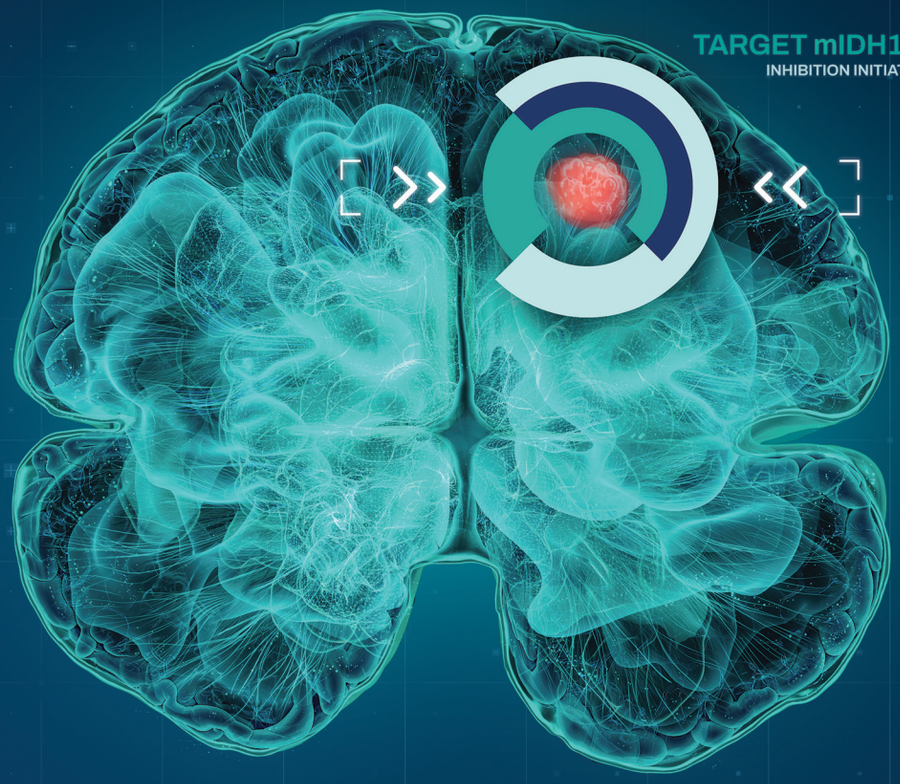
In patients with Grade 2 m*IDH1/2* astrocytoma or oligodendroglioma

HALT PROGRESSION WITH PRECISION

VORANIGO®—Proven to significantly extend progression-free survival (PFS)[1,2]



Primary analysis: 61% reduced risk of disease progression or death vs placebo (HR=0.39; 95% CI, 0.27-0.56; *P*<0.0001).[1]
Extended analysis: 65% reduced risk of disease progression or death vs placebo (HR=0.35; 95% CI, 0.25-0.49). Median PFS was not reached for VORANIGO (95% CI, 22.1-NE) vs 11.4 months for placebo (95% CI, 11.1-13.9).[2,a]

[a]The extended analysis includes an additional 6 months of data from the primary analysis data cutoff date of September 6, 2022, to the date of unblinding on March 7, 2023.[2]
HR, hazard ratio; mIDH1/2, mutant isocitrate dehydrogenase-1 or mutant isocitrate dehydrogenase-2; NE, not estimable.

INDICATION

VORANIGO (40 mg tablets) is indicated for the treatment of adult and pediatric patients 12 years and older with Grade 2 astrocytoma or oligodendroglioma with a susceptible isocitrate dehydrogenase-1 (IDH1) or isocitrate dehydrogenase-2 (IDH2) mutation following surgery including biopsy, sub-total resection, or gross total resection.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hepatotoxicity: VORANIGO can cause hepatic transaminase elevations, which can lead to hepatic failure, hepatic necrosis, and autoimmune hepatitis. Monitor liver laboratory tests (AST, ALT, GGT, total bilirubin, and alkaline phosphatase) prior to the start of VORANIGO, every 2 weeks during the first 2 months of treatment, then monthly for the first 2 years of treatment, and as clinically indicated, with more frequent testing in patients who develop transaminase elevations. Reduce the dose, withhold, or permanently discontinue VORANIGO based on severity.

Please see additional Important Safety Information on page 19 and accompanying Full Prescribing Information.

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Molecular profiling in glioma classification

Identifying mutations is the key to precisely classifying adult-type diffuse gliomas[3,4]

- The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend conducting initial *IDH* testing for the workup of all gliomas, followed by additional molecular characterization[3,4]
- Adult-type diffuse gliomas, a subtype of glioma, are further categorized into 3 subtypes according to the mutational status of *IDH* and 1p/19q-codeletion in the 2021 WHO classification[4]

2021 WHO classification of adult-type diffuse gliomas[4]

Adult-type diffuse glioma	Genes and altered molecular profiles	CNS WHO Grade
Astrocytoma	mutated *IDH1* or *IDH2*	2, 3, 4
Oligodendroglioma	mutated *IDH1* or *IDH2*, and 1p/19q-codeleted	2, 3
Glioblastoma	wild-type *IDH*	4

Gliomas with mutated *IDH1* and *IDH2* have improved prognoses compared to gliomas with wild-type *IDH* (glioblastoma)[5,6]

Test with IHC and NGS to identify all mutations[3]

- While IHC can identify the most common *IDH1* mutation, R132H, up to 16% of patients with m*IDH* glioma have an *IDH1* or *IDH2* mutation that requires NGS to be detected[7,8]

NCCN Guidelines

According to the NCCN Guidelines®, if the IHC result for m*IDH1*-R132H is negative for a patient under age 55, sequencing is required to detect less common *IDH1* and *IDH2* mutations[3]

CNS, central nervous system; IHC, immunohistochemistry; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network ® (NCCN®); NGS, next generation sequencing; STR, sub-total resection; WHO, World Health Organization.

