PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr] VORANIGO®

Vorasidenib tablets

Tablets, 10 mg and 40 mg, Oral

Antineoplastic Agent

Servier Canada Inc.

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Date of Initial Authorization:

AUG 27, 2024

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RECENT MAJOR LABEL CHANGES

None at the time of the most recent authorization.

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1. INDICATIONS

VORANIGO (vorasidenib tablets) is indicated for:

the treatment of Grade 2[a] astrocytoma or oligodendroglioma with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation or isocitrate dehydrogenase-2 (IDH2) mutation in adults and pediatric patients aged 12 years and older following surgical intervention.

Treatment with VORANIGO should be initiated following confirmation of an IDH1 or IDH2 mutation through a validated test.

[a.] World Health Organization (WHO) 2016, 2021 grading system

1.1 Pediatrics

Pediatrics (12 to 18 years): No patients under the age of 18 were treated with VORANIGO in the pivotal phase 3 study (INDIGO). Use of VORANIGO in pediatric patients 12 years and older is supported by evidence from studies in adults with additional population pharmacokinetic data demonstrating that age had no clinically meaningful effect on the pharmacokinetics of vorasidenib, that the exposure of vorasidenib is mostly similar between adults and pediatric patients age 12 years and older, and that the course of disease is sufficiently similar in adult and pediatric patients to allow extrapolation of data in adults to these pediatric patients. Pediatric patients may have a higher risk of adverse drug reactions (see 7 WARNINGS AND PRECAUTIONS, 10.3 Pharmacokinetics, 14.1 Clinical Trials by Indication, and 4.2 Recommended Dose and Dosage Adjustment, Dosage Modifications).

The safety and efficacy of VORANIGO in children under 12 years of age have not been established. No data are available.

1.2 Geriatrics

Geriatrics (>65 years): No overall differences in safety or effectiveness were observed for patients aged 65 years or older (see 10.3 Pharmacokinetics, 14.1 Clinical Trials by Indication, and 4 DOSAGE AND ADMINISTRATION).

2. CONTRAINDICATIONS

VORANIGO is contraindicated in patients with:

- Hypersensitivity to the active substance or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Select patients for the treatment of Grade 2[a] astrocytoma or oligodendroglioma with VORANIGO based on the presence of IDH1 or IDH2 mutations in tumour specimens using an appropriate diagnostic test prior to initiation of treatment with VORANIGO.

[a.] WHO 2016, 2021 grading system

Assess complete blood counts and liver laboratory tests (aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), total bilirubin and alkaline phosphatase), prior to the initiation of VORANIGO, every 2 weeks during the first 2 months of treatment, then once monthly for the first 2 years of treatment and as clinically indicated thereafter, with more frequent testing in patients who develop transaminase elevations (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

Administer VORANIGO until radiographic or clinical disease progression or unacceptable toxicity.

4.2 Recommended Dose and Dosage Adjustment

The recommended dosage of VORANIGO in adults and pediatric patients 12 years and older:

- For patients weighing at least 40 kg, take 40 mg orally once daily.
- For patients weighing less than 40 kg, take 20 mg orally once daily.

Pediatric patients may have a higher risk of adverse drug reactions (see 7 WARNINGS AND PRECAUTIONS, 10.3 Pharmacokinetics, 14.1 Clinical Trials by Indication, and 4.2 Recommended Dose and Dosage Adjustment, Dosage Modifications).

Dosage Modifications

Dose interruption or dose reduction may be required based on individual safety and tolerability. The recommended dose reduction levels are provided in Table 1.

Table 1 – Recommended Dose Reductions for VORANIGO

VORANIGO Dose level	Dose and schedule	Number and strength of tablets
Patients 12 years and older weighing at least 40 kg		
Starting dose	40 mg once daily	One 40 mg tablet / once daily
First dose reduction	20 mg once daily	Two 10 mg tablets / once daily
Second dose reduction	10 mg once daily	One 10 mg tablet / once daily
Patients 12 years and older weighing less than 40 kg		
Starting dose	20 mg once daily	Two 10 mg tablets / once daily
First dose reduction	10 mg once daily	One 10 mg tablet / once daily
Permanently discontinue VORANIGO in patients unable to tolerate 10 mg once daily.		

The recommended management and dosage modifications for adverse reactions are provided in Table 2.

