TIBSOVO® PRODUCT GUIDE

INDICATIONS

TIBSOVO is indicated for the treatment of acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test in:

- Adult patients with newly-diagnosed AML who are ≥75 years old or who have comorbidities that preclude use of intensive induction chemotherapy.
- Adult patients with relapsed or refractory AML.

SELECTED IMPORTANT SAFETY INFORMATION

WARNING: DIFFERENTIATION SYNDROME

Patients treated with TIBSOVO have experienced symptoms of differentiation syndrome, which can be fatal if not treated. 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 Important Safety Information throughout this piece and full Prescribing Information, including Boxed WARNING.

TIBSOVO®
ivosidenib tablets 250mg

Trial design[1]

TIBSOVO® was studied as a single agent in both the newly diagnosed and R/R AML settings

- The pivotal trial for TIBSOVO was an open-label, single-arm, multicenter trial
  - **28** IC-ineligible patients with **newly diagnosed** AML were evaluated for safety and efficacy
  - **179** patients were evaluated for safety and **174** for efficacy in the **R/R** AML population
- *IDH1* mutations were identified by a local or central diagnostic test and confirmed retrospectively using the Abbott RealTi*me*™ IDH1 assay, which is the FDA-approved test for selection of patients with AML for treatment with TIBSOVO

Patients were assigned a starting dose of TIBSOVO 500 mg daily and received treatment until disease progression, development of unacceptable toxicity, or undergoing hematopoietic stem cell transplantation.

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Differentiation Syndrome: See Boxed WARNING. In the clinical trial, 25% (7/28) of patients with newly diagnosed AML and 19% (34/179) of patients with relapsed or refractory AML treated with TIBSOVO experienced differentiation syndrome. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. 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. Of the 7 patients with newly diagnosed AML who experienced differentiation syndrome, 6 (86%) patients recovered. Of the 34 patients with relapsed or refractory AML who experienced differentiation syndrome, 27 (79%) patients recovered after treatment or after dose interruption of TIBSOVO. 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, 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.

Please see Important Safety Information throughout this piece and full Prescribing Information, including Boxed WARNING.

TIBSOVO delivered strong and durable responses as an oral, single agent[1,2]

In IC-ineligible patients with newly diagnosed AML (N=28)[1]:

- **43%** (12/28) achieved CR or CRh (95% CI, 24.5-62.8)[1]
- **58%** of those who achieved CR or CRh (7/12) were in remission at **12 months** after initiating treatment[2,a]
- **41%** of those who were transfusion dependent at baseline (7/17) became transfusion independent[1,b]

In patients with R/R AML (N=174)[1]:

- **33%** (57/174) achieved CR or CRh (95% CI, 25.8-40.3)
- Median DOCR+CRh was **8.2 months** (95% CI, 5.6-12)[c]
- **37%** of those who were transfusion dependent at baseline (41/110) became transfusion independent[b]

Choose TIBSOVO for **strength that can endure.**

[a]Median DOCR (duration of CR) and median DOCR+CRh (duration of CR+CRh) were not estimable (NE).[1]
[b]Patients were defined as transfusion dependent at baseline if they received any RBC or platelet transfusion occurring within 56 days prior to the first dose of TIBSOVO. Patients were defined as transfusion independent if they became independent of transfusions during any 56-day postbaseline period.[1]
[c]DOCR and DOCR+CRh were defined as time since first response of CR or CR/CRh, respectively, to relapse or death, whichever is earlier.[1]

CR, complete remission, defined as <5% blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets >100,000/microliter and absolute neutrophil counts >1000/microliter); CRh, complete remission with partial hematological recovery, defined as <5% blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/microliter and absolute neutrophil counts >500/microliter); IC, intensive chemotherapy; RBC, red blood cell; R/R, relapsed or refractory.[1]

TIBSOVO® ivosidenib tablets 250mg

Recommended dosing[1]

500 mg
(2 x 250-mg film-coated tablets)

Tablets not shown at actual size.

TIBSOVO® should be taken orally, with or without food, at about the same time each day

Treatment with TIBSOVO has not been studied in patients with pre-existing severe renal or hepatic impairment. For patients with pre-existing severe renal or hepatic impairment, consider the risks and potential benefits before initiating treatment with TIBSOVO.[1]

TIBSOVO should be taken at about the same time each day.

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. They should not take 2 doses within 12 hours.

If a dose is vomited, patients should not take a replacement dose; they should wait until the next scheduled dose is due.

TIBSOVO tablets should not be split, crushed, or chewed.

TIBSOVO can be taken with or without food but should not be taken with a high-fat meal because of an increase in ivosidenib concentration.[a]

[a]An example of a high-fat meal includes 2 eggs fried in butter, 2 strips of bacon, 2 slices of white bread with butter, 1 croissant with 1 slice of cheese, and 8 ounces of whole milk (approximately 1000 calories and 58 grams of fat).

