Drug Monograph

A - Drug Name

vorasidenib

COMMON TRADE NAME(S): Voranigo™

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B - Mechanism of Action and Pharmacokinetics

Vorasidenib is a an inhibitor of IDH1 and IDH2 enzymes. Mutations in IDH1 or IDH2 can lead to the production of 2-hydroxyglutarate (2-HG) and its accumulation in glioma tissues. This results in changes to DNA hydroxymethylation, gene expression, cellular differentiation, and the tumor microenvironment. IDH1 and IDH2 inhibition 2-HG production and partially restores cellular differentiation.

Absorption	T max	2 hours
	Time to reach steady state	14 days
	Effects with food	Increased peak concentration and exposure when given with a high-fat or low-fat meal.
Distribution	PPB	97%
	Cross blood brain barrier?	Yes
Metabolism	Vorasidenib is primarily metabolized by CYP1A2, with minor contributions from other CYP or non-CYP pathways.	

Elimination	Feces	85% (55% unchanged)
	Urine	5% (0% unchanged)
	Half-life	10 days (terminal)

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C - Indications and Status

Health Canada Approvals:

- Astrocytoma or oligodendroglioma

Refer to the product monograph for a full list and details of approved indications.

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D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

The following table lists adverse effects that occurred in ≥ 1 % of patients with grade 2 IDH-mutant glioma treated with vorasidenib (with a difference between arms of ≥2% compared with placebo) in the INDIGO Trial. It also includes severe, life-threatening adverse effects.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Gastrointestinal	Abdominal pain (8%)	E
	Anorexia (5%)	E
	Diarrhea (12%)	E
	Gastroesophageal reflux disease (4%)	E
General	Fatigue (23%)	E
Hepatobiliary	Hepatotoxicity (1%)	E
	↑ LFTs (39%) (10% severe)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for vorasidenib include ↑ LFTs, fatigue, and diarrhea.

Increased liver enzymes and bilirubin were transient; they improved or resolved with dose modification or treatment discontinuation. Two patients (1.2%) had concurrent ALT or AST > 3x ULN and total bilirubin > 2x ULN. Hepatic failure/necrosis or autoimmune hepatitis has also been observed.

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E - Dosing

Refer to protocol by which the patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

IDH1 or IDH2 mutation should be confirmed by a validated test prior to starting vorasidenib.

Adults:

For patients weighing ≥ 40 kg: 40 mg PO Daily

For patients weighing < 40 kg: 20 mg PO Daily

Dosage with Toxicity:

Dose Level	Vorasidenib Dose (mg daily)	
	Patients weighing ≥ 40 kg	Patients weighing < 40 kg
0	40	20
-1	20	10
-2	10	Discontinue
-3	Discontinue	Not Applicable

Toxicity	Grade/Severity			Action
Hepatotoxicity	**ALT or AST**		**Bilirubin**	
	>1 to 3 x ULN	and	≤ 2 x ULN	Continue at current dose. Monitor LFTs weekly until recovery to < Grade 1.
	>3 to 5 x ULN	and	≤ 2 x ULN	First Occurrence: Hold*. • Recovery in ≤ 28 days: Resume at the same dose. • Recovery in > 28 days: Resume at 1 dose level ↓.
				Recurrence: Hold*, then resume at 1 dose level ↓.
	>5 to 20 x ULN	and	≤ 2 x ULN	First Occurrence: Hold*. • Recovery in ≤ 28 days: Resume at 1 dose level ↓. • Recovery in > 28 days: Discontinue.
				Recurrence: Discontinue.
	>3 to 20 x ULN	and	> 2 x ULN	First Occurrence: Hold*. • Resume at 1 dose level ↓.
				Recurrence: Discontinue.
	> 20 x ULN	and	Any	Discontinue.
Other	Grade 3			First Occurrence: Hold*. • Resume at 1 dose level ↓.
				Recurrence: Discontinue.
	Grade 4			Discontinue.

* Hold until recovery to ≤ Grade 1 or baseline.

Dosage with Hepatic Impairment:

Hepatic Impairment	Vorasidenib Starting Dose
Mild (Child-Pugh Class A)	No dosage adjustment recommended.
Moderate (Child-Pugh Class B)	No dosage adjustment recommended.
Severe (Child-Pugh Class C)	No data available. Assess for benefit vs risk; monitor closely for adverse reactions.

Dosage with Renal Impairment:

Creatinine Clearance (mL/min)	Vorasidenib Starting Dose
> 40	No dosage adjustment recommended.
≤ 40 or requiring dialysis	No data available; caution.

Dosage in the elderly:

No dose adjustment is recommended for patients ≥ 65 years of age. No overall differences in safety or effectiveness were observed for patients aged 65 years or older.