Table 2 – Recommended Dosage Modifications and Management for Adverse Reactions

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	Continue VORANIGO at current dose. Monitor liver laboratory tests weekly until recovery to <Grade 1.

Adverse Reaction	Severity[a]	Management and Dosage Modifications
(see 7 WARNINGS AND PRECAUTIONS)	*without* concurrent total bilirubin >2 x ULN	
	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 1). Recurrence: Withhold VORANIGO until recovery to ≤Grade 1 or baseline, and resume VORANIGO at reduced dose (see Table 1).
	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 1). • If not recovered in ≤28 days, permanently discontinue VORANIGO. Recurrence: Permanently discontinue VORANIGO.
	Grade 2 or 3 Any 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 1). Recurrence: Permanently discontinue VORANIGO.
	Grade 4 Any ALT or AST >20 x ULN	Permanently discontinue VORANIGO.
Other Adverse Reactions (see 8 ADVERSE REACTIONS)	Grade 3	First Occurrence: Withhold VORANIGO until recovery to ≤Grade 1 or baseline. • Resume VORANIGO at reduced dose (see Table 1). Recurrence: Permanently discontinue VORANIGO.

Adverse Reaction	Severity[a]	Management and Dosage Modifications
	Grade 4	Permanently discontinue VORANIGO.

Abbreviations: ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; ULN = Upper limit of normal

[a] Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.

Special Populations

Geriatrics (≥65 years of age)

No dose adjustment is recommended for patients ≥65 years of age (see 10.3 Pharmacokinetics).

Renal Impairment

No dosage adjustment is recommended for patients with renal impairment (creatinine clearance [CL_{cr}] >40 mL/min estimated by Cockcroft-Gault). The pharmacokinetics and safety of vorasidenib have not been studied in patients with CL_{cr} ≤40 mL/min or renal impairment requiring dialysis. VORANIGO should be used with caution in patients with CL_{cr} ≤40 mL/min or who require dialysis (see 7 WARNINGS AND PRECAUTIONS, Renal and 10.3 Pharmacokinetics).

Hepatic Impairment

No dosage adjustment is recommended for patients with mild or moderate (Child-Pugh Class A or B) hepatic impairment. The pharmacokinetics and safety of vorasidenib have not been studied in patients with severe hepatic impairment (Child-Pugh Class C). For patients with severe hepatic impairment, monitor for increased adverse reactions (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic and 10.3 Pharmacokinetics).

4.4 Administration

The tablets should be taken once daily at about the same time each day. Patients should not eat food at least 2 hours before and 1 hour after taking VORANIGO. The tablets are to be swallowed whole with a glass of water and should not be split, crushed or chewed to ensure the full dose is administered.

4.5 Missed Dose

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 a dose is vomited, a replacement dose should not be taken. The dose should be taken as usual the following day.

5. OVERDOSAGE

In the event of overdose, toxicity is likely to manifest as exacerbation of the adverse reactions associated with VORANIGO (see 8 ADVERSE REACTIONS, 7 WARNINGS AND PRECAUTIONS, and 4.2 Recommended Dose and Dosage Adjustment). There is no specific antidote for VORANIGO overdose.

For management of a suspected drug overdose, contact your regional poison control centre.

6.DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	tablets 10 mg and 40 mg vorasidenib*	Croscarmellose sodium, hypromellose, lactose monohydrate, macrogol, magnesium stearate, microcrystalline cellulose, pharmaceutical ink, silicified microcrystalline cellulose, sodium lauryl sulfate, titanium dioxide

*as vorasidenib hemicitric acid, hemihydrate

VORANIGO is provided as film-coated tablets:

10 mg Film-coated Tablets

White to off-white, round, film-coated tablets, imprinted with ”10” in black ink on one side and plain on the other side.

40 mg Film-coated Tablets

White to off-white, oblong, film-coated tablets, imprinted with ”40” in black ink on one side and plain on the other side.

Sodium Content

The 10 mg or 40 mg film-coated tablets contain less than 1 mmol sodium (23 mg).

VORANIGO is supplied in a white high-density polyethylene (HDPE) bottle with a polypropylene child-resistant closure and polyethylene faced induction heat seal liner. Each bottle contains 30 film-coated tablets and a silica gel desiccant in 3 HDPE canisters.