For patients without disease progression or unacceptable toxicity, treat for a minimum of 6 months to allow time for clinical response[1]

Please see Important Safety Information throughout this piece and full Prescribing Information, including Boxed WARNING.

Drug-drug interactions

Strong or moderate CYP3A4 inhibitors	• Coadministration increased ivosidenib plasma concentrations, which may increase the risk of QTc interval prolongation[1] • Consider alternative therapies that are not strong or moderate CYP3A4 inhibitors[1] • 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[1] – In the clinical trial evaluating ivosidenib, concomitant use of CYP3A4 inhibitors and QT-prolonging medications was permitted with approval by the medical monitor and careful monitoring of the QT interval[3] • Monitor patients for increased risk of QTc interval prolongation[1]
Strong CYP3A4 inducers[1]	• Coadministration decreased ivosidenib plasma concentrations • Avoid coadministration
QTc-prolonging drugs[1]	• 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[1]	• 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 • Do not administer with itraconazole or ketoconazole (CYP3A4 substrates) due to expected loss of antifungal efficacy • Coadministration may decrease the concentrations of hormonal contraceptives. Consider alternative methods of contraception • If coadministration with sensitive CYP3A4 substrates or CYP2C9 substrates is unavoidable, monitor patients for loss of therapeutic effect of these drugs

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

Adverse reactions[1]

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

	TIBSOVO® (500 mg daily) Newly diagnosed AML N=28		TIBSOVO (500 mg daily) R/R AML N=179	
Body system Adverse reaction	All Grades	Grade ≥3	All Grades	Grade ≥3
Blood system and lymphatic system disorders				
Leukocytosis	36%	7%	38%	8%
Differentiation syndrome[a]	25%	11%	19%	13%
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%
Investigations				
Electrocardiogram QT prolonged	21%	11%	26%	10%
Metabolism and nutrition disorders				
Decreased appetite	39%	4%	18%	2%
Musculoskeletal and connective tissue disorders				
Arthralgia	32%	4%	36%	4%
Myalgia	25%	4%	18%	1%
Nervous system disorders				
Neuropathy	14%	0%	12%	1%
Headache	11%	0%	16%	0%
Respiratory, thoracic, and mediastinal disorders				
Dyspnea	29%	4%	33%	9%
Cough	14%	0%	22%	<1%
Skin and subcutaneous tissue disorders				
Rash	14%	4%	26%	2%

[a]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 Important Safety Information throughout this piece and full Prescribing Information, including Boxed WARNING.

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

	TIBSOVO (500 mg daily) Newly diagnosed AML, N=28	
Adverse reaction	**All Grades**	**Grade ≥3**
Dizziness	21%	0%
Pruritus	14%	4%
Dyspepsia	11%	0%
Weight decreased	11%	0%

- 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)
- Median duration of exposure to TIBSOVO: 4.3 months (range, 0.3-40.9 months)
  – 10 patients (36%) were exposed to TIBSOVO for ≥6 months and 6 patients (21%) for ≥1 year

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

	TIBSOVO (500 mg daily) 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%

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

Adverse reactions[1] (cont'd)

Laboratory abnormalities common to both the newly diagnosed and R/R settings reported in ≥10% (any grade) or ≥5% (Grade ≥3) of patients[a]				
	TIBSOVO® (500 mg daily) Newly diagnosed AML N=28		TIBSOVO (500 mg daily) R/R AML 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 is defined as new or worsened by at least one grade from baseline, or if baseline is unknown.

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

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

Please see Important Safety Information throughout this piece and full Prescribing Information, including Boxed WARNING.

Dose discontinuations, interruptions, and reductions		
	Newly diagnosed AML, N=28	**R/R AML, N=179**
Adverse reactions that led to permanent discontinuation	Diarrhea (4%), PRES (4%)	Guillain-Barré syndrome (1%), rash (1%), stomatitis (1%), creatinine increased (1%)
Most common adverse reactions that led to dose interruption	Electrocardiogram QT prolonged (14%), differentiation syndrome (11%)	Electrocardiogram QT prolonged (7%), differentiation syndrome (3%), leukocytosis (3%), dyspnea (3%)
Adverse reactions that led to dose reduction	Electrocardiogram QT prolonged (7%)	3% of patients required a dose reduction due to an adverse reaction – Adverse reactions leading to dose reduction included electrocardiogram QT prolonged (1%), diarrhea (1%), nausea (1%), decreased hemoglobin (1%), increased transaminases (1%)

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

QTc Interval Prolongation: Patients treated with TIBSOVO can develop QT (QTc) prolongation and ventricular arrhythmias. One patient developed ventricular fibrillation attributed to TIBSOVO. Concomitant use of TIBSOVO with drugs known to prolong the QTc interval (e.g., 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.

