TIBSOVO®
ivosidenib tablets 250mg

DOSING AND MANAGEMENT OF TIBSOVO® FOR TREATMENT OF m*IDH1* AML AND MDS

mIDH1, mutated IDH1.

INDICATIONS

TIBSOVO is indicated for patients with a susceptible isocitrate dehydrogenase-1 (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 the use of intensive induction chemotherapy

Relapsed or Refractory AML

- For the treatment of adult patients with relapsed or refractory AML

Relapsed or Refractory Myelodysplastic Syndromes (MDS)

- For the treatment of adult patients with relapsed or refractory MDS

IMPORTANT SAFETY INFORMATION

WARNING: DIFFERENTIATION SYNDROME IN AML AND MDS
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.

Please see additional Important Safety Information on pages 18 and 19 and Full Prescribing Information, including BOXED WARNING for AML and MDS patients.

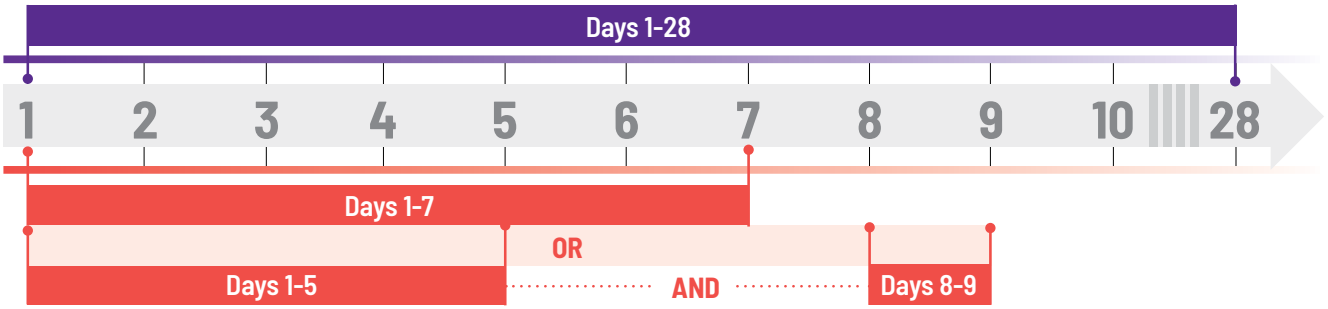
RECOMMENDED DOSING

TIBSOVO + azacitidine for the treatment of newly diagnosed AML

- 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

Dosing schedule for TIBSOVO + azacitidine

TIBSOVO 500 mg QD (approximately every 24 hours) orally



Azacitidine 75 mg/m^2/day SC or IV

TIBSOVO as monotherapy for the treatment of newly diagnosed AML, relapsed/refractory (R/R) AML, or R/R MDS

- The recommended dosage of TIBSOVO is 500 mg taken orally once daily until disease progression or unacceptable toxicity

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

Dosing and storage guidance

- TIBSOVO tablets should be taken orally at about the same time each day
- TIBSOVO can be taken with or without food but should not be taken with a high-fat meal (approximately 1000 calories and 58 grams of fat)
- TIBSOVO tablets should not be split, crushed, or chewed
- If a dose is vomited, patients should not take a replacement dose; they should wait until the next scheduled dose is due
- If a dose is missed or not taken at the usual time, patients should take the missed dose as soon as possible and at least 12 hours prior to the next scheduled dose. They should return to the normal schedule the following day. Patients should not take 2 doses within 12 hours
- Store TIBSOVO at room temperature from 20 to 25°C (68-77°F)
- Advise patients not to remove the desiccant canister from the bottle

Treatment with TIBSOVO has not been studied in patients with preexisting severe renal or hepatic impairment. For patients with preexisting severe renal or hepatic impairment, consider the risks and potential benefits before initiating treatment with TIBSOVO.

IV, intravenous; QD, once a day; SC, subcutaneous.

Please see additional Important Safety Information on pages 18 and 19 and Full Prescribing Information, including BOXED WARNING for AML and MDS patients.