7. WARNINGS AND PRECAUTIONS

General

Lactose

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

Hepatic/Biliary/Pancreatic

In the INDIGO clinical trial (Study AG881-C-004), 36.5% (61/167) of patients treated with VORANIGO experienced ALT elevations of any grade and 24.6% (41/167) experienced AST elevations of any grade. Among these patients, 1.2% (2/167) had concurrent ALT or AST elevations >3 times the ULN and total bilirubin >2 times the ULN (see 8 ADVERSE REACTIONS). Liver enzyme and bilirubin increases were transient and improved or resolved with dose modification or permanent discontinuation of treatment. Hepatic failure and hepatic necrosis were observed in one patient treated with VORANIGO and autoimmune hepatitis was observed in one patient treated with VORANIGO.

Monitor liver laboratory tests (ALT, AST, GGT, total bilirubin and alkaline phosphatase) prior to the start of VORANIGO, every 2 weeks during the first 2 months of treatment, then once monthly for the first 2 years, and as clinically indicated thereafter, with more frequent testing in patients who develop transaminase elevations. Weekly monitoring for ALT or AST elevations ≤3 times the ULN is recommended. Withhold, reduce dose or permanently discontinue VORANIGO based on the severity of the liver laboratory test abnormalities (see 4.2 Recommended Dose and Dosage Adjustment).

Patients with pre-existing severe hepatic impairment (Child-Pugh Class C) may be treated with VORANIGO only after careful risk/benefit assessment and should be closely monitored. The use of VORANIGO has not been evaluated in patients with pre-existing severe hepatic impairment (see 4.2 Recommended Dose and Dosage Adjustment and 10.3 Pharmacokinetics).

Monitoring and Laboratory Tests

Assess complete blood counts and liver laboratory tests (ALT, AST, GGT, total bilirubin and alkaline phosphatase) prior to the initiation of VORANIGO, every 2 weeks during the first 2 months of treatment, then once monthly for the first 2 years of treatment, and as clinically indicated thereafter, with more frequent testing in patients who develop transaminase elevations (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic). Manage any abnormalities in liver laboratory tests as outlined in Table 2.

Renal

The pharmacokinetics and safety of vorasidenib have not been studied in patients with renal impairment (CL_{cr} ≤40 mL/min) or renal impairment requiring dialysis. VORANIGO should be used with caution in these patients (see 4.2 Recommended Dose and Dosage Adjustment and 10.3 Pharmacokinetics).

Reproductive Health: Female and Male Potential

VORANIGO could cause fetal harm when administered to a pregnant woman. Pregnancy testing is recommended in women of childbearing potential prior to starting treatment with VORANIGO.

- **Fertility**

  There are no human data on the effect of vorasidenib on fertility. No fertility studies in animals have been conducted to evaluate the effect of vorasidenib. Findings of adverse effects on reproductive organs in both sexes of rats were observed in repeat-dose studies with partial recovery noted (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology). The clinical relevance of these effects is unknown. Patients who are planning to conceive a child should be advised to seek reproductive counselling before starting treatment.

- **Teratogenic Risk**

  Embryo-Fetal Toxicity: Based on findings from animal studies, VORANIGO can cause fetal harm when administered to a pregnant woman. In animal embryo-fetal development studies, oral administration of vorasidenib to pregnant rats during the period of organogenesis caused embryo-fetal toxicities at doses ≥31-fold the maximum human recommended dose (MRHD) of 40 mg based on the area under the concentration-time curve (AUC). Oral administration of vorasidenib to pregnant rabbits during the period of organogenesis resulted in embryo-fetal toxicity doses of ≥5-fold the MRHD of 40 mg based on AUC.

VORANIGO is not recommended during pregnancy and in women of childbearing potential not using contraception. Pregnant women, women of childbearing potential or male patients with female partners of childbearing potential should be advised on the potential risk to a fetus.

Pregnancy testing

Pregnancy testing is recommended in women of childbearing potential prior to starting treatment with VORANIGO.

Contraception

Females

Women of childbearing potential should use effective non-hormonal contraception during treatment with VORANIGO and for at least 3 months after the last dose. Since the effect of vorasidenib on the metabolism and efficacy of systemically acting hormonal contraceptives has not been investigated, barrier methods should be applied as a second form of contraception to avoid pregnancy (see 9.4 Drug-Drug Interactions).