Managing adverse reactions[1]

Periodic monitoring

- 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
- 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

Differentiation syndrome

- **25%** of patients with newly diagnosed AML (7/28) and **19%** of patients with R/R AML (34/179) experienced differentiation syndrome
  - Onset occurred as early as 1 day and up to 3 months after initiation of TIBSOVO and has been observed with or without concomitant leukocytosis
  - Symptoms 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
  - Of those who experienced differentiation syndrome, 86% of patients with newly diagnosed AML (6/7) and 79% of patients with R/R AML (27/34) recovered after treatment or after dose interruption of TIBSOVO

- 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 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
- Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid and/or hydroxyurea treatment

Noninfectious leukocytosis

- 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

ECG, electrocardiogram; IV, intravenous.

Please see Important Safety Information throughout this piece and full Prescribing Information, including Boxed WARNING.

QTc prolongation

Of the 258 patients treated with TIBSOVO in the trial:

- **9%** had a QTc interval >500 msec
- **14%** had a >60 msec increase from baseline QTc interval
- **One patient** developed ventricular fibrillation attributed to TIBSOVO

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 ≤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

Guillain-Barré syndrome

- **<1%** of patients treated with TIBSOVO (2/258) experienced Guillain-Barré syndrome
- Monitor patients 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

- Discontinue TIBSOVO permanently

Other Grade ≥3

Other Grade ≥3 toxicity considered related to treatment

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

Ordering and product information

National Drug Code (NDC)

NDCs	Dosage strength	Description
10-digit code: 71334-100-01 11-digit code: 71334-0100-01	250 mg/tablet	250-mg tablet: Blue oval-shaped film-coated tablet debossed "IVO" on one side and "250" on the other side[1]

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[1]

Storage: Store at 20°C to 25°C (68°F to 77°F)

Please see Important Safety Information throughout this piece and full Prescribing Information, including Boxed WARNING.

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

1-800-482-6700

mscs.mckesson.com

McKesson Plasma and Biologics

1-877-625-2566

mckesson.com/contact-us/form/contact-plasma-and-biologics-distribution

Cardinal Health (US)

Acute (Hospital)

1-855-855-0708

gmb-spd-csorderentry@cardinalhealth.com

Physician Office (Oncology)

1-877-453-3972

spdoncologyteam@cardinalhealth.com

Cardinal Health (Puerto Rico)

1-787-625-4100

1-787-625-4397

compras@cardinalhealth.com

Amerisource Bergen/ Oncology Supply

1-800-633-7555

1-800-248-8205

custserv@oncologysupply.com

ASD Healthcare Customer Service

1-800-746-6273

1-800-547-9413

asd.customerservice@asdhealthcare.com

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

Biologics

1-800-850-4306

1-800-823-4506

Diplomat

1-877-977-9118

1-800-550-6272

myAgios™ Patient Support Services

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

myAgios 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

To enroll patients in myAgios, visit **myAgios.com** or call **1-844-409-1141**, Monday through Friday, 8 AM to 6 PM ET.

Submission of the **myAgios Enrollment Form** is not required for the Commercial $25 Co-Pay Program. To apply on behalf of patients, please visit **myAgios-copay.com**.

Please see Important Safety Information throughout this piece and full Prescribing Information, including Boxed WARNING.

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

The Commercial $25 Co-Pay Program can help with out-of-pocket costs

- Lowers costs for eligible patients to no more than $25 per prescription if their co-pay exceeds that amount, with a maximum benefit of $25,000 per calendar year

- 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 myAgios 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

- Free 14-day prescription (allowing for 3 refills, for a total of 56 days) 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

Coverage Interruption Program

- Free 30-day prescription (allowing for 2 refills, for a total of 90 days) for commercially insured patients experiencing an interruption in coverage
- Patients participating in government healthcare insurance are not eligible

Please see myAgios.com for full Terms and Conditions for each program.

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

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Differentiation Syndrome: See Boxed WARNING. In the clinical trial, 25% (7/28) of patients with newly diagnosed AML and 19% (34/179) of patients with relapsed or refractory AML treated with TIBSOVO experienced differentiation syndrome. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. 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. Of the 7 patients with newly diagnosed AML who experienced differentiation syndrome, 6 (86%) patients recovered. Of the 34 patients with relapsed or refractory AML who experienced differentiation syndrome, 27 (79%) patients recovered after treatment or after dose interruption of TIBSOVO. 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, 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. One patient developed ventricular fibrillation attributed to TIBSOVO. Concomitant use of TIBSOVO with drugs known to prolong the QTc interval (e.g., 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 occurred in <1% (2/258) of patients treated with TIBSOVO in the clinical study. 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.

LACTATION

Because many drugs are excreted in human milk and because of the potential for adverse reactions in breastfed children, advise women not to breastfeed during treatment with TIBSOVO and for at least 1 month after the last dose.

Please see Important Safety Information throughout this piece and full Prescribing Information, including Boxed WARNING.

Visit TibsovoPro.com to learn more

References: 1. Tibsovo. Package insert. Agios Pharmaceuticals, Inc; 2019. **2.** Data on file. Agios Pharmaceuticals, Inc. **3.** DiNardo CD, Stein EM, de Botton S, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. *N Engl J Med.* 2018;378(25):2386-2398.

agios

TIBSOVO®
ivosidenib tablets 250mg