TIBSOVO® ivosidenib tablets 250mg

DRUG-DRUG INTERACTIONS

Strong or moderate CYP3A4 inhibitors

- Coadministration increased ivosidenib plasma concentrations, which may increase the risk of QTc interval prolongation
- Consider alternative therapies that are not strong or moderate CYP3A4 inhibitors during treatment with TIBSOVO
- If coadministration of a strong CYP3A4 inhibitor is unavoidable, reduce TIBSOVO 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
- Monitor patients for increased risk of QTc interval prolongation

Strong CYP3A4 inducers

- Coadministration decreased ivosidenib plasma concentrations
- Avoid coadministration with TIBSOVO

QTc-prolonging drugs

- Coadministration may increase the risk of QTc interval prolongation
- Avoid coadministration with TIBSOVO or replace with alternative therapies
- If coadministration is unavoidable, monitor patients for increased risk of QTc interval prolongation

Effect of TIBSOVO on other drugs

- Ivosidenib induces CYP3A4 and may induce CYP2C9
- Coadministration will decrease concentrations of drugs that are sensitive CYP3A4 substrates and may decrease concentrations of drugs that are sensitive CYP2C9 substrates
- Use alternative therapies that are not sensitive substrates of CYP3A4 and CYP2C9 inhibitors during treatment with TIBSOVO
- If coadministration of TIBSOVO with sensitive CYP3A4 substrates or CYP2C9 substrates is unavoidable, monitor patients for loss of therapeutic effect of these drugs
- Do not administer TIBSOVO with anti-fungal agents that are substrates of CYP3A4 due to expected loss of antifungal efficacy
- Coadministration may decrease the concentrations of hormonal contraceptives. Consider alternative methods of contraception

CYP3A4, cytochrome P450 3A4; CYP2C9, cytochrome P450 2C9.

AML COMBINATION THERAPY: ADVERSE REACTIONS

TIBSOVO in combination with azacitidine for the treatment of newly diagnosed AML

The safety of TIBSOVO was studied in AML patients treated in combination with azacitidine (Study AG120-C-009)

- Patients received at least one dose of either TIBSOVO 500 mg daily (n=72) or placebo (n=74) in combination with azacitidine
- Median duration of exposure to TIBSOVO was 6 months (range, 0 to 33)
  - 34 patients (48%) were exposed to TIBSOVO for at least 6 months
  - 22 patients (31%) were exposed to TIBSOVO for at least 1 year
- Fatal adverse reactions occurred in 4% of patients due to differentiation syndrome (3%) and one case of cerebral ischemia

Adverse reactions (≥10%) in patients with AML who received TIBSOVO + azacitidine with a difference of ≥2% between arms compared with placebo + azacitidine

	TIBSOVO + azacitidine (n=71)		Placebo + azacitidine (n=73)	
Body system Adverse reaction	All grades	Grade ≥3[a]	All grades	Grade ≥3
Gastrointestinal disorders				
Nausea	42%	3%	38%	4%
Vomiting	41%	0	27%	1%
Investigations				
Electrocardiogram QT prolonged	20%	10%	7%	3%
Psychiatric disorders				
Insomnia	18%	1%	12%	0
Blood system and lymphatic system disorders				
Differentiation syndrome[b]	15%	10%	8%	8%
Leukocytosis	13%	0	1%	0
Vascular disorders				
Hematoma	15%	0	4%	0
Hypertension	13%	4%	8%	5%
Musculoskeletal and connective tissue disorders				
Arthralgia	30%	4%	8%	1%
Respiratory, thoracic, and mediastinal disorders				
Dyspnea	20%	3%	15%	5%
Nervous system disorders				
Headache	11%	0	3%	0

[a]Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, and Grade 4 is life-threatening.
[b]Differentiation syndrome can be associated with other commonly reported events such as peripheral edema, leukocytosis, pyrexia, dyspnea, pleural effusion, hypotension, hypoxia, pulmonary edema, pneumonia, pericardial effusion, rash, fluid overload, tumor lysis syndrome, and creatinine increased.

Please see additional Important Safety Information on pages 18 and 19 and Full Prescribing Information, including BOXED WARNING for AML and MDS patients.