Males

Advise male patients with female partners of reproductive potential to use effective barrier contraception during treatment with VORANIGO and for at least 3 months after the last dose.

7.1 Special Populations

7.1.1 Pregnant Women

There are no data from the use of vorasidenib in pregnant women. Animal studies have shown reproductive toxicity with partial recovery and adverse effects on embryo-fetal development during the period of organogenesis (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology). Women of childbearing potential should use an effective non-hormonal method of contraception when taking VORANIGO.

7.1.2 Breast-feeding

No data exist on whether vorasidenib and its metabolites are excreted in human milk. Breast-feeding should be discontinued during treatment with VORANIGO and for at least 2 months after the last dose.

7.1.3 Pediatrics (>12 years)

No patients under the age of 18 were treated with VORANIGO in the pivotal phase 3 study (INDIGO). Use of VORANIGO in pediatric patients 12 years and older is supported by evidence from studies in adults with additional population pharmacokinetic data demonstrating that age had no clinically meaningful effect on the pharmacokinetics of vorasidenib, that the exposure of vorasidenib is mostly similar between adults and pediatric patients age 12 years and older, and that the course of disease is sufficiently similar in adult and pediatric patients to allow extrapolation of data in adults to these pediatric patients. Analysis of the population pharmacokinetic modelling indicated that pediatric female patients in the 40-50 kg weight range may have a higher exposure and a higher risk of adverse drug reactions (see 10.3 Pharmacokinetics, 14.1 Clinical Trials by Indication, and 4.2 Recommended Dose and Dosage Adjustment, Dosage Modifications).

7.1.4 Geriatrics (>65 years)

Of the 167 patients who were randomized and received VORANIGO 40 mg once daily in the INDIGO trial, 1.2% (2 patients) were 65 years or older. No overall differences in safety or effectiveness were observed for patients aged 65 years or older (see 10.3 Pharmacokinetics).

8. ADVERSE REACTIONS

8.1 Adverse Reaction Overview

In the INDIGO trial, the most common adverse reactions in Table 4 under VORANIGO reported in ≥1% of treated patients with a ≥2% difference between arms compared with Placebo, including laboratory abnormalities, were ALT increased (36.5%), AST increased (24.6%), fatigue (23.4%), GGT increased (13.2%), and diarrhea (12%).

The most common grade ≥3 adverse reactions were ALT increased (9.6%), AST increased (4.2%) and GGT increased (2.4%).

Serious adverse reactions were reported in 1 of 167 patients (0.6%) who received VORANIGO. The most common serious adverse reaction was ALT increased (0.6%).

Permanent discontinuation of VORANIGO was reported in 5 of 167 patients (3.0%). The most common adverse reaction leading to permanent discontinuation was ALT increased (3%).

Dose interruptions due to an adverse reaction occurred in 31 of 167 patients (18.6%) treated with VORANIGO. The most common adverse reactions requiring dose interruption were ALT increased (14.4%) and AST increased (6%).

Dose reductions of VORANIGO due to an adverse reaction occurred in 10.2% of patients. The most common adverse reaction requiring dose reduction was ALT increased (7.8%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Adverse reactions reported in patients treated with VORANIGO in the INDIGO trial (Study AG881-C-004) are listed below by MedDRA system organ class and by frequency are presented in Table 4.

Table 4 – Adverse Reactions Reported in ≥1% of Patients Receiving VORANIGO with a Difference Between Arms of ≥2% Compared with Placebo in the INDIGO Trial (Study AG881-C-004)

System Organ Class[a]	VORANIGO N=167 n (%)	Placebo N=163 n (%)
Metabolism and nutrition disorders		
Decreased appetite	9 (5.4)	5 (3.1)
Gastrointestinal disorders		

System Organ Class[a]	VORANIGO N=167 n (%)	Placebo N=163 n (%)
Diarrhea[b]	20 (12.0)	16 (9.8)
Abdominal pain[c]	13 (7.8)	6 (3.7)
Gastroesophageal reflux disease[d]	7 (4.2)	1 (0.6)
General Disorders		
Fatigue[e]	39 (23.4)	33 (20.2)
Investigations		
ALT increased	61 (36.5)	18 (11)
AST increased	41 (24.6)	9 (5.5)
GGT increased	22 (13.2)	5 (3.1)
Blood alkaline phosphatase increased	6 (3.6)	2 (1.2)

[a] Adverse reactions are listed according to MedDRA version 25.1 system organ class.

