



PRESS RELEASE

**Servier Announces FDA Approval of TIBSOVO® (ivosidenib tablets) in Combination with Azacitidine for Patients with Newly Diagnosed IDH1-mutated Acute Myeloid Leukemia**

*TIBSOVO is the first therapy targeting cancer metabolism approved in combination with azacitidine for patients with newly diagnosed IDH1-mutated acute myeloid leukemia*

*FDA approval based on data from the global, Phase 3 AGILE trial that demonstrated a statistically significant improvement in event-free survival and overall survival*

**BOSTON, May 25, 2022** – Servier, a leader in oncology committed to bringing the promise of tomorrow to the patients we serve, today announced that the U.S. Food and Drug Administration (FDA) approved TIBSOVO® (ivosidenib tablets) in combination with azacitidine for the treatment of patients with newly diagnosed IDH1-mutated acute myeloid leukemia (AML) in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy. TIBSOVO is the first therapy targeting cancer metabolism approved in combination with azacitidine for patients with newly diagnosed IDH1-mutated AML. The AGILE trial was the only Phase 3 trial designed specifically for newly diagnosed patients with IDH1-mutated AML who are ineligible for intensive chemotherapy.

The supplemental New Drug Application (sNDA) for TIBSOVO received Priority Review and was reviewed by the FDA under its Real-Time Oncology Review (RTOR) pilot program, which aims to ensure that safe and effective treatments are available to patients as early as possible.<sup>1</sup>

“Today’s approval builds on the established body of evidence for TIBSOVO, which is now approved across multiple IDH1-mutated cancer types,” said David K. Lee, Chief Executive Officer, Servier Pharmaceuticals. “As a leader in oncology pioneering the science behind targeted IDH inhibition, we are proud to bring a new therapeutic option to the acute myeloid leukemia community and remain committed to pushing the boundaries of healthcare innovation in oncology and beyond.”

The expanded approval of TIBSOVO is supported by data from the AGILE study, a global, Phase 3 trial in patients with previously untreated IDH1-mutated AML. Results from the AGILE trial demonstrated a statistically significant improvement in event-free survival (EFS) (hazard ratio [HR] = 0.35 [95% CI 0.17, 0.72], 2-sided p-value = 0.0038)<sup>2</sup> and overall survival (OS) (HR = 0.44 [95% CI 0.27, 0.73]; 2-sided p = 0.0010). TIBSOVO plus azacitidine treatment resulted in a threefold improvement in median OS (24 months) compared to placebo plus azacitidine (7.9 months) as a first-line treatment for IDH1-mutated AML. Results from the AGILE study were presented at the 2021 American Society of Hematology (ASH) Annual Meeting and Exposition, and recently published in the *New England Journal of Medicine* (NEJM).

“Acute myeloid leukemia is a rapidly progressing, difficult-to-treat blood cancer with a poor prognosis,” said Eytan M. Stein, M.D., Director, Program for Drug Development in Leukemia, Leukemia Service, Department of Medicine at Memorial Sloan Kettering Cancer Center. “In addition to a favorable safety profile, TIBSOVO is the first therapy targeting cancer metabolism to demonstrate an impressive, significant benefit in event-free survival and overall survival in combination with azacitidine, underscoring its importance as part of a new combination regimen for patients with newly diagnosed IDH1-mutated acute myeloid leukemia who are not candidates for intensive induction chemotherapy.”

AML is a difficult-to-treat cancer of the blood and bone marrow and is one of the most common types of leukemia in adults with approximately 20,000 new cases estimated in the U.S. each year.<sup>3,4</sup> IDH1 mutations are present in about 6 to 10 percent of AML cases.<sup>5</sup>

“People living with acute myeloid leukemia, especially those who are newly diagnosed and are not



eligible for intensive chemotherapy, have had few treatment options,” said Susan Pandya, M.D., Vice President Clinical Development and Head of Cancer Metabolism Global Development Oncology & Immuno-Oncology, Servier. “Today’s approval of TIBSOVO in combination with azacitidine represents a major advancement for patients with newly diagnosed IDH1-mutated acute myeloid leukemia in the United States, and we look forward to continuing our engagement with regulatory authorities worldwide.”