AML COMBINATION THERAPY: LABORATORY ABNORMALITIES AND DOSE MODIFICATIONS

Select laboratory abnormalities (≥10%) that worsened from baseline in patients with newly diagnosed AML who received TIBSOVO + azacitidine[a,b]

	TIBSOVO + azacitidine (n=71)		Placebo + azacitidine (n=73)	
Parameter	All grades	Grade ≥3	All grades	Grade ≥3
Hematology parameters				
Leukocytes decreased	65%	55%	64%	58%
Platelets decreased	58%	42%	71%	58%
Hemoglobin decreased	56%	46%	66%	58%
Neutrophils decreased	25%	23%	35%	32%
Lymphocytes increased	24%	1%	10%	1%
Chemistry parameters				
Glucose increased	56%	13%	47%	11%
Phosphate decreased	41%	10%	34%	12%
Aspartate aminotransferase increased	37%	0	23%	0
Magnesium decreased	35%	0	26%	0
Alkaline phosphatase increased	32%	0	29%	0
Potassium increased	24%	3%	12%	1%

[a]Laboratory abnormality was defined as new or worsened by at least one grade from baseline or if baseline was unknown.
[b]The denominator used to calculate percentages is the number of treated subjects who can be evaluated for Common Terminology for Adverse Events (CTCAE) criteria for each parameter in each arm.

Dose discontinuations, interruptions, and reductions

- Adverse reactions leading to discontinuation of TIBSOVO in ≥2% of patients were differentiation syndrome (3%) and pulmonary embolism (3%)
- The most common (>5%) adverse reactions leading to dose interruption of TIBSOVO were neutropenia (25%), electrocardiogram QT prolonged (7%), and thrombocytopenia (7%)
- Adverse reactions leading to dose reduction of TIBSOVO included electrocardiogram QT prolonged (8%), neutropenia (8%), and thrombocytopenia (1%)

AML MONOTHERAPY: ADVERSE REACTIONS

TIBSOVO monotherapy for the treatment of newly diagnosed and relapsed/refractory (R/R) AML

The safety profile of single-agent TIBSOVO was studied in 28 adults with newly diagnosed AML and 179 adults with R/R AML (Study AG120-C-001)

- Patients received 500 mg of TIBSOVO daily

Adverse reactions common to both the newly diagnosed and R/R settings reported in ≥10% (any grade) or ≥5% (Grade ≥3) of patients[a]

	TIBSOVO® Newly diagnosed AML (n=28)		TIBSOVO R/R AML (n=179)	
Body system Adverse reaction	All grades	Grade ≥3	All grades	Grade ≥3
Gastrointestinal disorders				
Diarrhea	61%	7%	34%	2%
Nausea	36%	7%	31%	1%
Abdominal pain	29%	4%	16%	1%
Constipation	21%	4%	20%	1%
Vomiting	21%	4%	18%	1%
Mucositis	21%	0%	28%	3%
General disorders and administration site conditions				
Fatigue	50%	14%	39%	3%
Edema	43%	0%	32%	1%
Metabolism and nutrition disorders				
Decreased appetite	39%	4%	18%	2%
Blood system and lymphatic system disorders				
Leukocytosis	36%	7%	38%	8%
Differentiation syndrome[b]	25%	11%	19%	13%
Musculoskeletal and connective tissue disorders				
Arthralgia	32%	4%	36%	4%
Myalgia	25%	4%	18%	1%
Respiratory, thoracic, and mediastinal disorders				
Dyspnea	29%	4%	33%	9%
Cough	14%	0%	22%	<1%
Investigations				
Electrocardiogram QT prolonged	21%	11%	26%	10%
Nervous system disorders				
Neuropathy	14%	0%	12%	1%
Headache	11%	0%	16%	0%
Skin and subcutaneous tissue disorders				
Rash	14%	4%	26%	2%

[a]Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, and Grade 4 is life-threatening.

[b]Differentiation syndrome can be associated with other commonly reported events such as peripheral edema, leukocytosis, pyrexia, dyspnea, pleural effusion, hypotension, hypoxia, pulmonary edema, pneumonia, pericardial effusion, rash, fluid overload, tumor lysis syndrome, and creatinine increased.

Please see additional Important Safety Information on pages 18 and 19 and Full Prescribing Information, including BOXED WARNING for AML and MDS patients.