[b] Grouped term diarrhea includes diarrhea, feces soft, and frequent bowel movements.

[c] Grouped term abdominal pain includes abdominal pain, abdominal pain upper, and abdominal discomfort.

[d] Grouped term gastroesophageal reflux disease includes gastroesophageal reflux disease, gastritis, and dyspepsia.

[e] Grouped term fatigue includes fatigue and asthenia.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

No pediatric safety data were obtained in the clinical trials (see 7.1.3 Pediatrics >12 years).

8.3 Less Common Clinical Trial Adverse Reactions

Not applicable.

8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

No pediatric safety data were obtained in the clinical trials.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Table 5 – Selected New or Worsened Laboratory Abnormalities ≥1% Reported in Patients Receiving VORANIGO with a Difference Between Arms of ≥2% Compared with Placebo in the INDIGO Trial (Study AG881-C-004)

	VORANIGO N=167	Placebo N=163
Parameter	**All grades n (%)**	**All grades n (%)**
Alanine aminotransferase (ALT) increased	61 (36.5)	18 (11)
Aspartate aminotransferase (AST) increased	41 (24.6)	9 (5.5)
Blood alkaline phosphatase increased	6 (3.6)	2 (1.2)
Gamma-glutamyl transferase (GGT) increased	22 (13.2)	5 (3.1)
Platelet count decreased	20 (12)	7 (4.3)

8.5 Post-Market Adverse Reactions

No safety information has been identified through post-marketing use.

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

The drugs listed in Table 6 are based on either drug interaction studies, or potential interactions due to the expected magnitude and seriousness of the interaction.

Table 6 – Established or Potential Drug-Drug Interactions

Proper name	Source of Evidence	Effect	Clinical comment
Moderate and Strong Cytochrome P450 (CYP) 1A2 Inhibitors ciprofloxacin (moderate CYP1A2 inhibitor) fluvoxamine (strong CYP1A2 inhibitor)	CT CT T	Concomitant use of 20 mg VORANIGO with a moderate CYP1A2 inhibitor (500 mg ciprofloxacin twice daily for 14 days) increased vorasidenib plasma C_{max} by 1.3-fold and AUC by 2.5-fold. Concomitant use of VORANIGO with strong inhibitors of CYP1A2 (fluvoxamine) is predicted to increase vorasidenib C_{max} by 5.7-fold and exposure by 7.2-fold.	Avoid concomitant use of VORANIGO with a moderate and strong CYP1A2 inhibitor. If concomitant use cannot be avoided, monitor for increased adverse reactions and modify the dosage as recommended (see Table 2).
Moderate CYP1A2 Inducers phenytoin and rifampicin	CT T	Concomitant use of VORANIGO with moderate CYP1A2 inducers and smoking tobacco is predicted to decrease vorasidenib steady-state C_{max} and AUC by 30 to 40%, which may decrease the efficacy of VORANIGO.	Avoid concomitant use of VORANIGO with moderate CYP1A2 inducers and smoking tobacco.
CYP Substrates with Narrow Therapeutic Index alfentanil, carbamazepine, cyclosporine, everolimus, fentanyl, ifosfamide, pimozide, quinidine, sirolimus, tacrolimus, tamoxifen	T	VORANIGO may decrease plasma concentrations and therapeutic effect of medications that are CYP2C19 and CYP3A4 substrates, where minimal concentration changes may lead to reduced therapeutic effect.	Avoid concomitant use of VORANIGO with CYP2C19 and CYP3A4 substrates where minimal concentration changes may lead to reduced efficacy.
Hormonal Contraceptives	T	Co-administration of VORANIGO may decrease concentrations of hormonal contraceptives which may lead to contraception failure.	Concomitant use of a barrier method of contraception is recommended during the treatment and for at least 3 months after the last dose.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Gastric Acid Reducing Agents

In healthy subjects, co-administration of a single dose of 50 mg vorasidenib with 40 mg of omeprazole under fasted conditions, after repeated dosing of omeprazole 40 mg once daily for 3 days, did not have a significant effect on vorasidenib exposure.

CYP Substrates

Based on physiologically-based pharmacokinetic modeling, vorasidenib is predicted 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.

UGT1A4 Substrate

No clinically significant difference in lamotrigine pharmacokinetics was observed following the administration of lamotrigine with multiple doses of vorasidenib.