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The need for a targeted therapy in m*IDH* glioma

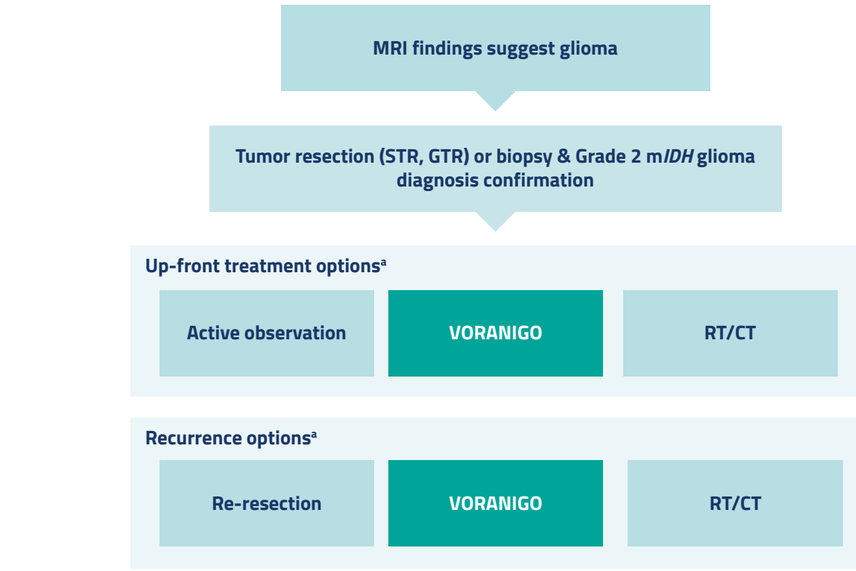
Even following gross total resection (GTR), m*IDH* gliomas continue to grow[9,10]

- *IDH1/2*-mutant astrocytomas and oligodendrogliomas grow continuously over time regardless of the extent of resection[9,10]
  - The presence of residual tumor cells remains after surgery due to the diffuse and infiltrative nature of m*IDH* gliomas[10,11]
  - These tumors eventually become aggressive and may lead to premature death[9,11]

VORANIGO—a novel mIDH1/2-targeted therapy that is the first advancement in the treatment of m*IDH* glioma in over 20 years[1,12,13]

- Prior to the approval of VORANIGO, an FDA-approved targeted treatment option specifically designed for m*IDH* glioma did not exist and treatment options were limited to active observation or radiotherapy and/or chemotherapy (RT/CT)

VORANIGO may be considered as a targeted option in multiple treatment settings[1,3,14]



[a]Additional treatment options, including clinical trial enrollment or palliative care, may be considered.

VORANIGO provides an FDA-approved, targeted intervention for patients with Grade 2 m*IDH* glioma[1]

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Appropriate patients for VORANIGO

VORANIGO is approved for patients (≥12 years) with Grade 2 m*IDH* glioma who have had prior surgery[1]

The patient criteria below illustrate types of appropriate patients for VORANIGO:

Age (years)	<12	12-39	>39	
Adult-type Diffuse Glioma Subtype	Oligodendroglioma (1p/19q-codeleted)	Astrocytoma	Glioblastoma	
IDH Status	*IDH1* mutated	*IDH2* mutated		
Surgery Status	No surgery	Biopsy only	Sub-total resection	Gross total resection
Prior Treatment	Surgery as only prior treatment	Surgery and prior treatment		
Time Since Surgery	0-11 months	>1 year		
Disease Status	Radiographically stable	Progressing		

Consistent with label

Not consistent with label

- Based on the approved indication and your clinical assessment, **VORANIGO can be used**:
  - Immediately after surgery
  - After sub-total resection or gross total resection
  - After surgery alone or after surgery and prior therapy

VORANIGO provides a targeted treatment option for many patient types across the Grade 2 m*IDH* glioma care continuum

Please see additional Important Safety Information on page 19 and accompanying Full Prescribing Information.

m*IDH* glioma mechanism of disease and VORANIGO mechanism of action

VORANIGO is the first and only FDA-approved oral inhibitor of mutant IDH1 and IDH2 in glioma[1]

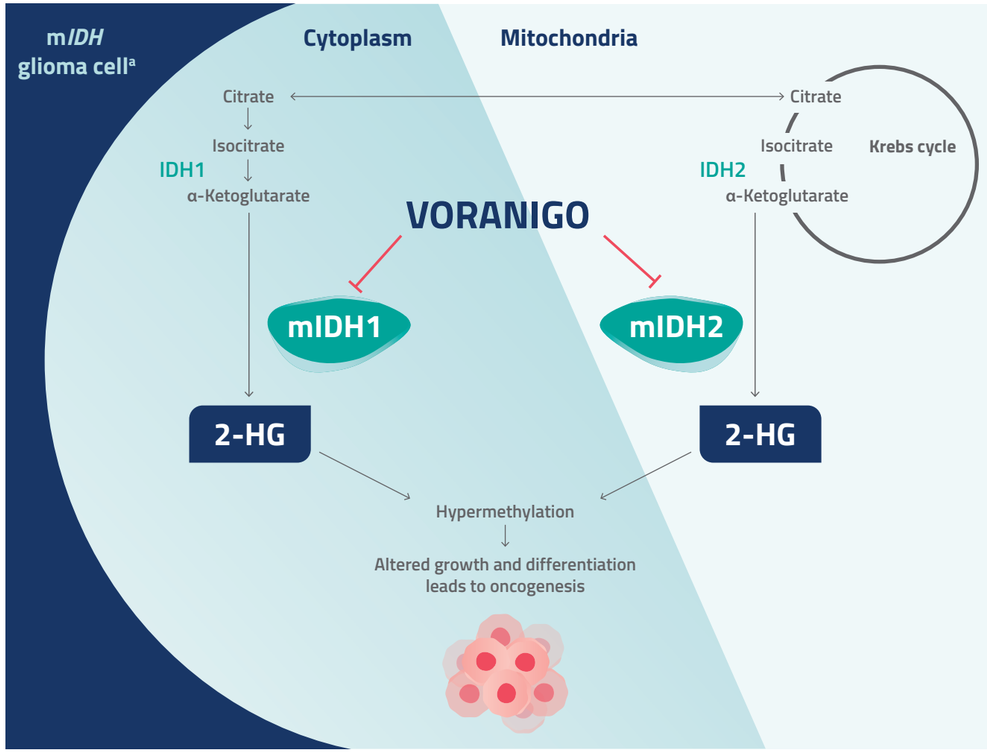
m*IDH* glioma mechanism of disease[15]