AML MONOTHERAPY: ADVERSE REACTIONS (cont'd)

Additional adverse reactions in the newly diagnosed setting reported in ≥10% (any grade) or ≥5% (Grade ≥3) of patients[a]

	TIBSOVO Newly diagnosed AML (n=28)	
Adverse reaction	All grades	Grade ≥3
Dizziness	21%	0%
Pruritus	14%	4%
Dyspepsia	11%	0%
Weight decreased	11%	0%

[a]Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, and Grade 4 is life-threatening.

- The median duration of exposure to TIBSOVO was 4.3 months (range, 0.3 to 40.9)
  - 10 patients (36%) were exposed to TIBSOVO for at least 6 months
  - 6 patients (21%) were exposed to TIBSOVO for at least 1 year
- Common (≥5%) serious adverse reactions included differentiation syndrome (18%), electrocardiogram QT prolonged (7%), and fatigue (7%). There was one case of posterior reversible encephalopathy syndrome (PRES)

Additional adverse reactions in the R/R setting reported in ≥10% (any grade) or ≥5% (Grade ≥3) of patients[b]

	TIBSOVO R/R AML (n=179)	
Adverse reaction	All grades	Grade ≥3
Pyrexia	23%	1%
Chest pain	16%	3%
Pleural effusion	13%	3%
Hypotension	12%	4%
Tumor lysis syndrome	8%	6%

[b]Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, Grade 4 is life-threatening.

- The median duration of exposure to TIBSOVO was 3.9 months (range, 0.1 to 39.5)
  - 65 patients (36%) were exposed to TIBSOVO for at least 6 months
  - 16 patients (9%) were exposed to TIBSOVO for at least 1 year
- Serious adverse reactions (≥5%) were differentiation syndrome (10%), leukocytosis (10%), and electrocardiogram QT prolonged (7%). There was one case of progressive multifocal leukoencephalopathy (PML)

AML MONOTHERAPY: LABORATORY ABNORMALITIES

Laboratory abnormalities common to both the newly diagnosed and R/R settings reported in ≥10% (any grade) or ≥5% (Grade ≥3) of patients who received TIBSOVO® monotherapy[a]

	Newly diagnosed AML (TIBSOVO monotherapy) (n=28)		R/R AML (TIBSOVO monotherapy) (n=179)	
Parameter	All grades	Grade ≥3	All grades	Grade ≥3
Hemoglobin decreased	54%	43%	60%	46%
Alkaline phosphatase increased	46%	0	27%	1%
Potassium decreased	43%	11%	31%	6%
Sodium decreased	39%	4%	39%	4%
Uric acid increased	29%	4%	32%	6%
Aspartate aminotransferase increased	29%	4%	27%	1%
Creatinine increased	29%	0	23%	1%
Magnesium decreased	25%	0	38%	0
Phosphate decreased	21%	7%	25%	8%
Alanine aminotransferase increased	14%	4%	15%	1%

[a]Laboratory abnormality was defined as new or worsened by at least one grade from baseline, or if baseline was unknown.

Additional laboratory abnormalities reported in ≥10% (any grade) or ≥5% (Grade ≥3) of patients who received TIBSOVO monotherapy:

- In patients with newly diagnosed AML: calcium decreased (all grades, 25%; Grade ≥3, 4%)
- In patients with relapsed or refractory AML: bilirubin increased (all grades, 16%; Grade ≥3, 1%)

R/R, relapsed/refractory.

AML MONOTHERAPY: DOSE MODIFICATIONS

Dose discontinuations, interruptions, and reductions in newly diagnosed AML

- One patient each required permanent discontinuation due to diarrhea and PRES
- Common (≥10%) adverse reactions leading to dose interruption included electrocardiogram QT prolonged (14%) and differentiation syndrome (11%)
- Two (7%) patients required a dose reduction due to electrocardiogram QT prolonged

Dose discontinuations, interruptions, and reductions in R/R AML

- Adverse reactions leading to permanent discontinuation included Guillain-Barré syndrome (1%), rash (1%), stomatitis (1%), and creatinine increased (1%)
- The most common adverse reactions leading to dose interruption were electrocardiogram QT prolonged (7%), differentiation syndrome (3%), leukocytosis (3%), and dyspnea (3%)
- Five out of 179 patients (3%) required a dose reduction due to an adverse reaction. Adverse reactions leading to a dose reduction included electrocardiogram QT prolonged (1%), diarrhea (1%), nausea (1%), decreased hemoglobin (1%), and increased transaminases (1%)

PRES, posterior reversible encephalopathy syndrome.