P-gp and BCRP substrates

In a model approach, vorasidenib is not predicted to have effect on pharmacokinetics of digoxin (P-gp substrate) and rosuvastatin (BCRP substrate).

In vitro Studies

Effect of vorasidenib on Drug Metabolizing Enzymes

Vorasidenib is an inducer of CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A and UGT1A4.

Effect of vorasidenib on transporter Mediated Drug-Drug Interaction

Vorasidenib is not a substrate of P-gp, BCRP, or OATP1B1 and OATP1B3. Vorasidenib may be an inhibitor of BCRP. Vorasidenib does not inhibit P-gp or SLC transporters. AGI-69460, a metabolite of vorasidenib, may be an inhibitor of OATP1B3.

9.5 Drug-Food Interactions

All clinical studies administered VORANIGO on modified fasting. VORANIGO should be taken after at least 2 hours of fasting, and food intake should be avoided for at least 1 hour after taking VORANIGO since high- and low-fat meals can lead to increased plasma concentrations.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10. CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Vorasidenib is a small molecule inhibitor of IDH1 and IDH2 enzymes. From in vitro and in vivo tumour models expressing IDH1 or IDH2 proteins, vorasidenib inhibited the IDH1 and IDH2 wild type and variants, including IDH1 R132H. Vorasidenib decreased the production of 2-hydroxyglutarate (2-HG) and may restore cellular differentiation.

10.2 Pharmacodynamics

Vorasidenib decreases 2-HG tumour concentrations in patients with IDH1 or IDH2 mutated glioma. Relative to tumours from subjects in the untreated group, the posterior median percentage reduction in tumour 2-HG was 63.5% (95% Credible Interval: 22.2%, 88.4%) to 92.6% (95% Credible Interval: 76.1%, 97.6%) in tumours from patients who received vorasidenib at exposures that were 0.3 to 0.8 times the exposure observed with the approved recommended dosage.

Cardiac electrophysiology

Vorasidenib did not prolong the QT interval to any clinically relevant extent at 4 times the recommended therapeutic dosage.

10.3 Pharmacokinetics

Vorasidenib maximum plasma concentration (C_{max}) and area under the curve (AUC) increases in a proportional manner between 10 and 50 mg.

Table 7 – Summary of vorasidenib Pharmacokinetic Parameters in fasted healthy adult population

	C_{max} (ng/mL)*	**T_{max}** (hr)*	**$t_{½}$** (hr)*	**$AUC_{0-\infty}$** (hr·ng /mL)*	**CL/F** (L/hr)*	**Vd/F** (L)*
Single dose	75.4 (44%)	2.0 (0.5, 4.1)	238 (57%)	2,860 (56%)	14.0 (56%)	3,930 (40%)

* PK parameters expressed as geometric mean (geometric CV%) except T_{max} which is summarized as median (min, max)

Absorption

Vorasidenib steady state mean (CV%) C_{max} was 133 ng/mL (73%) and AUC was 1,988 hr·ng/mL (95%).

Accumulation ratios were approximately 3.83 for C_{max} and 4.43 for AUC. Steady-state plasma levels were reached after 14 days of once-daily dosing.

Food effect

The mean C_{max} and AUC_T increased by 3.1-fold and 1.4-fold, respectively, when vorasidenib was administered with a high-fat meal. Administration of vorasidenib with a low-fat meal resulted in increases in C_{max} and AUC_T of 2.3- and 1.4-fold, respectively.

Distribution

Vorasidenib steady state mean (CV%) volume of distribution (Vd/F) is 3,930 L (40%).

The mean plasma protein binding of vorasidenib is 97% independent of concentration. The brain tumour-to-plasma concentration ratio is 1.6.

Metabolism

Vorasidenib is primarily metabolized by CYP1A2 with minor contributions from CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5. Non-CYP pathways may contribute up to 30% of vorasidenib liver metabolic clearance.

Elimination

Following oral administration of radiolabeled vorasidenib, 85% of the dose was recovered in feces and 4.5% in urine. Most of the administered radioactivity that was recovered in feces was unchanged vorasidenib (55%) while no unchanged vorasidenib was detected in urine.

