# Servier's VORANIGO® (vorasidenib) Tablets Receives FDA Approval as First Targeted Therapy for Grade 2 IDH-mutant Glioma

- **VORANIGO is the first and only FDA-approved targeted treatment in Grade 2 IDH-mutant glioma**
- **VORANIGO demonstrated significant improvement in progression free survival with a favorable safety profile in a pivotal Phase 3 study of patients with Grade 2 IDH-mutant glioma**
- **VORANIGO is the sixth approval for Servier in the field of IDH-mutant targeted therapies**

**BOSTON, Mass. – August 6, 2024 –** Servier today announced that the U.S. Food and Drug Administration (FDA) has approved VORANIGO®, an isocitrate dehydrogenase-1 (IDH1) and isocitrate dehydrogenase-2 (IDH2) inhibitor, indicated for the treatment of adult and pediatric patients 12 years and older with Grade 2 astrocytoma or oligodendroglioma with a susceptible IDH1 or IDH2 mutation following surgery including biopsy, sub-total resection, or gross total resection. VORANIGO is available and offers glioma patients the ability to actively manage their disease with the convenience of a once-daily pill.

Gliomas are types of brain cancer that can hinder normal brain function and cause a variety of symptoms. Diffuse gliomas with IDH mutations represent the most common malignant primary brain tumors diagnosed in adults younger than 50 years of age. They are not curable with current therapies and without treatment they continue to grow and infiltrate normal brain tissue. [1 2 3]

"Today's approval of VORANIGO is an enormous leap forward in cancer care, and a defining moment for people living with Grade 2 IDH-mutant glioma," said Arjun H. Prasad, Chief Commercial Officer, Servier Pharmaceuticals. "VORANIGO, which is the first breakthrough in this specific disease area in nearly 25 years, offers patients unprecedented improvement in progression free survival. We are proud to deliver this first-of-its-kind therapy to patients in need, and we remain committed to bringing innovative targeted therapies to people with cancer."

In healthy human cells, a family of genes called isocitrate dehydrogenases (IDH) help break down nutrients and generate energy for cells. Mutations in IDH1 and IDH2 are associated with a variety of cancers, where they prevent cells from differentiating, or specializing, into the kind of cells they are ultimately supposed to become. When cells cannot differentiate properly, they may begin to grow

[1] Mandonnet E, Delattre JY, Tanguy ML, et al. Continuous growth of mean tumor diameter in a subset of grade II gliomas. *Ann Neurol* 2003;53:524-528.
[2] Rees J, Watt H, Jäger HR, et al. Volumes and growth rates of untreated adult low-grade gliomas indicate risk of early malignant transformation. *Eur J Radiol* 2009;72:54-64.
[3] Miller JJ, Gonzalez Castro LN, McBrayer S, et al. Isocitrate dehydrogenase (IDH) mutant gliomas: a Society for Neuro-Oncology (SNO) consensus review on diagnosis, management, and future directions. *Neuro Oncol* 2023;25:4-25.

out of control.[4] In IDH-mutant gliomas, VORANIGO works by reducing the activity of the mutant IDH1 and IDH2 enzymes, to help control the disease.

"Patients living with Grade 2 IDH-mutant gliomas have long faced the harsh reality of an incurable disease with very limited post-surgery treatment options," said Ralph DeVitto, President & CEO, of the American Brain Tumor Association. "The FDA approval of VORANIGO marks a monumental breakthrough in glioma treatment, offering renewed hope for patients and their families living with this relentless disease."

The approval of VORANIGO is supported by results from the pivotal Phase 3 INDIGO clinical trial published in *The New England Journal of Medicine* and presented during the Plenary Session at the 2023 Annual Meeting of the American Society of Clinical Oncology (ASCO), which showed that VORANIGO significantly extended progression free survival and time to next intervention, when compared to placebo. The INDIGO study showed that VORANIGO was well tolerated, and its safety profile was consistent with results from the Phase 1 studies. The most common (≥15%) adverse reactions were fatigue, COVID-19, musculoskeletal pain, diarrhea and seizure.[5]

"Glioma is a unique cancer. Many of the patients I've met are in their 30's and 40's and in the prime of their lives. They have small children and are at the height of their careers. A glioma diagnosis is devastating. VORANIGO can offer patients and their families hope for the future," said David K. Lee, CEO, Servier Pharmaceuticals. "As we advance more targeted therapies, identifying mutations and understanding how these mutations impact cancer and its progression are key to helping the right patients find the right treatment, at the right time. We are humbled to lead the field of IDH-mutant inhibition, and we are committed to researching its applicability in glioma and other cancers."

**About the INDIGO Phase 3 Trial (NCT04164901)[5]**

INDIGO, the pivotal Phase 3 clinical trial, met its major efficacy outcome of progression free survival (PFS) per a blinded independent review committee (BIRC) and key secondary endpoint of time to next intervention (TTNI) at the prespecified second interim analysis. The major efficacy outcome, PFS was statistically significant and clinically meaningful in favor of the vorasidenib arm. Median PFS was 27.7 months in the vorasidenib group, compared with 11.1 months in the placebo group (Hazard Ratio [HR], 0.39; 95% Confidence Interval [CI], 0.27 to 0.56; 1-sided P<0.001). TTNI was also statistically significant (HR, 0.26; 95% CI, 0.15 to 0.43; 1-sided P<0.001). Median TTNI was not reached for vorasidenib and was 17.8 months for placebo. Vorasidenib was also shown to reduce the