MDS MONOTHERAPY: ADVERSE REACTIONS

TIBSOVO monotherapy for the treatment of relapsed or refractory MDS

The safety profile of single-agent TIBSOVO was studied in 19 adults with relapsed or refractory MDS (Study AG120-C-001).

- Patients received 500 mg of TIBSOVO daily

Adverse reactions reported in ≥10% (any grade) or ≥5% (grade ≥3) of patients with relapsed or refractory MDS

	TIBSOVO (500 mg daily) (N=19)	
Body system Adverse reaction	All grades %	Grade 3 or 4 %
Musculoskeletal and connective tissue disorders		
Arthralgia	42	16
Myalgia	26	0
General disorders and administration site conditions		
Fatigue	37	11
Respiratory, thoracic, and mediastinal disorders		
Cough	32	0
Dyspnea	21	0
Gastrointestinal disorders		
Diarrhea	32	0
Mucositis	26	5
Constipation	16	0
Nausea	16	0
Skin and subcutaneous tissue disorders		
Pruritus	26	0
Rash	26	0
Metabolism and nutrition disorders		
Decreased appetite	26	0
Blood system and lymphatic system disorders		
Leukocytosis	16	5
Differentiation syndrome	11	0
Nervous system disorders		
Headache	16	0
Vascular disorders		
Hypertension	16	16
Investigations		
Electrocardiogram QT prolonged	11	0

MDS MONOTHERAPY: LABORATORY ABNORMALITIES AND DOSE MODIFICATIONS

Select laboratory abnormalities[g] ≥15% that worsened from baseline in patients with R/R MDS[a]

	TIBSOVO (500 mg daily) (N=19)	
Laboratory abnormality	All grades %	Grade 3 or 4 %
Creatinine increased	95	5
Hemoglobin decreased	42	32
Albumin decreased	37	0
Aspartate aminotransferase increased	37	5
Sodium decreased	32	5
Phosphate decreased	26	5
Alanine aminotransferase increased	21	5
Bilirubin increased	21	0
Magnesium decreased	21	0
Alkaline phosphatase increased	16	0
Potassium increased	16	0

[a]Laboratory abnormality is defined as new or worsened by at least one grade from baseline, or if baseline is unknown.

The median duration of exposure of TIBSOVO was 9.3 months (range 3.3 to 78.8 months).

- Fourteen patients (74%) were exposed to TIBSOVO for at least 6 months
- Eight patients (42%) were exposed to TIBSOVO for at least 1 year

Dose discontinuations, interruptions, and reductions

- Permanent discontinuation of TIBSOVO due to an adverse reaction occurred in 1 (5%) patient. The adverse reaction that resulted in permanent discontinuation was fatigue
- Adverse reactions leading to dose interruption of TIBSOVO occurred in 16% of patients. Adverse reactions that required dose interruption in ≥5% were differentiation syndrome, leukocytosis, and rash
- Dose reductions of TIBSOVO due to an adverse reaction occurred in 16% of patients. Adverse reactions that required a dose reduction in ≥5% included differentiation syndrome, fatigue, and rash

MONITORING AND MANAGING ADVERSE REACTIONS

Periodic monitoring

- 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
- 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

Differentiation syndrome

- Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal
- Symptoms of differentiation syndrome in patients treated with TIBSOVO included noninfectious leukocytosis, peripheral edema, pyrexia, dyspnea, pleural effusion, hypotension, hypoxia, pulmonary edema, pneumonitis, pericardial effusion, rash, fluid overload, tumor lysis syndrome, and creatinine increased
- In the AML combination clinical trial AG120-C-009, differentiation syndrome occurred as early as 3 days after start of therapy and during the first month on treatment
- In the AML monotherapy clinical trial AG120-C-001, differentiation syndrome occurred as early as 1 day and up to 3 months after TIBSOVO initiation and has been observed with or without concomitant leukocytosis
- In the MDS monotherapy clinical trial AG120-C-001, differentiation syndrome occurred as early as 1 day and up to 3 months after TIBSOVO initiation and has been observed with or without concomitant leukocytosis