The combination of TIBSOVO plus azacitidine demonstrated a safety profile consistent with previously published data. The most common adverse reactions ( $\geq 10\%$ ) in newly diagnosed AML patients receiving TIBSOVO in combination with azacitidine were nausea, vomiting, electrocardiogram QT prolonged, insomnia, differentiation syndrome, leukocytosis, hematoma, hypertension, arthralgia, dyspnea, and headache. The select laboratory abnormalities ( $\geq 10\%$ ) were leukocytes decreased, platelets decreased, hemoglobin decreased, neutrophils decreased, lymphocytes increased, glucose increased, phosphate decreased, aspartate aminotransferase increased, magnesium decreased, alkaline phosphatase increased, and potassium increased.

The recommended dosage of TIBSOVO for newly diagnosed IDH1-mutated AML is 500mg once daily via oral administration.

In an effort to support the patient communities it serves, Servier Pharmaceuticals recently introduced ServierONE Patient Support Services, a program that offers one-on-one support to help patients who are prescribed TIBSOVO or other Servier products navigate their cancer journey. Eligible patients will have access to financial assistance, emotional support and other resources. More information can be found at [www.servierone.com](http://www.servierone.com).

TIBSOVO<sup>i</sup> is also approved in the U.S. as monotherapy for the treatment of adults with IDH1-mutant relapsed or refractory AML, and for adults with newly diagnosed IDH1-mutated AML who are  $\geq 75$  years old or who have comorbidities that preclude the use of intensive induction chemotherapy. Last year, TIBSOVO garnered its first approval in a non-hematologic malignancy for patients with previously treated IDH1-mutated cholangiocarcinoma.

#### **About the NCT03173248 AGILE Phase 3 AML Trial<sup>6</sup>**

The AGILE trial is a global, Phase 3, multicenter, double-blind, randomized, placebo-controlled clinical trial designed to evaluate the efficacy and safety of TIBSOVO in combination with azacitidine compared with placebo in combination with azacitidine, in adults with previously untreated IDH1-mutated acute myeloid leukemia (AML) who are not candidates for intensive chemotherapy ( $\geq 75$  years old or who have comorbidities that preclude the use of intensive induction chemotherapy). The study’s primary endpoint is event-free survival (EFS), defined as the time from randomization until treatment failure, relapse from remission, or death from any cause, whichever occurs first. Treatment failure is defined as failure to achieve complete remission (CR) by Week 24.

Key secondary endpoints included CR rate, defined as the proportion of participants who achieve a CR; overall survival (OS), defined as the time from date of randomization to the date of death due to any cause; CR and complete remission with partial hematologic recovery (CRh) rate, defined as the proportion of participants who achieve a CR or CRh; and objective response rate (ORR), defined as the rate of CR, CR with incomplete hematologic recovery (CRi) (including CR with incomplete platelet recovery [CRp]), partial remission (PR), and morphologic leukemia-free state (MLFS).

#### **About Acute Myeloid Leukemia**

Acute myeloid leukemia (AML) a cancer of blood and bone marrow characterized by rapid disease progression, is the most common acute leukemia affecting adults, with approximately 20,000 new cases in the U.S., and 43,000 cases in Europe each year.<sup>2,3</sup> AML incidence significantly increases with age, and the median age of diagnosis is 68.<sup>2</sup> The five-year survival rate is approximately 29.5%.<sup>2</sup> For 6 to 10 percent of AML patients, the mutated IDH1 enzyme blocks normal blood stem cell differentiation, contributing to the genesis of acute leukemia.<sup>5</sup>

#### **About Servier Pharmaceuticals**

Servier Pharmaceuticals LLC is a commercial-stage company with a passion for innovation and



improving the lives of patients, their families and caregivers. As a privately held company, Servier has the unique freedom to devote all its time and energy towards patients who require our treatments, care and innovation in areas of unmet medical need.