- Mutations to *IDH1/2* genes produce mutated IDH1/2 enzymes, which are key components of the Krebs cycle
- These mutated enzymes lead to the overproduction of 2-hydroxyglutarate (2-HG), which disrupts normal cellular processes, contributing to impaired cellular differentiation and subsequent oncogenesis

VORANIGO mechanism of action

- VORANIGO directly inhibits the gain-of-function activity of mIDH1/2 enzymes to block the abnormal production of 2-HG, a known driver of oncogenesis[1,15]
- VORANIGO crosses the blood-brain barrier and penetrates brain tumors[1,16]

Oncogenesis in m*IDH* glioma and the inhibition of mIDH1/2 with VORANIGO[1,15,17]



[a]m*IDH* glioma cells include astrocytes and oligodendrocytes that are mutated in adult-type diffuse glioma.

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Patient criteria
MOD and MOA

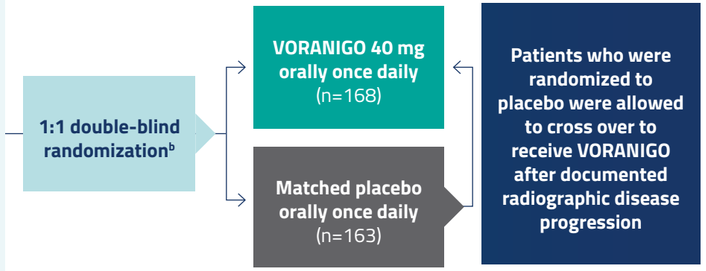
INDIGO trial design

The INDIGO trial evaluated the safety and efficacy of VORANIGO in patients with Grade 2 m*IDH1/2* astrocytoma or oligodendroglioma vs placebo[1]

The INDIGO trial was a phase 3, randomized, multicenter, double-blind, placebo-controlled trial (N=331)[1,13]

Patients in the INDIGO trial:

- Were at least 12 years of age
- Had *IDH1*- or *IDH2*-mutant Grade 2 astrocytoma or oligodendroglioma[a]
- Had prior surgery for glioma
- Had measurable, non-enhancing disease
- Had not received prior anticancer therapy, including chemotherapy and radiotherapy



Treatment continued until radiographic disease progression or unacceptable toxicity.[1] Tumor assessments were performed every 12 weeks.

INDIGO trial efficacy outcomes

Following the primary analysis data cutoff of September 6, 2022, the extended analysis includes 6 months of additional data to the date of unblinding on March 7, 2023[2]

The extended analysis for progression-free survival (PFS), time to next intervention (TTNI), tumor growth rate (TGR), and seizure activity was not controlled for multiplicity.

Major efficacy outcome: PFS
The time from randomization to the date of the first documented disease progression or death due to any cause.[13,c]

Key secondary outcome: TTNI
The time from randomization to the initiation of the first subsequent anticancer therapy or death due to any cause.[1]

Other secondary outcome: TGR
The on-treatment percentage change in tumor volume every 6 months.[13]

Exploratory outcome: Seizure activity
The number and severity of seizures were self-reported using a diary during each cycle.[2]

[a] *IDH1* or *IDH2* mutation status was prospectively determined by the Life Technologies Corporation Oncomine Dx Target Test.[1]

[b] Randomization was stratified by local 1p/19q status (codeleted or not codeleted) and baseline tumor size (diameter ≥2 cm or <2 cm).[1]

[c] PFS was evaluated by a BIRC per modified RANO-LGG.[1] The RANO criteria for LGGs define progressive disease as either a radiographic disease response (a ≥25% increase in the sum of the products of perpendicular T2-weighted or T2-weighted fluid-attenuated inversion recovery), or the presence of a new lesion as a newly measurable or increased enhancement.[13]

BIRC, blinded independent review committee; RANO-LGG, Response Assessment in Neuro-Oncology for Low Grade Glioma.

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INDIGO patient characteristics

The study population was generally balanced across treatment arms, including age, histologic subtype, and type of surgery[13,18]

More than 50% of patients treated with VORANIGO had gross total resection at the time of surgery

Demographic and disease characteristics	**VORANIGO** (n=168)	**Placebo** (n=163)
Demographics		
Age		
Median years (range)	40.5 (21-71)	39 (16-65)
Age distribution, %		
16 or 17 years	0	0.6
18 to 39 years	45	53
40 to 64 years	54	45
≥65 years	1.2	0.6
Male sex, %	60	53
Disease characteristics		
Histologic subtype, %		
Oligodendroglioma (1p/19q-codeleted)	52	52
Astrocytoma (1p/19q-non-codeleted)	48	49
Number of previous surgeries for glioma, %		
1	75	82
≥2	25	18
Surgery type, %		
Biopsy	14	12
Sub-total resection	48	41
Gross total resection	51	58
***IDH* mutation status, %**		
IDH1-positive[d]	97	93
R132H	87	85
R132C	4.8	4.3
R132G	3.0	0.6
R132L	1.2	2.5
R132S	1.2	1.2
IDH2-positive	3.0	7
R172K	1.8	6
R172G	1.2	0
R172W	0	0.6

[d] Two patients in the placebo group had CDKN2A homozygous deletion.[13]