- If differentiation syndrome is suspected, administer systemic corticosteroids and initiate hemodynamic monitoring until symptom resolution and for a minimum of 3 days
- Interrupt TIBSOVO if severe signs and/or symptoms persist for more than 48 hours after initiation of systemic corticosteroids
- Resume TIBSOVO when signs and symptoms improve to Grade 2[a] or lower
- Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid and/or hydroxyurea treatment

Noninfectious leukocytosis

Defined as 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
- Taper hydroxyurea only after leukocytosis improves or resolves
- Interrupt TIBSOVO if leukocytosis is not improved with hydroxyurea, and then resume TIBSOVO at 500 mg daily when leukocytosis has resolved

Guillain-Barré syndrome

Guillain-Barré syndrome can develop in patients treated with TIBSOVO.

- Guillain-Barré syndrome occurred in <1% (2/265) of patients treated with TIBSOVO in Study AG120-C-001

- Monitor patients taking TIBSOVO for onset of new signs or symptoms of motor and/or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, paresthesias, or difficulty breathing
- Permanently discontinue TIBSOVO in patients who are diagnosed with Guillain-Barré syndrome

Please see additional Important Safety Information on pages 18 and 19 and Full Prescribing Information, including BOXED WARNING for AML and MDS patients.

MONITORING AND MANAGING ADVERSE REACTIONS (cont'd)

QTc interval prolongation

Patients treated with TIBSOVO can develop QT (QTc) prolongation and ventricular arrhythmias.

- Concomitant use of TIBSOVO with drugs known to prolong the QTc interval (eg, anti-arrhythmic medicines, fluoroquinolones, triazole anti-fungals, 5-HT_3 receptor antagonists) and CYP3A4 inhibitors may increase the risk of QTc interval prolongation
- Conduct monitoring of electrocardiograms (ECGs) and electrolytes
- In patients with congenital long QTc syndrome, congestive heart failure, or electrolyte abnormalities or in those who are taking medications known to prolong the QTc interval, more frequent monitoring may be necessary

QTc interval >480 to 500 msec

- Monitor and supplement electrolyte levels as clinically indicated
- Review and adjust concomitant medications with known QTc interval–prolonging effects
- Interrupt TIBSOVO
- Restart TIBSOVO at 500 mg once daily after the QTc interval returns to less than or equal to 480 msec
- Monitor ECGs at least weekly for 2 weeks following resolution of QTc prolongation

QTc interval >500 msec

- Monitor and supplement electrolyte levels as clinically indicated
- Review and adjust concomitant medications with known QTc interval–prolonging effects
- Interrupt TIBSOVO
- Resume TIBSOVO at a reduced dose of 250 mg once daily when QTc interval returns to within 30 msec of baseline or ≤480 msec
- Monitor ECGs at least weekly for 2 weeks following resolution of QTc prolongation
- Consider re-escalating the dose of TIBSOVO to 500 mg daily if an alternative etiology for QTc prolongation can be identified

QTc interval prolongation with signs/symptoms of life-threatening arrhythmia

- Discontinue TIBSOVO permanently

Other Grade 3 toxicity considered related to treatment[a]

AML in combination with azacitidine

- 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)
- If Grade 3 toxicity recurs (a second time), reduce TIBSOVO dose to 250 mg daily until the toxicity resolves, then resume 500 mg daily
- If Grade 3 toxicity recurs (a third time), or Grade 4 toxicity recurs, discontinue TIBSOVO

AML monotherapy

- Interrupt TIBSOVO until toxicity resolves to Grade 2 or lower
- Resume TIBSOVO at 250 mg once daily; may increase to 500 mg once daily if toxicities resolve to Grade 1 or lower
- If Grade 3 or higher toxicity recurs, discontinue TIBSOVO

MDS monotherapy

- Interrupt TIBSOVO until toxicity resolves to Grade 2 or lower
- Resume TIBSOVO at 250 mg once daily; may increase to 500 mg once daily if toxicities resolve to Grade 1 or lower
- If Grade 3 or higher toxicity recurs, discontinue TIBSOVO

[a]Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, and Grade 4 is life-threatening.