As a leader in oncology, Servier is committed to finding solutions that will address today's challenges. The company's oncology portfolio includes innovative medicines designed to bring more life-saving treatments to a greater number of patients, across the entire spectrum of disease and in a variety of tumor types. Servier has significantly accelerated its investment in hard-to-treat cancers with more than 50% of research and development dedicated to delivering significant advances in areas of high unmet need that may truly move the needle for our patients.

Servier believes co-creation is fundamental to driving innovation and is actively building alliances, acquisitions, licensing deals and partnerships that bring solutions and accelerate access to therapies. With the company's commercial expertise, global reach, scientific expertise and commitment to clinical excellence, Servier Pharmaceuticals is dedicated to bringing the promise of tomorrow to the patients that we serve.

More information: [www.servier.us](http://www.servier.us)

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### **About Servier Group**

Servier is a global pharmaceutical group governed by a Foundation. With a strong international presence in 150 countries and a total revenue of 4.7 billion euros in 2021, Servier employs 21,800 people worldwide. Servier is an independent group that invests over 20% of its brand-name revenue in Research and Development every year. To accelerate therapeutic innovation for the benefit of patients, the Group is committed to open and collaborative innovation with academic partners, pharmaceutical groups, and biotech companies. It also integrates the patient's voice at the heart of its activities.

A leader in cardiology, the ambition of the Servier Group is to become a renowned and innovative player in oncology. Its growth is based on a sustained commitment to cardiovascular and metabolic diseases, oncology, neuroscience and immuno-inflammatory diseases. To promote access to healthcare for all, the Servier Group also offers a range of quality generic drugs covering most pathologies.

More information: [www.servier.com](http://www.servier.com)

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The estimates, strategies, and views expressed in this document are based upon past or current data and information and are subject to change without notice.

## **About TIBSOVO (ivosidenib tablets)**

### **INDICATIONS**

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 the use of intensive induction chemotherapy

#### Relapsed or Refractory AML

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

#### Locally Advanced or Metastatic Cholangiocarcinoma

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

### **IMPORTANT SAFETY 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.**



## WARNINGS AND PRECAUTIONS

**Differentiation Syndrome in AML:** In the combination study AG120-C-009, 15% (11/71) of patients with newly diagnosed AML treated with TIBSOVO plus azacitidine experienced 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. Of the 11 patients with newly diagnosed AML who experienced differentiation syndrome with TIBSOVO plus azacitidine, 8 (73%) recovered. Differentiation syndrome occurred as early as 3 days after start of therapy and during the first month on treatment.

In the monotherapy clinical trial AG120-C-001, 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. 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. Concomitant use of TIBSOVO with drugs known to prolong the QTc interval (e.g., anti-arrhythmic medicines, fluoroquinolones, triazole anti-fungals, 5-HT<sub>3</sub> 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.

## ADVERSE REACTIONS

- **In patients with AML**, the most common adverse reactions including laboratory abnormalities ( $\geq 25\%$ ) 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 cholangiocarcinoma**, the most common adverse reactions ( $\geq 15\%$ ) are fatigue, nausea, abdominal pain, diarrhea, cough, decreased appetite, ascites, vomiting, anemia, and rash. The most common laboratory abnormalities ( $\geq 10\%$ ) in patients with cholangiocarcinoma are hemoglobin decreased, aspartate aminotransferase increased, and bilirubin increased

#### **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**

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 1 month after the last dose.

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

#### **References**

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<sup>i</sup> Servier has granted an exclusive license to CStone to develop and commercialize the product in Mainland China, Taiwan, Hong Kong, Macau and Singapore. TIBSOVO is also currently approved by the NMPA of China for the treatment of adult patients with relapsed or refractory AML who have a susceptible IDH1 mutation.