

VORANIGO®

Category:

Best Product for Orphan/Rare Diseases

Company Name:

Servier Pharmaceuticals

Product/Solution Name:

VORANIGO®

Compound/Tech Name:

vorasidenib

Trade Name:

VORANIGO® (vorasidenib tablets)

Corporate Name:

Servier Pharmaceuticals LLC

Date of Approval:

2024-08-06

Indications:

VORANIGO is a prescription medicine used to treat adults and children 12 years of age and older with astrocytoma or oligodendroglioma brain tumors with an isocitrate dehydrogenase-1 (IDH1) or isocitrate dehydrogenase-2 (IDH2) mutation, following surgery.

Therapeutic Areas:

Oncology

General Information File Document upload:

Background information and need for drug / device:

Gliomas make up approximately 82% of all malignant primary brain tumor in adults, with six cases diagnosed per 100,000 individuals every year in the U.S. Gliomas are categorized by the World Health Organization (WHO) into tumor subtypes and tumor grades according to a combination of histological and molecular features.

Mutations in the genes encoding the metabolic enzymes isocitrate dehydrogenase 1 (IDH1) or 2 (IDH2) are present in nearly all Grade 2 diffuse gliomas in adults and are a hallmark of many other cancer types as well. Diffuse gliomas with IDH mutations represent the most common malignant primary brain tumors in patients under 50 years old.ⁱ

Gliomas with an IDH mutation are malignant and incurable brain tumors that continue to grow and relentlessly infiltrate the brain, even after surgery.ⁱⁱ Patients with this condition are often young - in their 30s and 40s - and otherwise healthy.ⁱⁱⁱ They are generally in the prime of their lives, starting families, building their careers, and planning for their future. The impact on patients and their families is profoundly life-altering.

Historically, treatment options for glioma patients have been extremely limited. Surgery is often the first option for treating glioma, aiming to remove as much of the tumor as possible without compromising neurological function, though total resection of diffuse gliomas is rarely achievable through surgery because of the tumor's infiltrative nature. Post-surgery radiation and chemotherapy are usually reserved for advanced cases due to the risk of long-term toxicities, especially among younger patients. This has created a treatment gap, leaving many in a \"watch and wait\" approach, enduring ongoing monitoring and living with the constant fear of disease progression. \"Watch and wait,\" also known as an observational period, is typically an intervention agnostic approach, that requires patients to have regular scans to track tumor growth.

Considering this disease's poor prognosis, the lack of treatment options, and the known gap in care, the approval of VORANIGO marked a defining moment for people living with Grade 2 IDH-mutant glioma. Taken as a once daily oral pill, VORANIGO is the first breakthrough in this specific disease area in more than 20 years and ushered in a profound shift in patient care.

Background File Document upload:

[Servier VORANIGO Hallmarks of IDH Mutant Gliomas 1.pdf](#)

[Servier VORANIGO MoA Video 1.mp4](#)

[Servier VORANIGO Media Clip 60 secs 1.mp4](#)

History of the development of the solution/product:

After bringing a first-of-its-kind treatment for IDH-mutant blood cancers to market, Servier hypothesized that targeting IDH mutations could be an effective treatment strategy in certain gliomas and designed an innovative development program to evaluate VORANIGO in Grade 2 IDH-mutant glioma.

The Phase 1 peri-operative study was particularly unique because it was designed to assess VORANIGO's brain penetration properties and mechanism of action. VORANIGO works by inhibiting the activity of the mutant IDH1 and IDH2 enzymes to help control the disease. In addition to suppressing the mutant IDH enzymes that promote tumor growth, VORANIGO was designed to traverse the blood-brain barrier after being taken orally. This is noteworthy because many drugs, including most anticancer drugs, are unable to penetrate the brain or spinal cord, regardless of administration route (e.g., ingested, injected, or infused).

The Phase 1 assessment showed that VORANIGO effectively crossed the blood-brain barrier and reached significant levels of target engagement. Building on the encouraging early data, the Phase 3 INDIGO trial was designed to select the appropriate patient population and characterize them using clinically relevant and patient-specific inclusion and exclusion criteria.

To ensure patient experience was at the forefront of the trial design, Servier worked closely with patient advocacy groups, including the National Brain Tumor Society, to understand the profound impact of the short- and long-term toxicity of existing therapies on quality of life, as well as the burden of the \"watch and wait\" approach. This valuable perspective encouraged Servier to include study endpoints evaluating patients' quality of life, neurocognition, and other relevant factors. Moreover, it prompted a focus on developing the drug in the earliest stage of the disease post-surgery. This resonated with patients, and the trial fully enrolled in two years, despite the pandemic-related challenges of site closures, limited access, and social distancing requirements.

