FDA and EMA Accept Vorasidenib Regulatory Submissions for Marketing Approval of Vorasidenib for the Treatment of IDH-mutant Diffuse Glioma

Vorasidenib would be the first targeted therapy, if approved, in IDH-mutant diffuse glioma, a malignant and incurable brain tumor.

In clinical studies, vorasidenib has demonstrated strong blood-brain barrier penetrance alongside clinically meaningful and statistically significant improvements in progression-free survival and time-to-next intervention.

Approval of vorasidenib would mark Servier's sixth approval for a first-in-class treatment option in IDH-mutant cancer.

Suresnes, France, Boston, MA, February 20th, 2024 – Servier, a global leader in oncology focused on delivering meaningful therapeutic progress for the patients it serves, today announced the FDA filing acceptance and priority review for a New Drug Application (NDA) for vorasidenib, as well as the EMA agreed for an accelerated assessment for the vorasidenib Marketing Authorization Application (MAA). This innovative targeted therapy is an oral, selective, highly brain-penetrant dual inhibitor of mutant isocitrate dehydrogenase 1 and 2 (IDH1/2) enzymes for the treatment of IDH-mutant diffuse glioma. Vorasidenib would become a first-in-class targeted therapy for patients with IDH-mutant gliomas and would mark Servier's sixth approval across IDH-mutant cancers, if approved. The FDA has assigned a Prescription Drug User Fee Act (PDUFA) action date of August 20th, 2024, and the European Commission approval is expected in the second half of 2024.

"In the realm of glioma treatment, innovation has been stagnant for nearly a quarter-century, posing challenges for patients who, post-surgery, may opt to defer treatment due to concerns around potential toxic side effects. As a drug specifically designed to be highly blood-brain barrier penetrant, vorasidenib has demonstrated clinically meaningful efficacy in patients with IDH1/2 mutant gliomas alongside a consistently manageable safety profile," said **Susan Pandya, M.D., Head of Cancer Metabolism Global Development Oncology & Immuno-Oncology, Servier**. *"This promising outcome brings hope to patients grappling with IDH-mutant diffuse gliomas, offering a potential breakthrough for those eagerly awaiting a new therapeutic option."*

Adult-type diffuse gliomas represent approximately 81% of primary malignant brain tumors. Of those, approximately 20% harbor an IDH mutation, including 100% of grade 2 and grade 3 adult-type diffuse gliomas, as well as a much smaller portion of the grade 4 tumors.[1,2] Testing for IDH mutations is essential for the accurate diagnosis of adult-type diffuse gliomas and can offer more information on the pathogenesis and prognosis of the disease.[3] The 2021 WHO Classification includes disease defining histologic and molecular features, including IDH mutation status, to diagnose adult-type diffuse gliomas.[4] Additionally, the National Clinical Practice Guidelines in Oncology (NCCN Guidelines) recommend IDH mutation testing in all patients with glioma, noting IDH mutation status impacts diagnosis, prognosis and treatment recommendations.[5]

"As a pioneer in the field of mutant IDH inhibition, Servier has consistently spearheaded the development of cutting-edge treatment options for various cancer types characterized by IDH mutations. The compelling efficacy results observed with vorasidenib in the INDIGO study underscore its full potential to emerge as the benchmark treatment for patients grappling with IDH-mutant diffuse glioma harboring IDH1/2 mutations," **stated Claude Bertrand**, **Executive Vice-President of Research & Development and Chief Scientific Officer at Servier**. *"The submission of global regulatory filings for vorasidenib serve as validation of Servier's global oncology commitment while marking a possibly significant milestone for patients who have endured more than two decades without access to new therapeutic solutions."*

