

Servier receives European Commission approval of Tibsovo® (ivosidenib tablets) in IDH1-mutated Acute Myeloid Leukemia and IDH1-mutated Cholangiocarcinoma



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Servier Pharmaceuticals →
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- **Marketing Authorization granted for Tibsovo® as the first and only approved IDH1 targeted therapy in Europe**
- **IDH1-mutated Acute Myeloid Leukemia and IDH1-mutated Cholangiocarcinoma, difficult and hard-to-treat cancer**

PARIS and BOSTON, May 10, 2023 /PRNewswire/ -- Servier, a global pharmaceutical group, today announced that the European Commission (EC) has approved Tibsovo® (ivosidenib tablets) as a targeted therapy in two indications: in combination with azacitidine for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive standard induction chemotherapy; as well as in monotherapy for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation who were previously treated by at least one prior line of systemic therapy.

Tibsovo® is the first and only IDH1 inhibitor approved in Europe. It has received orphan medicine designation recognizing the significant benefit brought to patients by Tibsovo® over available therapies for both CCA and AML.

"The prognosis for patients diagnosed with acute myeloid leukemia or cholangiocarcinoma has historically been poor with very limited treatment options. With today's approval by the European Commission, Tibsovo® is now the first targeted IDH1 inhibitor approved in Europe. This further affirms our unparalleled scientific leadership in harnessing the IDH mutation and commitment to finding new therapeutic solutions for patients with difficult and hard-to-treat cancers," **said Arnaud Lallouette, M.D., Executive Vice President, Global Medical & Patient Affairs at Servier.**

"IDH1 mutations are major drivers of disease progression in acute myeloid leukemia and cholangiocarcinoma, which are usually diagnosed at an advanced stage, highlighting the urgent need for a targeted therapeutic option. The development of new targeted therapies such as Tibsovo®, which works differently from traditional chemotherapies, is now providing treatment options that may increase the life expectancy and quality of life for patients," **said Philippe Connard, M.D., Executive Vice President, Global Product Strategy at Servier.**

AML is a cancer of the blood and bone marrow marked by rapid disease progression. It is the most common acute leukemia in adults and affects 5/100,000 inhabitants in Europe, i.e., more than 20,000 new cases each year.ⁱ The two-year survival rate of 75 years-old patients with AML is below 10%.ⁱⁱ

The approval by the European Commission in AML is supported by data from the AGILE study, a global, Phase 3, multicenter, double-blind, randomized, placebo-controlled clinical trial published in the *New England Journal of Medicine*. Results demonstrated a statistically significant improvement in event-free survival (EFS) (hazard ratio [HR] 0.33; 95% CI [0.16, 0.69]) and overall survival (OS) (HR 0.44; 95% CI [0.27, 0.73]) of patients with IDH1-mutated AML treated with Tibsovo® in combination with azacitidine compared to azacitidine plus placebo. The median OS (95% CI) for Tibsovo® + azacitidine and placebo + azacitidine was 24.0 (11.3, 34.1) and 7.9 (4.1, 11.3) months, respectively. In addition to the primary endpoint of EFS, the study met all key secondary endpoints, including complete remission (CR) rate, OS, and complete remission with partial hematologic recovery (CRh) rate, as well as objective response

rate (ORR). These results prove that Tibsovo®, in combination with azacitidine, is an effective combination treatment option for patients with newly diagnosed IDH1-mutated AML. The most common adverse reactions were vomiting, neutropenia, thrombocytopenia, electrocardiogram QT prolonged, and insomnia.

Cholangiocarcinoma, a cancer of the bile duct, is a rare and aggressive tumor often linked to medical history such as cirrhosis or liver infection. Cholangiocarcinoma affects 1-3 in 100,000 people in Europe, with approximately 10,000 new cases each year.ⁱⁱⁱ The five-year survival rate is 9%, but 0% if metastasized.^{iv} Only surgery has been shown to cure patients, but this treatment option is only possible for a limited number of patients, and the risk of relapse remains high. Chemotherapy and immunotherapy are the standard therapy for patients with cholangiocarcinoma who are not eligible for surgery or whose disease has progressed after surgery.

The European Commission's approval in cholangiocarcinoma is supported by data from the ClarIDHy trial, the first and only randomized Phase 3 trial for previously treated IDH1-mutated cholangiocarcinoma. Results from the ClarIDHy study demonstrated a statistically significant improvement in the primary endpoint of progression-free survival (PFS) by an independent review committee (HR 0.37; 95% CI [0.25, 0.54], $p < 0.001$)^v. The median PFS (95% CI) for Tibsovo® and placebo was 2.7 (1.6, 4.2) and 1.4 (1.4, 1.6) months, respectively. Thirty-two percent and 22% of patients randomized to Tibsovo® remained free of progression or death at 6 and 12 months, respectively, versus none on the placebo arm. The most common adverse reactions were fatigue, nausea, abdominal pain, diarrhea, decreased appetite, ascites, vomiting, anemia, and rash.