Dosage based on gender:

No clinically significant effects on the pharmacokinetics of vorasidenib were observed based on gender.

Dosage based on ethnicity:

No clinically significant effects on the pharmacokinetics of vorasidenib were observed among white, Black or African American, Asian, American Indian/Alaskan Native, Native Hawaiian or Other Pacific Islander, Hispanic, or non-Hispanic patients.

Children:

The use of vorasidenib in pediatric patients 12 years and older was extrapolated from population pharmacokinetic data and course of disease in adult patients. Pediatric patients may have a higher risk of adverse drug reactions.

The safety and efficacy of vorasidenib in children under 12 years of age have not been established.

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F - Administration Guidelines

- Vorasidenib should be taken on an empty stomach, at least 1 hour before or 2 hours after a meal.
- Tablets should be swallowed whole with a glass of water, and not split, crushed or chewed.
- If a dose is missed by less than 6 hours, give the missed dose as soon as possible. If a dose is missed by more than 6 hours, skip the missed dose, and give the next dose at the usual time.
- If a patient vomits after taking a dose, a replacement dose should not be given. The next dose should be given as usual the following day.
- Store at room temperature (15°C to 30°C). Once the original bottle is opened, vorasidenib should be used within 60 days.

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components

Other Warnings/Precautions:

- Vorasidenib contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medication.

Other Drug Properties:

- Carcinogenicity: No information available

Pregnancy and Lactation:

- Genotoxicity: Not observed in vitro
- Mutagenicity: Not observed in vitro
- Embryotoxicity: Documented in animals
- Fetotoxicity: Documented in animals
- Pregnancy:
  Vorasidenib is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **3 months** after the last dose.
  Use an additional non-hormonal (e.g., barrier) method of contraception since vorasidenib may reduce the effectiveness of hormonal contraceptives (See Interactions section).
- Breastfeeding:
  Breastfeeding is not recommended during treatment and for at least **2 months** after the last dose.
- Fertility effects: Documented in animals
  Discuss fertility preservation with patients prior to starting treatment.

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H - Interactions

Vorasidenib is primarily metabolized by CYP1A2 with minor contributions from CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5.

Pharmacokinetic modeling predicted vorasidenib to have a strong induction effect on sensitive CYP3A substrates, weak-to-moderate induction effect on sensitive CYP2C19 substrates, and weak induction effect on sensitive CYP2B6 substrates.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Moderate and Strong CYP 1A2 inhibitors (e.g. ciprofloxacin, fluvoxamine)	↑ vorasidenib exposure (up to 2.5x with moderate inhibitor and 7.2x with strong inhibitor) and/or ↑ risk of toxicity	↓ metabolism of vorasidenib	Avoid concomitant use. If must co-administer, monitor for increased adverse reactions.
Moderate CYP 1A2 inducers (e.g. phenytoin, rifampicin, smoking tobacco)	↓ vorasidenib exposure by 30-40% and/or ↓ efficacy	↑ metabolism of vorasidenib	Avoid concomitant use
CYP substrates with narrow therapeutic indices (e.g. alfentanil, carbamazepine, cyclosporine, everolimus, fentanyl, ifosfamide, pimozide, quinidine, sirolimus, tacrolimus, tamoxifen)	↓ concentration and/or efficacy of medications that are CYP2C19 and CYP3A4 substrates	Vorasidenib can induce CYP 2C19 and CYP 3A4	Avoid concomitant use with CYP2C19 and CYP3A4 substrates with narrow therapeutic indices
Hormonal Contraceptives	May ↓ hormonal contraceptives concentration and/or efficacy	↑ CYP3A4-mediated metabolism of hormonal contraceptives	Concomitant use of a barrier method of contraception is recommended during the treatment and for at least 3 months after the last dose.

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Liver function tests	Baseline, every 2 weeks during the first 2 months, then once monthly for the first 2 years, and as clinically indicated (more frequently in patients with ↑ LFTs).
CBC	Baseline and at each visit
Renal function tests	Baseline and as clinically indicated
Clinical toxicity assessment for fatigue and GI effects	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- vorasidenib - For the treatment of Grade 2 astrocytoma or oligodendroglioma in patients with a susceptible IDH1 mutation or IDH2 mutation following surgery, based on criteria

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K - References

Mellinghoff et al. Vorasidenib in IDH1- or IDH2-Mutant Low-Grade Glioma. N Engl J Med. 2023 Aug 17;389(7):589-601.

Prescribing Information: (VORANIGO™). Servier Pharmaceuticals LLC. August 2024.

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UpToDate Inc. (2025). Vorasidenib [Drug information]. UpToDate Lexidrug. Accessed January 16, 2025.

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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