

**Company**

Servier Pharmaceuticals

**Drug or Device Name**

TIBSOVO®

**Category**

Pharmaceutical

**Compound/Technical Name**

Ivosidenib tablets

**Trade Name**

TIBSOVO®;

**Date of Approval**

08/25/2021

**Therapeutic Categories**

Cholangiocarcinoma (CCA): TIBSOVO is indicated as the first and only targeted therapy approved for the treatment of adult patients with previously treated, locally advanced or metastatic cholangiocarcinoma (CCA) with an IDH1 mutation as detected by an FDA-approved test.

**Indications**

TIBSOVO is also approved in the U.S. as monotherapy for the treatment of adults with IDH1-mutated relapsed or refractory acute myeloid leukemia (AML) and for adults with newly diagnosed IDH1-mutated AML who are 75 years old or older or who have comorbidities that preclude the use of intensive induction chemotherapy. TIBSOVO was also approved 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. Most recently, TIBSOVO was approved by the European Commission 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.

**Background**

Cholangiocarcinoma (CCA) also known as bile duct cancer, is a rare and aggressive type of cancer that affects the bile ducts, which carry digestive fluid (bile) and connect your liver, gallbladder and small intestine. It is known as a difficult-to-treat cancer with few treatment options. Approximately 8,000 people in the U.S. are diagnosed with CCA each year, but the actual number of cases may be higher. CCA can be hard to diagnose, leading to misclassification as other types of cancers. About 40% of

biliary tract cancers have potential targetable genetic driver mutations. Isocitrate dehydrogenase (IDH) mutations occur in a wide range of blood and solid tumor cancers, including CCA. Present in up to 20% of cholangiocarcinoma cases in the U.S., IDH1 mutations remain the most prevalent alterations in CCA, and they are not associated with prognosis. While CCA has historically been difficult-to-treat with few effective treatment options, genetic sequencing has identified new potential therapeutic targets for this cancer. Prior to the approval of TIBSOVO there were three standard treatment options for newly diagnosed CCA: surgery, radiation therapy and chemotherapy. Patients living with IDH1-mutated CCA, especially those whose disease progresses following chemotherapy, have been in urgent need of new treatment options. With this approval, TIBSOVO now provides an important therapeutic option for patients with IDH1-mutated CCA.

## Development

TIBSOVO had already previously been approved in the U.S. as monotherapy for the treatment of adults with IDH1-mutated relapsed or refractory acute myeloid leukemia (AML) and for adults with newly diagnosed IDH1-mutated AML who are 75 years or older or who have comorbidities that preclude the use of intensive induction chemotherapy. In addition to recently being approved for CCA, TIBSOVO received an additional FDA approval on May 25, 2022, in combination with azacitidine for the treatment of patients with newly diagnosed IDH1-mutated AML in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy. TIBSOVO is currently being explored in other therapeutic areas, as IDH1 is seen across a variety of tumor types. Servier is pioneering the science behind IDH mutations, exploring the significant potential of inhibiting mutant IDH enzymes as a novel approach to treating cancers with high unmet needs. The FDA approval of TIBSOVO for CCA was supported by data from the ClarIDHy study, the first and only randomized Phase 3 trial for previously treated IDH1-mutated CCA. Results from the ClarIDHy study demonstrated a statistically significant improvement in the primary endpoint of progression-free survival (PFS) in patients randomized to TIBSOVO compared to those randomized to placebo. The ClarIDHy study is also evidence of the feasibility of conducting a global targeted-therapy trial in what is considered a rare disease. Importantly, it highlighted the advantage of engaging key opinion leaders and other stakeholders, including physicians, patient advocacy groups, and patients, in designing a study in CCA to encourage patient participation and allowing for a patient crossover to active drug at the first sign of progression. By designing the trial through an inclusive, cross-functional partnership, the team was able to forward a clinical trial that was best for the patients. This trial showed a new way to approach drug development. The approach taken allowed for real time amendments to the protocol and trial design that were reflective of the clinical and patient community feedback. This is what made the ClarIDHy study not only unique and innovative, but also was a critical component of its success. TIBSOVO is a targeted therapy that selectively inhibits mutant IDH1 enzyme. Since TIBSOVO targets the IDH1 mutation, it can be used to treat adults with CCA with an IDH1 mutation. Additionally, because TIBSOVO is a targeted therapy, it works differently from traditional chemotherapy. It's an oral therapy which offers patients the chance to take it at home, thus allowing for fewer hospital visits and overall greater flexibility. Once TIBSOVO gained approval for this third indication, it became the first and only targeted therapy approved for patients with previously treated IDH1-mutated cholangiocarcinoma. The devoted team at Servier understood the importance of TIBSOVO to CCA community. It was only through the tireless efforts of the dedicated researchers, participants, and entire research team that this product was able to weather incredible change and challenges to bring this life-changing medication to patients on the same timelines. Servier is committed to finding solutions that will address today's challenges and serve our patients with the utmost treatment and care to improve the potential for survival.