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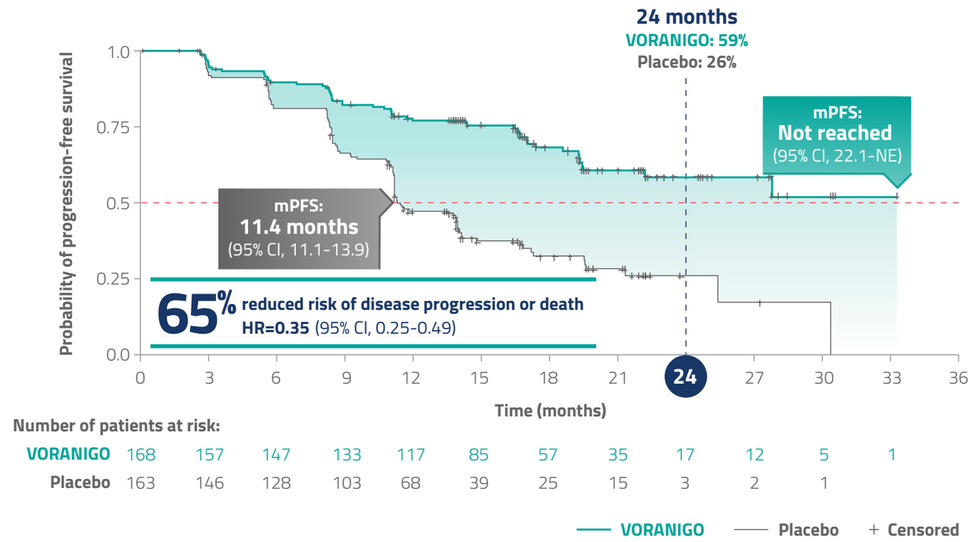
Major efficacy outcome: Progression-free survival (PFS)

VORANIGO significantly extended PFS, giving patients with m*IDH* glioma more time without disease progression vs placebo[1]

Primary analysis: 61% reduced risk of disease progression or death with VORANIGO vs placebo (HR=0.39; 95% CI, 0.27-0.56; *P*<0.0001)[1]

In the extended analysis, median PFS was not reached for VORANIGO vs 11.4 months with placebo[2]

Kaplan-Meier Curve for PFS per BIRC in the INDIGO trial: extended analysis



PFS in patients with m*IDH* glioma

Efficacy parameter	Primary analysis[1]		Extended analysis[2]	
	VORANIGO (n=168)	**Placebo** (n=163)	**VORANIGO** (n=168)	**Placebo** (n=163)
Number of events,[a] n (%)	47 (28)	88 (54)	54 (32)	104 (64)
HR (95% CI)	0.39 (0.27-0.56)		0.35 (0.25-0.49)	

The extended analysis for PFS and TTNI was not controlled for multiplicity.

[a]Number of events include progressive disease and death.[1]
[b]Number of events include first subsequent anticancer therapy (except crossover), crossover to VORANIGO, and death.[18]
mPFS, median PFS; mTTNI, median time to next intervention.

Please see additional Important Safety Information on page 19 and accompanying Full Prescribing Information.

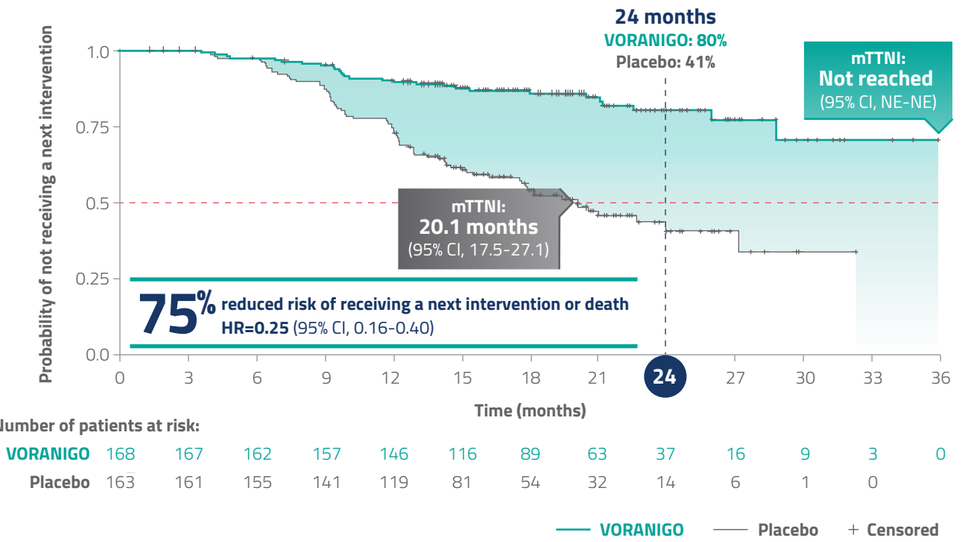
Secondary outcome: Time to next intervention (TTNI)

VORANIGO provided more time before subsequent treatment was initiated compared with placebo in the INDIGO trial[1]

Primary analysis: Median TTNI was not reached for VORANIGO vs 17.8 months with placebo (HR=0.26; 95% CI, 0.15-0.43; *P*<0.0001)[1]

In the extended analysis, median TTNI was not reached for VORANIGO vs 20.1 months with placebo[2]

Kaplan-Meier Curve for TTNI in the INDIGO trial: extended analysis



TTNI in patients with m*IDH* glioma

Efficacy parameter	Primary analysis[1,13]		Extended analysis[2]	
	VORANIGO (n=168)	**Placebo** (n=163)	**VORANIGO** (n=168)	**Placebo** (n=163)
Number of events,[b] N (%)	19 (11)	58 (36)	28 (17)	78 (48)
HR (95% CI)	0.26 (0.15-0.43)		0.25 (0.16-0.40)	

VORANIGO—proven to halt progression and delay the need for another intervention in your patients with m*IDH* glioma[1,2]