The submissions are based on results from the pivotal Phase 3 INDIGO clinical trial, which met its primary endpoint of progression-free survival (PFS) per blinded independent review committee (BIRC) and key secondary endpoint of time to next intervention (TTNI) at the prespecified second interim analysis. The primary endpoint, PFS per BIRC, was statistically significant and clinically meaningful in favor of the vorasidenib arm (Hazard Ratio [HR], 0.39; 95% Confidence Interval [CI], 0.27 to 0.56; 1-sided P=0.000000067), median PFS for vorasidenib and placebo was 27.7 and 11.1 months, respectively. TTNI was also statistically significant (HR, 0.26; 95% CI, 0.15 to 0.43; 1-sided P=0.000000019). Median TTNI was not reached for vorasidenib and was 17.8 months for placebo. Vorasidenib was also shown to reduce the tumor volume by a mean of 2.5% (TGR of –2.5%; 95% CI: -4.7% to -0.2%) every 6 months, while tumor volume increased by a mean of 13.9% (TGR of 13.9%; 95% CI: 11.1% to 16.8%) every 6 months for patients randomized to the placebo arm, as measured by a blinded independent radiology committee.

The INDIGO study showed that vorasidenib was well-tolerated, and its safety profile was consistent with results from the Phase 1 studies. Overall, vorasidenib was associated with mainly low-grade adverse events. Adverse events of grade 3 or higher occurred in 22.8% of the patients who received vorasidenib and in 13.5% of those who received placebo. An increased alanine aminotransferase level of grade 3 or higher occurred in 9.6% of the patients who received vorasidenib and in no patients who received placebo.

The results of INDIGO were presented at the 2023 Annual Meeting of the American Society of Clinical Oncology (ASCO) and simultaneously published in *The New England Journal of Medicine*. The results of additional secondary endpoints, including vorasidenib's impact on tumor growth rate (TGR) of IDH-mutant gliomas, were presented at the 2023 Annual Meeting of the Society for Neuro-Oncology (SNO) among other presentations including results on health-related quality of life, seizure control, neurocognition, and preliminary molecular translational analyses.

Priority Review is granted to FDA applications for medicines that, if approved, would provide significant improvements in the effectiveness or safety of the treatment, diagnosis or prevention of serious conditions.[6] Vorasidenib was granted Fast Track Designation by the FDA in February 2023 and Breakthrough Therapy Designation by the FDA in August 2023.

The EMA's accelerated assessment is granted if the Committee for Medicinal Products for Human Use decides the new medicine is expected to be of major public health interest, particularly from the viewpoint of therapeutic innovation.[7]

Servier has also submitted an application for project Orbis member countries, including Brazil, Canada, Australia, Israel and Switzerland. In addition, Servier plans to submit a Marketing Autorization Application in the United Kingdom after the positive CHMP opinion. More information about Project Orbis can be found on the FDA website.

About the INDIGO Phase 3 Trial (NCT04164901)

INDIGO was a registration-enabling Phase 3 global, randomized, double-blind placebo-controlled study of vorasidenib in patients with residual or recurrent grade 2 glioma with an isocitrate dehydrogenase 1/2 (IDH1/2) mutation who have undergone surgery as their only treatment. Results were published in *The New England Journal of Medicine*.

About Glioma[8]

Adult-type diffuse gliomas represent approximately 81% of primary malignant brain tumors. Of those, approximately 20% harbor an IDH mutation, including 100% of grade 2 and grade 3 adult-type diffuse gliomas, as well as a much smaller portion of the grade 4 tumors.[1,2] Establishing the IDH mutation status of these tumors is essential to both diagnosis and prognosis, per the 2021 WHO classification of CNS tumors and the NCCN treatment guidelines, respectively. As of 2021, adult-type diffuse gliomas are sub-divided into only three categories:

- Astrocytoma, IDH-mutant (CNS WHO grades 2-4)
- Oligodendroglioma, IDH-mutant and 1p19q-codeleted (CNS WHO grades 2-3)
- Glioblastoma, IDH-wildtype (CNS WHO grade 4)

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 21,900 employees of the Group are committed to this shared vocation, source of inspiration every day.

As a world leader in cardiology, Servier's ambition is to become a focused and innovative player in oncology by targeting hard-to-treat cancers. That is why the Group allocates over 70% of its R&D budget to developing targeted and innovative therapies in 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 €5.3 billion in 2023.

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Press Contacts

Servier Group (Global)
marion.breyer@servier.com

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