Special Populations and Conditions

- **Pediatrics** No patients under the age of 18 were treated with VORANIGO in the pivotal phase 3 study (INDIGO). Use of VORANIGO in pediatric patients 12 years and older is supported by evidence from studies in adults with additional population pharmacokinetic data demonstrating that age had no clinically meaningful effect on the pharmacokinetics of vorasidenib, that the exposure of vorasidenib is mostly similar between adults and pediatric patients age 12 years and older, and that the course of disease is sufficiently similar in adult and pediatric patients to allow extrapolation of data in adults to these pediatric patients. Analysis of the population pharmacokinetic modelling indicated that female pediatric patients in the 40-50 kg weight range may have a higher exposure and a higher risk of adverse drug reactions (see 7 WARNINGS AND PRECAUTIONS, 14.1 Clinical Trials by Indication, and 4.2 Recommended Dose and Dosage Adjustment, Dosage Modifications).

  The safety and effectiveness of VORANIGO have not been established in pediatric patients less than 12 years of age with Grade 2[a] astrocytoma or oligodendroglioma who have an IDH1 or IDH2 mutation.

  [a.] WHO 2016, 2021 guidelines

- **Geriatrics (> 65 years)** Of the 167 patients randomized to receive VORANIGO 40 mg once daily in the INDIGO trial, 1.2% (2 patients) were 65 years or older. No overall differences in safety or effectiveness were observed in patients aged 65 years or older.

- **Sex** No clinically significant effects on the pharmacokinetics of vorasidenib were observed based on sex. Elevated liver laboratory tests were seen more often in female patients, however the cause for such is unknown. All patients should have their liver laboratory tests monitored as described above.

- **Ethnic Origin** No clinically significant effects on the pharmacokinetics of vorasidenib were observed based on age (16 to 75 years), race (White, Black or African American, Asian, American Indian/Alaskan Native, Native Hawaiian or Other Pacific Islander, Other), ethnicity (Hispanic and non-Hispanic) or body weight (43.5 to 168 kg).

- **Hepatic Insufficiency** No clinically significant effects on the pharmacokinetics of vorasidenib were observed based on mild or moderate hepatic impairment (Child-Pugh Class A or B). The pharmacokinetics of vorasidenib have not been studied in patients with severe hepatic impairment (Child-Pugh Class C) (see 4.2 Recommended Dose and Dosage Adjustment and 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic)**.**

- **Renal Insufficiency** No clinically significant effects on the pharmacokinetics of vorasidenib were observed based on mild or moderate renal impairment (CL_{cr} >40 mL/min). The pharmacokinetics of vorasidenib have not been studied in patients with CL_{cr} ≤40 mL/min or renal impairment requiring dialysis (see 7 WARNINGS AND PRECAUTIONS).

11. STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15°C to 30°C).

Once opened, VORANIGO should be used within 60 days.

Keep out of reach and sight of children.

12. SPECIAL HANDLING INSTRUCTIONS

No special requirements.

PART II: SCIENTIFIC INFORMATION

13. PHARMACEUTICAL INFORMATION

Drug Substance

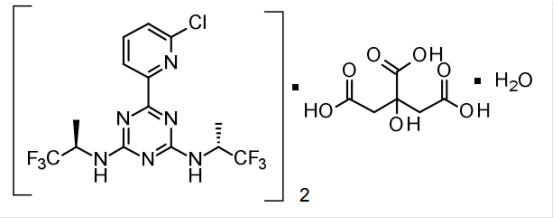
Proper/common name: vorasidenib

Chemical name: 6-(6-chloropyridin-2-yl)-N^2,N^4-bis[(2*R*)-1,1,1-trifluoropropan-2-yl]-1,3,5-triazine-2,4-diamine, 2-hydroxypropane-1,2,3-tricarboxylic acid, hydrate (2:1:1)

Molecular formula and molecular mass:

The molecular formula is $C_{14}H_{13}ClF_6N_6 \cdot ½\ C_6H_8O_7 \cdot ½\ H_2O$ and the molecular weight is 519.8 g/mol.

Structural formula:



Physicochemical properties: vorasidenib (as vorasidenib hemicitric acid, hemihydrate) is a white to off-white solid and is practically insoluble in aqueous solutions between pH 1.2 to 6.8.