ORDERING AND PRODUCT INFORMATION

National Drug Code (NDC)

NDCs	Dosage strength	Description
10-digit code: 72694-617-60 11-digit code: 72694-0617-60	250 mg/tablet	250-mg tablet: Blue oval-shaped film-coated tablet debossed "IVO" on one side and "250" on the other side

The red zero converts the 10-digit NDC to the 11-digit NDC. Some payers may require each NDC to be listed on the claim. Payer requirements regarding the use of NDCs may vary. Electronic data exchange generally requires use of the 11-digit NDC.

Product information

How TIBSOVO is supplied: 250-mg tablets, supplied in 60-count bottles (30-day supply) with a desiccant canister

Storage: Store at 20-25 °C (68-77 °F)

ORDERING AND PRODUCT INFORMATION (cont'd)

Distribution network for TIBSOVO

TIBSOVO is only available through specialty distributors and specialty pharmacies.

Specialty distributors: TIBSOVO is available through specialty distributors for shipment directly to office- or hospital-based pharmacies.

McKesson Specialty Health

Multispecialty

1-855-477-9800

https://mscs.mckesson.com

Oncology

1-800-482-6700

https://mscs.mckesson.com

Cardinal Health Specialty Pharmaceutical Distribution (US)

Physician Office

1-877-453-3972

https://specialtyonline.cardinalhealth.com

Hospitals/All Other

1-866-677-4844

https://orderexpress.cardinalhealth.com

Cardinal Health (Puerto Rico)

1-787-625-4100

https://cardinalhealth.pr

ASD Healthcare Customer Service

1-800-746-6273

https://www.asdhealthcare.com

Oncology Supply

1-800-633-7555

https://www.oncologysupply.com

Network specialty pharmacies: TIBSOVO ships directly from the specialty pharmacy to your patient's home or preferred location.

Biologics by McKesson

1-800-850-4306

https://www.biologics.mckesson.com

Onco360

1-877-662-6633

https://www.Onco360.com

ServierONE PATIENT SUPPORT SERVICES

ServierONE Patient Support Services is a program that helps with access and financial assistance

ServierONE Patient Support Services for TIBSOVO includes:

- Support with insurance coverage and reimbursement
- Financial assistance to help patients pay for TIBSOVO
- Prescription fulfillment through our network of specialty pharmacies and distributors

Please visit **ServierONE.com** for full program details and information on how to enroll patients.

ServierONE PATIENT SUPPORT SERVICES (cont'd)

ServierONE can connect your patients to financial assistance and coverage support programs

The Commercial Co-Pay Program can lower out-of-pocket costs

- There are no income restrictions
- Available to eligible patients with commercial/private insurance
- Patients participating in government healthcare insurance are not eligible

Independent foundations[a]

- Network specialty pharmacies or ServierONE can provide more information

Patient Assistance Program

- Offers free prescriptions to eligible uninsured and underinsured patients (may apply to commercial or government insurance)

QuickStart Program

- Receive a free 30-day supply of therapy for up to two (2) dispenses for eligible patients
- For new patients with commercial or government insurance
- Must be experiencing a coverage delay of 5 or more days after submission of a completed prior authorization

[a]Eligibility is determined by the individual foundation. Servier is not affiliated with these organizations.

IMPORTANT SAFETY INFORMATION

INDICATIONS

TIBSOVO is indicated for patients with a susceptible isocitrate dehydrogenase-1 (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 the use of intensive induction chemotherapy

Relapsed or Refractory AML

- For the treatment of adult patients with relapsed or refractory AML

Relapsed or Refractory Myelodysplastic Syndromes (MDS)

- For the treatment of adult patients with relapsed or refractory MDS

IMPORTANT SAFETY INFORMATION

WARNING: DIFFERENTIATION SYNDROME IN AML AND MDS
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.

WARNINGS AND PRECAUTIONS

Differentiation Syndrome in AML and MDS: Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal. Symptoms of differentiation syndrome in patients treated with TIBSOVO included noninfectious leukocytosis, peripheral edema, pyrexia, dyspnea, pleural effusion, hypotension, hypoxia, pulmonary edema, pneumonitis, pericardial effusion, rash, fluid overload, tumor lysis syndrome, and creatinine increased.