## Innovation

TIBSOVO offers new hope for those with IDH1-mutated CCA, providing a targeted therapy option that's specific to their diagnosis. Prior to the approval of TIBSOVO, there were no approved targeted therapies for IDH1-mutated CCA, and limited chemotherapy options are available in the advanced setting. Gemcitabine-based chemotherapy is often recommended for newly diagnosed advanced or metastatic disease. However, this treatment can only be administered as an infusion into a vein, requiring extensive hospital or doctor's office visits. Not only is TIBSOVO the first targeted agent to show a survival benefit in the treatment of CCA patients harboring IDH1 mutations, but TIBSOVO offers convenient, once-daily oral dosing that offers patients the chance to take therapy at home. TIBSOVO is not only giving CCA patients a chance at survival, but also part of their life back. The therapeutic exploitation of IDH mutations is the first successful example of precision medicine in CCA. The identification of IDH mutations across multiple cancer types including both solid and hematologic malignancies has revolutionized the understanding of development certain diseases, allowing for more potential targeted therapeutics using small molecule inhibitors. The company's IDH programs continue to produce promising results, and Servier is excited to further advance clinical studies that will potentially bring more cutting-edge, effective treatment option to patients. TIBSOVO for CCA is a revolutionary treatment, as it is the first and only targeted therapy approved for the treatment of adult patients with previously treated, locally advanced or metastatic cholangiocarcinoma with an IDH1 mutation as detected by an FDA-approved test. As an oral therapy, TIBSOVO also offers patients the chance to take therapy at home, thus giving them back a part of their life. However, the impact of this drug far extends the CCA community. The approval of this drug improves patient care across disease states. By requiring a biomarker test to be eligible for treatment, TIBSOVO is underscoring the value of biomarker testing or molecular profiling, as some refer to it. Over the last two decades, new advancements have made it possible to look very closely inside a person's genetic makeup to see exactly which mutations are present in cancerous cells. Molecular profiling, which can also be referred to as molecular testing, scientists have gained a much better understanding of how cancer operates in the body, opening the door to targeted therapies that best respond to a specific type of cancer. Molecular profiling can be an incredibly important tool that helps oncologists gain a broader understanding of a patient's specific biomarker, consequently allowing them to identify targeted therapies that will work best for them, like TIBSOVO. The identification of IDH mutations across multiple cancer types including both solid and hematologic malignancies has revolutionized the understanding of development certain diseases, allowing for more potential targeted therapeutics using small molecule inhibitors. The previous approval of TIBSOVO for AML and approval of TIBSOVO for CCA is only the beginning of Servier's IDH program. Servier was also able to expand the indication of TIBSOVO for AML with the approval of TIBSOVO in combination with azacitidine for the treatment of patients with newly diagnosed IDH1-mutated AML in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy. Most recently, TIBSOVO was approved by the European Commission 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.

Servier continues to evaluate the opportunity to pursue launches in additional geographies. Additionally, Servier continues to seek label expansion opportunities for TIBSOVO through ongoing

research and development efforts. Being a privately held company, Servier has the freedom to invest in areas where others may have failed or considered too risky like cholangiocarcinoma. A considerable portion of the company's R&D investment –50%– goes to fighting cancer and addressing critical unmet patient needs. With its growing IDH program, Servier is pioneering the science behind IDH mutations and bringing new therapeutic options to patients. Servier Pharmaceuticals is committed to delivering important therapies to the patients that it serves and evolving the standard of care for difficult to treat cancers, like CCA. As a leader in oncology, Servier is committed to investing in partnering in scientific innovation that addresses critical unmet needs in difficult-to-treat cancers and delivers significant advances for all patients.

**Pubmed**

1. Zhu A, et al. Final results from ClarIDHy, a global, phase 3, randomized, double-blind study of ivosidenib vs placebo in patients with previously treated cholangiocarcinoma and an isocitrate dehydrogenase 1 (IDH1) mutation. Presented at Gastrointestinal Cancer Symposium 2021. Available at: [https://www.servier.us/sites/default/files/2021-04/ASCO-GI21 ClarIDHy.pdf](https://www.servier.us/sites/default/files/2021-04/ASCO-GI21%20ClarIDHy.pdf).

**Attachments**

- Servier receives European Commission approval of Tibsovo ivosidenib tablets in IDH1mutated Acute Myeloid Leukemia and IDH1mutated Cholangiocarcinoma.pdf

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