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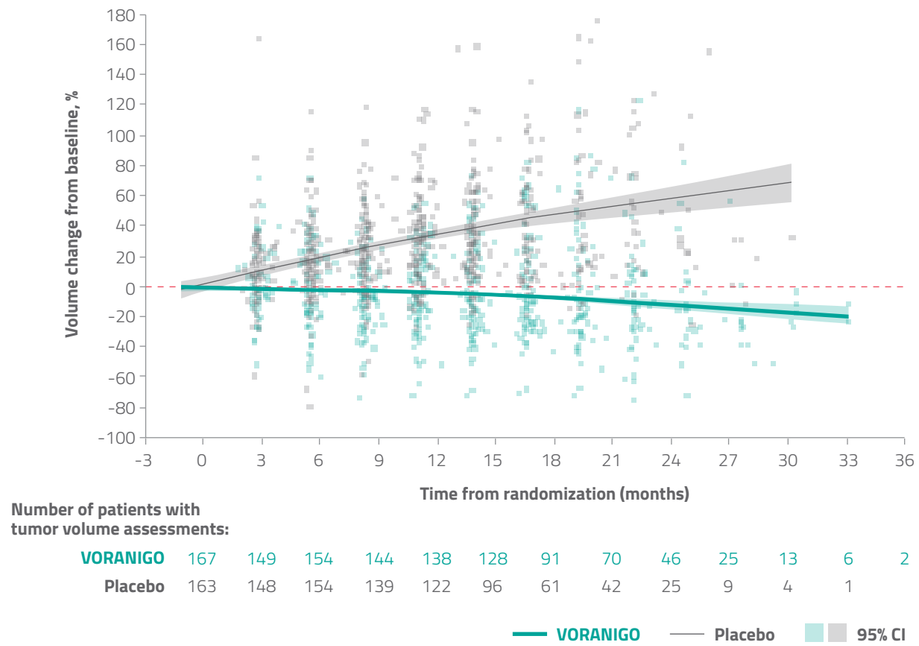
Secondary outcome: Tumor growth rate (TGR)

In the extended analysis, TGR in the VORANIGO arm was -1.3% vs 14.4% in the placebo arm[2,a]

Percent change in tumor volume every 6 months[b]

	VORANIGO (n=167)	Placebo (n=161)
Tumor growth rate per BIRC	**-1.3%** (95% CI, -3.2 to 0.7)	**14.4%** (95% CI, 12.0 to 16.8)
Difference between slopes	15.9% (95% CI, 12.6 to 19.3)	

On-treatment TGR[c]



The TGR endpoint has not been validated and the clinical significance of the changes observed is not known. This outcome was not controlled for multiplicity.

[a]n was the number of patients who had at least one volume record during the corresponding period.

[b]The table depicts the TGR estimated from the linear mixed effect model, for which the treatment group, time, treatment group by time interaction, log of tumor volume at baseline, and codeletion randomization stratification stratum are fixed effects. Tumor volume was measured per BIRC using modified RANO-LGG criteria at baseline and after randomization following a schedule of tumor assessments.

[c]The figure shows the percent change of volume from baseline plotted against time from randomization based on nonparametric LOESS regression.

LOESS, locally estimated scatterplot smoothing.

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Exploratory outcome: Seizure activity—subgroup analysis

In the INDIGO trial, investigators reported seizure[d] as an adverse event (AE) for all grades in 16% of patients treated with VORANIGO and 15% of patients treated with placebo[1]

Seizure AEs were assessed and reported in the prescribing information if qualified as an AE. Seizure activity was also assessed as an exploratory outcome, including the frequency, severity, and type of seizures, and changes in antiseizure medications.[18]

Subgroup analysis in patients who reported at least 1 seizure while on treatment[2]

Data based on patient self-reported diary that captured the number and severity of seizures during each cycle

- Only patients with controlled seizures were included in the INDIGO trial[e]
- Antiseizure medication was prescribed at the investigator's discretion

Seizure activity in patients who had at least 1 seizure[f]

	VORANIGO (n=167)	Placebo (n=163)
Patients with ≥1 seizure	**54**	**56**
Total number of on-treatment seizure events	**1541**	**5124**
Rate of on-treatment seizures per person-year	**18.2** (95% CI, 8.4-39.5)	**51.2** (95% CI, 22.9-114.8)
Ratio of rates: VORANIGO vs placebo	**0.36** (95% CI, 0.14-0.89)	

The seizure rate for VORANIGO was 64% lower compared to placebo[2]

A rigorous statistical conclusion cannot be made because seizure activity was an exploratory outcome, and the results should be interpreted with caution. This outcome was not controlled for multiplicity.

[d]Grouped term includes partial seizures, generalized tonic-clonic seizure, epilepsy, clonic convulsion, and simple partial seizures.[1]

[e]Uncontrolled seizures were defined as persistent seizures interfering with activities of daily life and failed 3 lines of antiepileptic drug regimens including at least 1 combination regimen.[13]

[f]On-treatment seizure activity was calculated using a negative binomial model, a commonly used statistical model in epilepsy evaluations. The model was adjusted by baseline seizure number and stratification factors (chromosome 1p/19q-codeletion status and tumor size at baseline).[2]

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Dosing and administration

VORANIGO is taken orally at the same time each day with or without food at home, at work, or wherever is best for your patients[1]

Recommended dosage:

Adult patients

- 40 mg orally once daily

Pediatric patients 12 years and older

- Patients weighing ≥40 kg: 40 mg orally once daily
- Patients weighing <40 kg: 20 mg orally once daily

Each bottle contains 30 tablets.
Tablet not shown at actual size.

Swallow tablets whole with water with or without food.

Do not split, crush, or chew tablets.

VORANIGO tablets are supplied in two strengths: 10 mg or 40 mg tablets in 30-count bottles

Continue VORANIGO until disease progression or unacceptable toxicity.