If differentiation syndrome is suspected, initiate dexamethasone 10 mg IV every 12 hours (or an equivalent dose of an alternative oral or IV corticosteroid) and hemodynamic monitoring until improvement. If concomitant noninfectious leukocytosis is observed, initiate treatment with hydroxyurea or leukapheresis, as clinically indicated. Taper corticosteroids and hydroxyurea after resolution of symptoms and administer corticosteroids for a minimum of 3 days. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid and/or hydroxyurea treatment. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, interrupt TIBSOVO until signs and symptoms are no longer severe.

QTc Interval Prolongation: Patients treated with TIBSOVO can develop QT (QTc) prolongation and ventricular arrhythmias. Concomitant use of TIBSOVO with drugs known to prolong the QTc interval (eg, anti-arrhythmic medicines, fluoroquinolones, triazole anti-fungals, 5-HT_3 receptor antagonists) and CYP3A4 inhibitors may increase the risk of QTc interval prolongation. Conduct monitoring of electrocardiograms (ECGs) and electrolytes. In patients with congenital long QTc syndrome, congestive heart failure, or electrolyte abnormalities, or in those who are taking medications known to prolong the QTc interval, more frequent monitoring may be necessary.

Interrupt TIBSOVO if QTc increases to greater than 480 msec and less than 500 msec. Interrupt and reduce TIBSOVO if QTc increases to greater than 500 msec. Permanently discontinue TIBSOVO in patients who develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia.

Guillain-Barré Syndrome: Guillain-Barré syndrome can develop in patients treated with TIBSOVO. Monitor patients taking TIBSOVO for onset of new signs or symptoms of motor and/or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, paresthesias, or difficulty breathing. Permanently discontinue TIBSOVO in patients who are diagnosed with Guillain-Barré syndrome.

Please see Full Prescribing Information, including BOXED WARNING for AML and MDS patients.

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IMPORTANT SAFETY INFORMATION (cont'd)

ADVERSE REACTIONS

- **In patients with AML,** the most common adverse reactions including laboratory abnormalities (≥25%) 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
- **In patients with MDS,** the most common adverse reactions including laboratory abnormalities (≥25%) are creatinine increased, hemoglobin decreased, arthralgia, albumin decreased, aspartate aminotransferase increased, fatigue, diarrhea, cough, sodium decreased, mucositis, decreased appetite, myalgia, phosphate decreased, pruritus, and rash

DRUG INTERACTIONS

Strong or Moderate CYP3A4 Inhibitors: Reduce TIBSOVO dose with strong CYP3A4 inhibitors. Monitor patients for increased risk of QTc interval prolongation.

Strong CYP3A4 Inducers: Avoid concomitant use with TIBSOVO.

Sensitive CYP3A4 Substrates: Avoid concomitant use with TIBSOVO.

QTc Prolonging Drugs: Avoid concomitant use with TIBSOVO. If co-administration is unavoidable, monitor patients for increased risk of QTc interval prolongation.

LACTATION

Advise women not to breastfeed.

Please see Full Prescribing Information, including BOXED WARNING for AML and MDS patients.

TIBSOVO IS THE FIRST-IN-CLASS DIFFERENTIATION THERAPY TO TARGET MUTATED IDH1 IN AML AND MDS

- TIBSOVO has a well-characterized safety profile studied in nearly 300 patients with *IDH1*-mutated AML and MDS
- TIBSOVO offers a straightforward dosing regimen with no titration needed
- TIBSOVO offers convenient, once-daily oral dosing and can be taken at home

Visit **TibsovoPro.com** to learn more

INDICATIONS

TIBSOVO is indicated for patients with a susceptible isocitrate dehydrogenase-1 (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 the use of intensive induction chemotherapy

Relapsed or Refractory AML

- For the treatment of adult patients with relapsed or refractory AML

Relapsed or Refractory Myelodysplastic Syndromes (MDS)

- For the treatment of adult patients with relapsed or refractory MDS

IMPORTANT SAFETY INFORMATION

WARNING: DIFFERENTIATION SYNDROME IN AML AND MDS

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.

Reference: Tibsovo. Package insert. Servier Pharmaceuticals LLC; 2023.

Please see additional Important Safety Information on pages 18 and 19 and Full Prescribing Information, including BOXED WARNING for AML and MDS patients.

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