The Phase 3 results were groundbreaking, capturing the attention of the global medical community when presented at the 2023 Annual Meeting of the American Society of Clinical Oncology plenary session and published in The New England Journal of Medicine. The results demonstrated the first ever positive Phase 3 study of a targeted systemic therapy in Grade 2 IDH-mutant glioma, with a remarkable reduction of the risk of disease progression in these patients by 60% compared to placebo. The study also met its key secondary endpoint of time to next intervention (TTNI). In stark contrast to the placebo group's median TTNI of 17.8 months, the median TTNI was not reached in the VORANIGO group, indicating most patients didn't need another intervention during the study.

These findings paved the regulatory pathway to bring this transformative treatment option to patients living with glioma and set a new standard of care. VORANIGO was granted Fast Track, Breakthrough and Orphan Drug Designations, as well as Priority Review, and was approved by the U.S. Food and Drug Administration on August 6, 2024.

Development File Document upload:

[Servier VORANIGO US PI 2.pdf](#)

[Servier VORANIGO NEJM Data 1.pdf](#)

Why this drug or device is innovative, the broad implications for future research, and/or how it will improve the human condition:

After more than 20 years without any new treatment advancements in this disease area, the August 2024 approval of VORANIGO was a long-awaited breakthrough for glioma patients in need of additional treatment options. VORANIGO is the first FDA-approved therapy specifically designed to target mutant IDH enzymes in Grade 2 glioma and has brought an undeniable shift to the treatment paradigm. VORANIGO provides patients an alternative to \"watching and waiting\" for disease progression and offers the potential to significantly delay radiation and chemotherapy, giving patients and physicians the opportunity to actively control the disease.

VORANIGO's unique ability to cross the blood-brain barrier and penetrate the brain after being taken orally is a truly innovative scientific feat that many anti-cancer drugs are unable to achieve, and its utility is supported by a decade of clinical research.

VORANIGO has also demonstrated improved seizure control, a common and burdensome symptom among glioma patients and a frequent cause of distress, hospitalizations, and disability. A longer-term analysis of an additional six months of data from the Phase 3 INDIGO trial - which was presented at the 2024 Society for Neuro-Oncology Annual Meeting - demonstrated treatment with VORANIGO was associated with better seizure control compared to placebo. This crucial clinical benefit observed in the longer-term analysis can be attributed in part to VORANIGO's innovative mechanism, which inhibits the activity of the mutant IDH1 and IDH2 enzymes to help control the disease.

Supported by the unprecedented efficacy observed in the pivotal trial, Servier is continuing to pursue research that will further clarify VORANIGO's long-term impact in this setting and expand understanding of IDH inhibition in glioma and other cancers.

For the first time ever, glioma patients have access to a treatment option that addresses the biology of their tumor, delays progression, and potentially reduces or postpones the need for radiation and chemotherapy. With VORANIGO, patients in the

prime of their lives can experience more meaningful time with the preservation of cognitive function, independence, and quality of life.

The approval of VORANIGO is a landmark moment for patients, clinicians, and the broader oncology community, addressing an urgent unmet need and laying the foundation for future innovation in glioma care. VORANIGO represents a new era of precision therapies for patients with difficult-to-treat tumors and has redefined the standard of care, offering new hope and improved outcomes to glioma patients and their families.

Innovation File Document upload:

Servier VORANIGO SNO Data 1.pptx

Please provide appropriate references (PubMed, Abstract, Website):

i Ostrom QT, Gittleman H, Liao P, Vecchione-Koval T, Wolinsky Y, Kruchko C, Barnholtz-Sloan JS. CBTRUS Statistical Report: Primary brain and other central nervous system tumors diagnosed in the United States in 2010-2014. Neuro Oncol. 2017 Nov 6;19(suppl_5):v1-v88.

ii Mellinghoff I, et al. N Engl J Med. 2023;389(7):589-601

iii Molinaro A, et al. Nat Rev. Biotech. 2019;15: 405-417

References File Document upload:

Servier VORANIGO Reference 2 Mellinghoff 1.pdf

Servier VORANIGO Reference 3 Molinaro 1.pdf

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