[4] Julie Grisham Monday, J. 1. (2019, July 1). *Research clarifies how IDH mutations cause cancer*. Memorial Sloan Kettering Cancer Center. https://www.mskcc.org/news/research-clarifies-how-idh-mutations-cause

[5] Mellinghoff, I. K., van den Bent, M. J., Blumenthal, D. T., Touat, M., Peters, K. B., Clarke, J., Mendez, J., Yust-Katz, S., Welsh, L., Mason, W. P., Ducray, F., Umemura, Y., Nabors, B., Holdhoff, M., Hottinger, A. F., Arakawa, Y., Sepulveda, J. M., Wick, W., Soffietti, R., … Cloughesy, T. F. (2023). Vorasidenib in idh1- or IDH2-mutant low-grade glioma. New England Journal of Medicine, 389(7), 589–601. https://doi.org/10.1056/nejmoa2304194

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 BIRC.
The INDIGO study showed that vorasidenib was well tolerated, and its safety profile was consistent with results from the Phase 1 studies.

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.

**About Glioma[6]**
Gliomas are tumors that arise from glial or precursor cells within the central nervous system (CNS). The 2021 World Health Organization (WHO) classification recognizes four general groups of gliomas, one of which is adult-type diffuse gliomas. These diffuse gliomas are the most common primary malignant brain tumors in adults. The pathogenesis and prognosis of these tumors are tightly linked to mutations (or lack thereof) in the metabolic enzyme isocitrate dehydrogenase (IDH), and molecular testing is required for proper diagnosis. 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 and1p19q-codeleted (CNS WHO grades 2-3)
- Glioblastoma, IDH-wildtype (CNS WHO grade 4)

**About Servier in Oncology**
Servier is a global leader in oncology, governed by a non-profit foundation. Servier approaches innovation with a long-term vision, free of influence from fiduciary responsibilities.

Servier is the leader in IDH-mutant targeted therapies and devotes more than 65% of its research and development budget to Oncology. Servier aspires to advance more targeted therapies by identifying mutations and understanding how these mutations impact cancer and its progression. Servier believes we can serve more people by helping the right patients find the right treatment, at the right time.

Servier takes a One Innovation Engine approach to R&D and is actively seeking alliances, partnerships and acquisitions at various stages of the portfolio.

[6] Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, Hawkins C, Ng HK, Pfister SM, Reifenberger G, Soffietti R, von Deimling A, Ellison DW. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro Oncol. 2021 Aug 2;23(8):1231-1251. doi: 10.1093/neuonc/noab106. PMID: 34185076; PMCID: PMC8328013.

For more information about working with Servier to bring the promise of tomorrow to the patients it serves, visit Servier.us.

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**VORANIGO IMPORTANT SAFETY INFORMATION**

**What is VORANIGO?**
VORANIGO (40 mg tablets) is a prescription medicine used to treat adults and children 12 years of age and older with certain types of brain tumors called astrocytoma or oligodendroglioma with an isocitrate dehydrogenase-1 (IDH1) or isocitrate dehydrogenase-2 (IDH2) mutation, following surgery. Your healthcare provider will perform a test to make sure that VORANIGO is right for you. It is not known if VORANIGO is safe and effective in children under 12 years of age.

**What are the possible side effects of VORANIGO?**

**VORANIGO may cause serious side effects, including:**

- **Liver problems.** Changes in liver function blood tests may happen during treatment with VORANIGO and can be serious. Your healthcare provider will do blood tests to check your liver function before and during treatment with VORANIGO. Tell your healthcare provider right away if you develop any of the following signs and symptoms of liver problems:
  - yellowing of your skin or the white part of your eyes (jaundice)
  - dark tea-colored urine
  - loss of appetite
  - pain on the upper right side of your stomach area
  - feeling very tired or weak

**The most common side effects of VORANIGO include:**

- increased liver enzyme levels in the blood
- lack of energy, tiredness
- headache
- COVID-19
- muscle aches or stiffness
- diarrhea
- nausea
- seizure

**Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with VORANIGO if you have certain side effects.**

VORANIGO may affect fertility in females and males, which may affect the ability to have children. Talk to your healthcare provider if this is a concern for you.

These are not all of the possible side effects of VORANIGO.

**Before taking VORANIGO, tell your healthcare provider about all of your medical conditions, including if you:**

- have liver problems
- have kidney problems or are on dialysis
- smoke tobacco
- are pregnant or plan to become pregnant. VORANIGO can harm your unborn baby

**Females who are able to become pregnant:**

- Your healthcare provider will do a pregnancy test before you start treatment with VORANIGO
- You should use effective nonhormonal birth control during treatment with VORANIGO and for 3 months after the last dose. VORANIGO may affect how hormonal contraceptives (birth control) work and cause them to not work well. Talk to your healthcare provider about birth control methods that may be right for you during treatment with VORANIGO
- Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with VORANIGO

**Males with female partners who are able to become pregnant:**

- You should use effective birth control during treatment with VORANIGO and for 3 months after the last dose
- Tell your healthcare provider right away if your partner becomes pregnant or thinks she may be pregnant during your treatment with VORANIGO

Tell your healthcare provider if you are breastfeeding or plan to breastfeed. It is not known if VORANIGO passes into breast milk. **Do not** breastfeed during treatment with VORANIGO and for 2 months after the last dose.

**Tell your healthcare provider about all the medicines you take,** including prescription and over-the-counter medicines, vitamins, and herbal supplements. VORANIGO may affect the way other medicines work, and other medicines may affect how VORANIGO works.

**Please click here for full prescribing information.**

**Disclosures**

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