- Take VORANIGO tablets at about the same time each day
  - If a dose is missed by less than 6 hours, take the missed dose as soon as possible
  - If a dose is missed by more than 6 hours, skip the missed dose and take the next dose at the usual time
- If vomiting occurs after taking a dose, do not take a replacement dose, and take the next dose at the scheduled time on the following day

Recommended dosage reductions of VORANIGO due to adverse reactions (ARs)

Dosage reduction	Recommended dose and schedule
Adult patients and pediatric patients 12 years and older weighing ≥40 kg	
First	20 mg once daily
Second	10 mg once daily
Pediatric patients 12 years and older weighing <40 kg	
First	10 mg once daily
Permanently discontinue VORANIGO in patients unable to tolerate 10 mg once daily	

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Dosing changes and most common ARs to VORANIGO in INDIGO

The median duration of exposure to VORANIGO was 12.7 months (range: 1 to 30 months)[1]

Duration of exposure to VORANIGO	Number of patients
≥6 months	153 (92%)
≥1 year	89 (53%)

Dosage interruptions and discontinuations in patients treated with VORANIGO in the INDIGO trial[1]

Dosage interruptions

- Dosage interruptions of VORANIGO due to an AR occurred in 30% of patients
- ARs which required dose interruption in ≥5% of patients included ALT increased (14%), COVID-19 (9%), and AST increased (6%)

Dose reductions

- Dose reductions of VORANIGO due to an AR occurred in 11% of patients
- ARs which required dose reduction in ≥5% of patients included ALT increased (8%)

Discontinuations

Permanent discontinuation of VORANIGO due to an AR occurred in 3.6% of patients

- ARs which resulted in permanent discontinuation of VORANIGO in ≥2% of patients included ALT increased (3%)

The most common and severe ARs in patients who received VORANIGO[1]

- The most common (≥15%) ARs were fatigue (37%), COVID-19 (33%), musculoskeletal pain (26%), diarrhea (25%), and seizure (16%)
- Grade 3 or 4 (≥2%) laboratory abnormalities were ALT increased (10%), AST increased (4.8%), GGT increased (3%), and neutrophil decreased (2.4%)
- Serious ARs occurred in 7% of patients who received VORANIGO. The most common serious ARs occurring in ≥2% of patients who received VORANIGO includes seizure (3%)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase.

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Adverse reactions

The INDIGO trial assessed ARs of VORANIGO compared with placebo[1]

ARs reported in ≥5% of patients in the INDIGO trial

Adverse reaction[a]	All Grades (%)	Grades 3 or 4 (%)
	VORANIGO 40 mg daily (n=167) / Placebo (n=163)	
General disorders		
Fatigue[b]	37 / 36	0.6 / 1.2
Infections and infestations		
COVID-19	33 / 29	0 / 0
Nervous system disorders		
Seizure[c]	16 / 15	4.2 / 3.7
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[d]	26 / 25	0 / 1.8
Gastrointestinal disorders		
Diarrhea[e]	25 / 17	0.6 / 0.6
Constipation	13 / 12	0 / 0
Abdominal pain[f]	13 / 12	0 / 0
Decreased appetite	9 / 3.7	0 / 0

- The safety results shown are based on the primary analysis.[1] The safety profile of VORANIGO for the extended analysis was consistent with the primary analysis[2]

[a] ARs are based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.
[b] Grouped term includes asthenia.
[c] Grouped term includes partial seizures, generalized tonic-clonic seizure, epilepsy, clonic convulsion, and simple partial seizures.
[d] Grouped term includes arthralgia, back pain, non-cardiac chest pain, pain in extremity, myalgia, neck pain, musculoskeletal chest pain, arthritis, and musculoskeletal stiffness.
[e] Grouped term includes feces soft and frequent bowel movements.
[f] Grouped term includes abdominal pain upper, abdominal discomfort, abdominal pain lower, abdominal tenderness, and epigastric discomfort.
ALP, alkaline phosphatase.

Please see additional Important Safety Information on page 19 and accompanying Full Prescribing Information.

Select lab abnormalities

The INDIGO trial assessed lab abnormalities of VORANIGO compared with placebo[1]

Select laboratory abnormalities worsening from baseline occurring in ≥5% of patients

Parameter	All Grades[g] (%[h])	Grades[g] 3 or 4 (%[h])
	VORANIGO 40 mg daily (n=167) / Placebo (n=163)	
Chemistry		
Increased ALT	59 / 25	10 / 0
Increased AST	46 / 20	4.8 / 0
Increased creatinine	11 / 7	0.6 / 0
Decreased calcium	10 / 7	0 / 0
Increased glucose[i]	10 / 4.3	0 / 0
Increased GGT	38 / 10	3 / 1.8
Decreased phosphate[j]	8 / 4.9	0.6 / 0
Increased potassium	23 / 20	0.6 / 0
Increased ALP	10 / 7	1.2 / 0.6
Hematology		
Increased hemoglobin	13 / 3.1	0 / 0
Decreased lymphocytes	11 / 8	1.8 / 0.6
Decreased leukocytes	13 / 12	0.6 / 0.6
Decreased neutrophils	14 / 12	2.4 / 1.8
Decreased platelets	12 / 4.3	0 / 0

Transaminase elevations resolved to Grade 1 or baseline levels after modifying or discontinuing treatment with VORANIGO[13]

[g] Based on NCI CTCAE v5.0.
[h] The denominator used to calculate percentages is N, the number of subjects in the Safety Analysis Set within each treatment group.
[i] Includes AR term hyperglycemia.
[j] Includes AR terms hypophosphatemia and blood phosphorus decreased.

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Monitoring and treatment considerations for VORANIGO

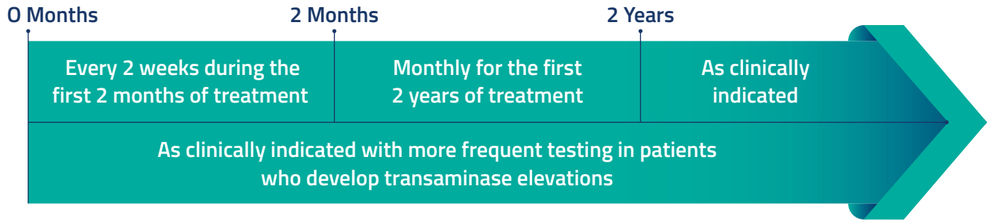
Liver laboratory tests are the only monitoring recommendations for VORANIGO[1]

Before initiating VORANIGO

- Evaluate blood chemistry and liver laboratory tests
- Verify pregnancy status in females of reproductive potential

During treatment with VORANIGO

Monitor liver laboratory tests: AST, ALT, GGT, total bilirubin, and ALP.



Reduce the dose, withhold, or permanently discontinue VORANIGO based on severity.

