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

- **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, France, May 10th, 2023 – 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 Gonnard, 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, 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 the treatment 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 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, diarrhoea, decreased appetite, ascites, vomiting, anaemia 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.

Press contacts

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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

Important Safety Information

Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Concomitant administration of strong CYP3A4 inducers or dabigatran
Congenital long QT syndrome.
Familial history of sudden death or polymorphic ventricular arrhythmia.
QT/QTc interval > 500 msec, regardless of the correction method.

Warnings

Differentiation syndrome in patients with AML:
Differentiation syndrome may be life-threatening or fatal if not treated. Patients must be informed of signs and symptoms of differentiation syndrome, be advised to contact their physician immediately if these occur and the need to carry the Patient Alert Card with them at all times. Interrupt treatment with Tibsovo if severe signs/symptoms persist for more than 48 hours after the initiation of systemic corticosteroids.

QTc interval prolongation:
Any abnormalities should be managed promptly. In case of suggestive symptomatology, an ECG should be performed. In case of severe vomiting and/or diarrhea, an assessment of serum electrolytes abnormalities must be performed. Patients should be informed of the risk of QT prolongation, its signs and symptoms and be advised to contact their physician immediately if these occur. Patients should be treated with caution and closely monitored for QTc interval prolongation if use of a suitable alternative to medicinal products known to prolong the QTc interval, or moderate or strong CYP3A4 inhibitors is not possible. Closely monitor patients with congestive heart failure, electrolyte abnormalities or if administration of furosemide is clinically indicated to manage differentiation syndrome. Treatment should be permanently discontinued if patients develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia. Use with caution in patients who have either albumin levels below the normal range or are underweight.

Severe renal impairment: use with caution and closely monitor.

Hepatic impairment: use with caution and closely monitor in patients with moderate and severe hepatic impairment (Child-Pugh classes B and C). Use with caution in patients with mild hepatic impairment (Child-Pugh class A).

Excipients: contains lactose and sodium (essentially 'sodium free').

This is not a complete summary of all safety information.
See Tibsovo (ivosidenib) SmPC at www.ema.europa.eu. Globally, prescribing information varies; refer to the individual country product label for complete information.

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[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.