500 mg once daily if toxicities resolve to Grade 1* or lower.<br>• If Grade 3* or higher toxicity recurs, discontinue TIBSOVO.<br>*AML in combination with azacitidine, Cholangiocarcinoma*:<br>• Interrupt TIBSOVO until toxicity resolves to Grade 1* or lower, or baseline, then resume at 500 mg daily (Grade 3 toxicity) or 250 mg daily (Grade 4 toxicity).<br>• If Grade 3 toxicity recurs (a second time), reduce TIBSOVO dose to 250 mg daily until the toxicity resolves, then resume 500 mg daily.<br>• If Grade 3 toxicity recurs (a third time), or Grade 4 toxicity recurs, discontinue TIBSOVO. |

*Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, Grade 4 is life-threatening.

Patients with Acute Myeloid Leukemia

Assess blood counts and blood chemistries prior to the initiation of TIBSOVO, at least once weekly for the first month, once every other week for the second month, and once monthly for the duration of therapy. Monitor blood creatine phosphokinase weekly for the first month of therapy.

### 2.4 Dosage Modification for Use with Strong CYP3A4 Inhibitors

If a strong CYP3A4 inhibitor must be coadministered, reduce the TIBSOVO dose to 250 mg once daily. If the strong inhibitor is discontinued, increase the TIBSOVO dose (after at least 5 half-lives of the strong CYP3A4 inhibitor) to the recommended dose of 500 mg once daily.

## 3 DOSAGE FORMS AND STRENGTHS

Tablets: 250 mg as a blue oval-shaped film-coated tablet debossed “IVO” on one side and “250” on the other side.

## 4 CONTRAINDICATIONS

None.

DOCKET ALARM

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