Dosage interruption, reduction, or treatment discontinuation may be needed in patients who develop transaminase elevations[1]

Considerations for your patients who are pregnant or planning to become pregnant[1]

- Based on animal embryo-fetal toxicity studies, VORANIGO can cause fetal harm when administered to pregnant women
- Based on findings in animals, VORANIGO may impair fertility in females and males of reproductive potential. The effects on female and male fertility were reversible in monkeys and were not reversible in rats. No fertility information is currently available for the use of VORANIGO in humans
- Advise females of reproductive potential to use effective nonhormonal contraception during treatment with VORANIGO and for 3 months after the last dose. VORANIGO can render some hormonal contraceptives ineffective
- Advise male patients with female partners of reproductive potential to use effective contraception during treatment with VORANIGO and for 3 months after the last dose
- Because of the potential for adverse reactions in breastfed children from VORANIGO, advise women not to breastfeed during treatment with VORANIGO and for 2 months after the last dose

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Adjustments to treatment for ARs

Additional blood counts, including liver laboratory tests, and dose modifications may be recommended for increases in ALT, AST, and total bilirubin based on severity[1]

Recommended VORANIGO dosage modifications and management for ARs

Adverse reaction	Severity[a]	Management and dosage modifications
Hepatotoxicity (Elevation of ALT or AST)	**Grade 1** ALT or AST increase >ULN to 3 x ULN *without* concurrent total bilirubin >2 x ULN	Continue VORANIGO at current dose Monitor liver laboratory tests weekly until recovery to <Grade 1
	Grade 2 ALT or AST >3 to 5 x ULN *without* concurrent total bilirubin >2 x ULN	**First occurrence:** Withhold VORANIGO until recovery to ≤Grade 1 or baseline ▪ Recovery in ≤28 days, resume VORANIGO at the same dose ▪ Recovery in >28 days, resume VORANIGO at reduced dose [See Table on page 12] **Recurrence:** Withhold VORANIGO until recovery to ≤Grade 1 or baseline, and resume VORANIGO at reduced dose [See Table on page 12]
	Grade 3 ALT or AST >5 to 20 x ULN *without* concurrent total bilirubin >2 x ULN	**First occurrence:** Withhold VORANIGO until recovery to ≤Grade 1 or baseline ▪ Recovery in ≤28 days, resume VORANIGO at reduced dose [see Table on page 12] ▪ If not recovered in ≤28 days, permanently discontinue VORANIGO **Recurrence:** Permanently discontinue VORANIGO
	Grade 2 or 3 ALT or AST >3 to 20 x ULN *with* concurrent total bilirubin >2 x ULN	**First occurrence:** Withhold VORANIGO until recovery to ≤Grade 1 or baseline ▪ Resume VORANIGO at reduced dose [See Table on page 12] **Recurrence:** Permanently discontinue VORANIGO
	Grade 4 Any ALT or AST >20 x ULN	Permanently discontinue VORANIGO
Other ARs	**Grade 3**	**First occurrence:** Withhold VORANIGO until recovery to ≤Grade 1 or baseline ▪ Resume VORANIGO at reduced dose [See Table on page 12] **Recurrence:** Permanently discontinue VORANIGO
	Grade 4	Permanently discontinue VORANIGO

[a]ARs graded by NCI CTCAE v5.0.
ULN, upper limit of normal.

Voranigo® vorasidenib tablets

Resources for your practice and your patients

ServierONE Patient Support Services

ServierONE offers helpful resources and tools to help your patients navigate treatment care, costs, and education throughout their journeys.

ServierONE Patient Support Services for VORANIGO® (vorasidenib tablets 40 mg) includes:

- Support with insurance coverage and reimbursement
- Financial assistance to help patients pay for VORANIGO
- Prescription fulfillment through our network of specialty pharmacies and distributors
- Tools and resources to navigate the world of insurance

Visit ServierONE.com, email USPatientServices@servier.com, or call 1-800-813-5905 (Monday-Friday, 8 AM to 8 PM ET). Register your patients online for the Commercial Copay Program at ServierONE-copay.com

References: 1. Voranigo. Package insert. Servier Pharmaceuticals LLC; 2024. **2.** Mellinghoff IK, van den Bent, MJ, Touat M, et al. A global, randomized, double-blinded, Phase 3 study of vorasidenib versus placebo in patients with adult-type diffuse glioma with an IDH1/2 mutation (INDIGO): UPDATED RESULTS. Presented at: Society for Neuro-Oncology Annual Meeting; November 21-24, 2024; Houston, TX. **3.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Central Nervous System Cancers V.4.2024. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed January 24, 2025. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **4.** Louis DN, Perry A, Wesseling P, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro Oncol.* 2021;23(8):1231-1251. doi:10.1093/neuonc/noab106 **5.** Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med.* 2005;352(10):987-996. doi:10.1056/NEJMoa043330 **6.** Pekmezci M, Rice T, Molinaro AM, et al. Adult infiltrating gliomas with WHO 2016 integrated diagnosis: additional prognostic roles of ATRX and TERT. *Acta Neuropathol.* 2017;133(6):1001-1016. doi:10.1007/s00401-017-1690-1 **7.** Tesileanu CMS, Vallentgoed WR, Sanson M, et al. Non-IDH1-R132H IDH1/2 mutations are associated with increased DNA methylation and improved survival in astrocytomas, compared to IDH1-R132H mutations. *Acta Neuropathol.* 2021;141(6):945- 957. doi:10.1007/s00401-021-02291-6 **8.** Yan H, Parsons DW, Jin G, et al. IDH1 and IDH2 mutations in gliomas. *N Engl J Med.* 2009;360(8):765-773. doi:10.1056/NEJMoa0808710 **9.** Bhatia A, Moreno R, Reiner AS, et al. Tumor volume growth rates and doubling times during active surveillance of IDH-mutant low-grade glioma. *Clin Cancer Res.* 2024;30(1):106-115. doi:10.1158/1078-0432.CCR-23-1180 **10.** Hervey-Jumper SL, Zhang Y, Phillips JJ, et al. Interactive effects of molecular, therapeutic, and patient factors on outcome of diffuse low-grade glioma. *J Clin Oncol.* 2023;41(11):2029-2042. doi:10.1200/JCO.21.02929 **11.** Smits A, Jakola AS. Clinical presentation, natural history, and prognosis of diffuse low-grade gliomas. *Neurosurg Clin N Am.* 2019;30(1):35-42. doi:10.1016/j.nec.2018.08.002 **12.** Ninatti G, Moresco RM, Sollini M. Molecular imaging of IDH-mutant gliomas in the new era of IDH inhibitors: preparing for future challenges. *Eur J Nucl Med Mol Imaging.* 2024;51(5):1421-1422. doi:10.1007/s00259-024-06591-3 **13.** Mellinghoff IK, van den Bent MJ, Blumenthal DT, et al. Vorasidenib in IDH1- or IDH2-mutant low-grade glioma. *N Engl J Med.* 2023;389(7):589-601. doi:10.1056/NEJMoa2304194 **14.** Darlix A, Preusser M, Hervey-Jumper SL, Shih HA, Mandonnet E, Taylor JW. Who will benefit from vorasidenib? Review of data from the literature and open questions. *Neuro-Oncology Practice.* 2024. doi.org/10.1093/nop/npae104 **15.** Peters KB. Targeting mutant IDH to treat low-grade glioma. *touchREVIEWS in Oncology & Haematology.* 2023;19(2):7-11. https://doi.org/10.17925/OHR.2023.19.2.3 **16.** Kulkarni AD, Patel HM, Surana SJ, Belgamwar VS, Pardeshi CV. Brain-blood ratio: implications in brain drug delivery. *Expert Opin Drug Deliv.* 2016;13(1):85-92. doi:10.1517/17425247.2016.1092519 **17.** Cohen AL, Holmen SL, Colman H. IDH1 and IDH2 mutations in gliomas. *Curr Neurol Neurosci Rep.* 2013;13(5):345. doi:10.1007/s11910-013-0345-4 **18.** Data on file. Servier Pharmaceuticals LLC.