Tibsovo® is currently approved in the U.S. as monotherapy for the treatment of adults with IDH1-mutant relapsed or refractory AML and in monotherapy or in combination with azacitidine for adults with newly diagnosed IDH1-mutant AML who are ≥75 years old or who have comorbidities that preclude the use of intensive induction chemotherapy. Tibsovo® has also been approved in the U.S. and Australia for patients with previously treated IDH1-mutated cholangiocarcinoma. Tibsovo® is also approved in China^{vi} for the treatment of adult patients with relapsed or refractory AML who have a susceptible IDH1 mutation.

The Marketing Authorization covers the 27 countries^{vii} of the European Union as well as Iceland, Liechtenstein and Norway.

Find out more about cholangiocarcinoma and acute myeloid leukemia on servier.com.

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About the AGILE Phase 3 AML Trial^{viii}

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 (≥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 include 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 ClarIDHy Phase 3 cholangiocarcinoma trial



The ClarIDHy trial is a global, randomized Phase 3 trial in previously treated IDH1-mutant cholangiocarcinoma patients who have documented disease progression following one or two systemic therapies in the advanced setting. Patients were randomized 2:1 to receive either single-agent Tibsovo® 500 mg once daily or placebo with crossover to Tibsovo® permitted at the time of documented radiographic progression per RECIST 1.1. The primary endpoint of the ClarIDHy trial is progression-free survival (PFS) as evaluated by independent radiology review. Secondary endpoints include investigator-evaluated PFS, safety and tolerability, overall response rate, OS, duration of response, pharmacokinetics, pharmacodynamics and quality of life assessments.

About Servier

Founded to serve health, Servier is a global pharmaceutical group governed by a Foundation that aspires to have a meaningful social impact, both for patients and for a sustainable world. With its unique governance model, it can fully serve its vocation with a long-term vision: being committed to therapeutic progress to serve patient needs. The 21,400 employees of the Group are committed to this shared vocation, a source of inspiration every day.

As a world leader in cardiology, Servier's ambition is to become a renowned, focused and innovative player in oncology by targeting difficult and hard-to-treat cancers. That is why the Group allocates over 50% of its R&D budget to Oncology.

Neuroscience and immuno-inflammatory diseases are the future growth drivers. In these areas, Servier is focused on a limited number of diseases in which accurate patient profiling makes it possible to offer a targeted therapeutic response through precision medicine.

To promote access to quality care for all at a lower cost, the Group also offers a range of quality generic drugs covering most pathologies, relying on strong brands in France, Eastern Europe, Brazil and Nigeria.

In all these areas, the Group includes the patient voice at each stage of the life cycle of a medicine.

Headquartered in France, Servier relies on a strong geographical footprint in over 150 countries and achieved a revenue of €4.9 billion in 2022.

More information on the new Group website: servier.com

Follow us on social media: [LinkedIn](#), [Facebook](#), [Twitter](#), Instagram

About Servier in the U.S.

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 difficult and hard-to-treat cancers with more than 50% of its research and development dedicated to delivering significant advances in areas 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 in the U.S. is dedicated to bringing the promise of tomorrow to the patients that we serve.

For more information: www.servier.us.

About TIBSOVO® (ivosidenib tablets)

TIBSOVO® (ivosidenib tablets) is approved in the U.S. in combination with azacitidine for the treatment of patients with newly-diagnosed IDH1-mutated acute myeloid leukemia (AML) in adults 75 years of age 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.



TIBSOVO 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 ≥ 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.

Please see the TIBSOVO indications and Important Safety Information with a link to the full Prescribing Information below.

TIBSOVO IMPORTANT SAFETY INFORMATION AND INDICATION FOR U.S. PATIENTS

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-HT₃ 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



*Servier has an exclusive collaboration and license agreement with CStone for the development and commercialization of TIBSOVO (ivosidenib tablets) in Mainland China, Taiwan, Hong Kong, Macau and Singapore

ⁱ ESMO Guidelines 2020 - Acute myeloid leukemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

ⁱⁱ *National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER) Program. Cancer Stat Facts: Acute Myeloid Leukemia (AML).*
<https://seer.cancer.gov/statfacts/html/amyl.html>.

ⁱⁱⁱ Valle JW, et al. *Ann Oncol.* 2016;27(Suppl. 5):v28-v37

^{iv} Oliveira IS, et al. *Abdom Radiol (NY).* 2017;42(6):1637-1649

^v Abou-Alfa GK, et al. *Lancet Oncol.* 2020;21(6):796-807

^{vi} Conditional NDA approval for this indication from NMPA. In Mainland China, Taiwan, Hong Kong, Macau and Singapore, Servier has granted to CStone a co-exclusive license for the development and an exclusive license agreement for commercialization of Tibsovo (ivosidenib tablets).

^{vii} Centralized Marketing Authorization does not include approval in Great Britain (England, Scotland and Wales)

^{viii} ClinicalTrials.gov. Study of AG-120 (Ivosidenib) vs. Placebo in Combination with Azacitidine in Patients with Previously Untreated Acute Myeloid Leukemia With an IDH1 Mutation (AGILE). Available at: <https://clinicaltrials.gov/ct2/show/NCT03173248>.

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