Please see accompanying Full Prescribing Information.

Important Safety Information

WARNINGS AND PRECAUTIONS

Hepatotoxicity: VORANIGO can cause hepatic transaminase elevations, which can lead to hepatic failure, hepatic necrosis, and autoimmune hepatitis. Monitor liver laboratory tests (AST, ALT, GGT, total bilirubin, and alkaline phosphatase) prior to the start of VORANIGO, every 2 weeks during the first 2 months of treatment, then monthly for the first 2 years of treatment, and as clinically indicated, with more frequent testing in patients who develop transaminase elevations. Reduce the dose, withhold, or permanently discontinue VORANIGO based on severity.

Embryo-Fetal Toxicity: Based on findings from animal studies, VORANIGO can cause fetal harm when administered to a pregnant woman. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective nonhormonal contraception during treatment with VORANIGO and for 3 months after the last dose, since VORANIGO can render some hormonal contraceptives ineffective. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with VORANIGO and for 3 months after the last dose.

ADVERSE REACTIONS

The most common (≥15%) adverse reactions included fatigue, headache, COVID-19, musculoskeletal pain, diarrhea, nausea, and seizure. Grade 3 or 4 (≥2%) laboratory abnormalities were ALT increased, AST increased, GGT increased, and neutrophils decreased.

DRUG INTERACTIONS

Avoid concomitant use of VORANIGO with strong and moderate CYP1A2 inhibitors. Avoid concomitant use with moderate CYP1A2 inducers and smoking tobacco. Avoid concomitant use with CYP3A substrates, where a minimal concentration change can reduce efficacy. If concomitant use of hormonal contraception cannot be avoided, use nonhormonal contraception methods.

LACTATION

Advise women not to breastfeed during VORANIGO treatment and for 2 months after the last dose.

IMPAIRED FERTILITY

VORANIGO may impair fertility of females and males of reproductive potential.

Voranigo® vorasidenib tablets

VORANIGO is the first FDA-approved treatment in >20 years for m*IDH* glioma

Offer your patients a chance at improved outcomes with VORANIGO

Significantly extended PFS

- **Primary analysis:** 61% reduced risk of disease progression or death vs placebo (HR=0.39; 95% CI, 0.27-0.56; *P*<0.0001)[1]
- **Extended analysis:** 65% reduced risk of disease progression or death vs placebo (HR=0.35; 95% CI, 0.25-0.49). Median PFS was not reached for VORANIGO (95% CI, 22.1-NE) vs 11.4 months with placebo (95% CI, 11.1-13.9)[2]

Safety profile[1]

- The most common (≥15%) ARs were fatigue, COVID-19, musculoskeletal pain, diarrhea, and seizure
- Grade 3 or 4 (≥2%) laboratory abnormalities were ALT increased (10%), AST increased (4.8%), GGT increased (3%), and neutrophil decreased (2.4%)
- Permanent discontinuation due to ARs occurred in 3.6% of patients

Additional data on tumor growth rate and seizure activity are now available.
Please refer to pages 10 and 11 for the full analysis.

Scan to visit **VoranigoHCP.com** for more information about VORANIGO.

INDICATION

VORANIGO (40 mg tablets) is indicated for the treatment of adult and pediatric patients 12 years and older with Grade 2 astrocytoma or oligodendroglioma with a susceptible isocitrate dehydrogenase-1 (IDH1) or isocitrate dehydrogenase-2 (IDH2) mutation following surgery including biopsy, sub-total resection, or gross total resection.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hepatotoxicity: VORANIGO can cause hepatic transaminase elevations, which can lead to hepatic failure, hepatic necrosis, and autoimmune hepatitis. Monitor liver laboratory tests (AST, ALT, GGT, total bilirubin, and alkaline phosphatase) prior to the start of VORANIGO, every 2 weeks during the first 2 months of treatment, then monthly for the first 2 years of treatment, and as clinically indicated, with more frequent testing in patients who develop transaminase elevations. Reduce the dose, withhold, or permanently discontinue VORANIGO based on severity.

Please see additional Important Safety Information on page 19 and accompanying Full Prescribing Information.

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