14. CLINICAL TRIALS

14.1 Clinical Trials by Indication

Grade 2 IDH 1/2 Mutant Glioma

INDIGO trial (AG881-C-004)

Table 8 – Summary of patient demographics for INDIGO clinical trial in Grade 2 IDH1/2 mutant glioma

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Median age (Min, Max)	Sex (%)
AG881-C-004	Phase 3, randomized (1:1), multicenter, double-blind, placebo-controlled	40 mg orally once daily or matched placebo until radiographic disease progression or unacceptable toxicity	VORANIGO n=168	40.5 (21-71)	M 60.1 / F 39.9
			placebo n=163	39 (16-65)	M 52.8 / F 47.2

The efficacy of VORANIGO was evaluated in the INDIGO trial (Study AG881-C-004), a phase 3, randomized (1:1), multicenter, double-blind, placebo-controlled study of 331 adults and pediatric

patients ≥12 years old weighing ≥40 kg. Eligible patients were required to have Grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 mutation or IDH2 R172 mutation and prior surgery (gross total resection, subtotal resection or biopsy) for glioma. Patients with non-enhancing tumours or minimal tumour enhancement (includes tumours with no enhancement or minimal, non-nodular, and non-measurable enhancement that has not changed between the 2 most recent scans), including non-nodular or non-measurable lesions, were permitted to enroll. The INDIGO trial excluded patients who received prior anti-cancer treatment, including chemotherapy or radiation therapy. IDH1 or IDH2 mutation status was prospectively determined using the Oncomine Dx Target Test.

Patients were randomized to receive either VORANIGO 40 mg orally once daily or matched placebo until radiographic disease progression or unacceptable toxicity. Randomization was stratified by local 1p19q status (co-deleted or not co-deleted) and baseline tumour size (diameter ≥2 cm or <2 cm). Patients who were randomized to placebo were allowed to cross over to receive VORANIGO after centrally confirmed radiographic disease progression.

Patient demographics and disease characteristics were balanced between the treatment arms. Among the 168 patients randomized to VORANIGO, the median age was 41 years (range: 21 to 71 years), with 98.8% aged 18-64 years. A single pediatric patient aged 16 years was randomized to placebo, and no patient under the age of 18 was randomized to VORANIGO. A majority of patients were male (60.1%), 74.4% were White, 3.0% Asian, 1.2% Black, 1.2% other, 19.6% not reported and 53.6% had a Karnofsky Performance Status (KPS) score of 100. Most patients had 1 prior surgery for glioma (75%) and 25% had ≥2 prior surgeries (50.6% gross total, 48.2% sub-total, 14.3% biopsy). Across both arms, 95% of patients had an R132 mutation and 5% had an R172 mutation.

14.2 Study Results

The primary efficacy outcome measure was radiographic progression-free survival (PFS) as evaluated by a blinded independent review committee (BIRC) according to modified Response Assessment in Neuro-Oncology for Low Grade Glioma (RANO-LGG) criteria. Time to next intervention (TTNI), the time from randomization to the initiation of first subsequent anticancer therapy or death due to any cause, was the key secondary outcome measure.

Efficacy results for PFS and TTNI are summarized in Table 9 and Figure 1.

Table 9 – Efficacy Results for INDIGO Trial (Study AG881-C-004)

Efficacy parameter	**VORANIGO 40 mg daily (n=168)[a]**	**Placebo (n=163)**
Progression-free survival (PFS)		
Number of events, n (%)		
Progressive disease	47 (28.0)	88 (54.0)
Death	0	0
Median PFS, months (95% CI)[b]	27.7 (17.0, NE)	11.1 (11.0, 13.7)
Hazard ratio (95% CI)[c]	0.39 (0.27, 0.56)	
p-value[d]	0.000000067	
Time to next intervention (TTNI)		
Number of events, n (%)		
First subsequent therapy	19 (11.3)	6 (3.7)
Crossover to VORANIGO	0	52 (31.9)

Table 9 – Efficacy Results for INDIGO Trial (Study AG881-C-004)

Efficacy parameter	VORANIGO 40 mg daily (n=168)[a]	Placebo (n=163)
Median TTNI, months (95% CI)[b]	NE (NE, NE)	17.8 (15.0, NE)
Hazard ratio (95% CI)[c]	0.26 (0.15, 0.43)	
p-value[e]	0.000000019	

Abbreviations: CI = Confidence interval; NE = Not estimable; PFS = Progression-free survival; TTNI = Time to next intervention

[a] The efficacy analyses were based on all patients who were randomized.

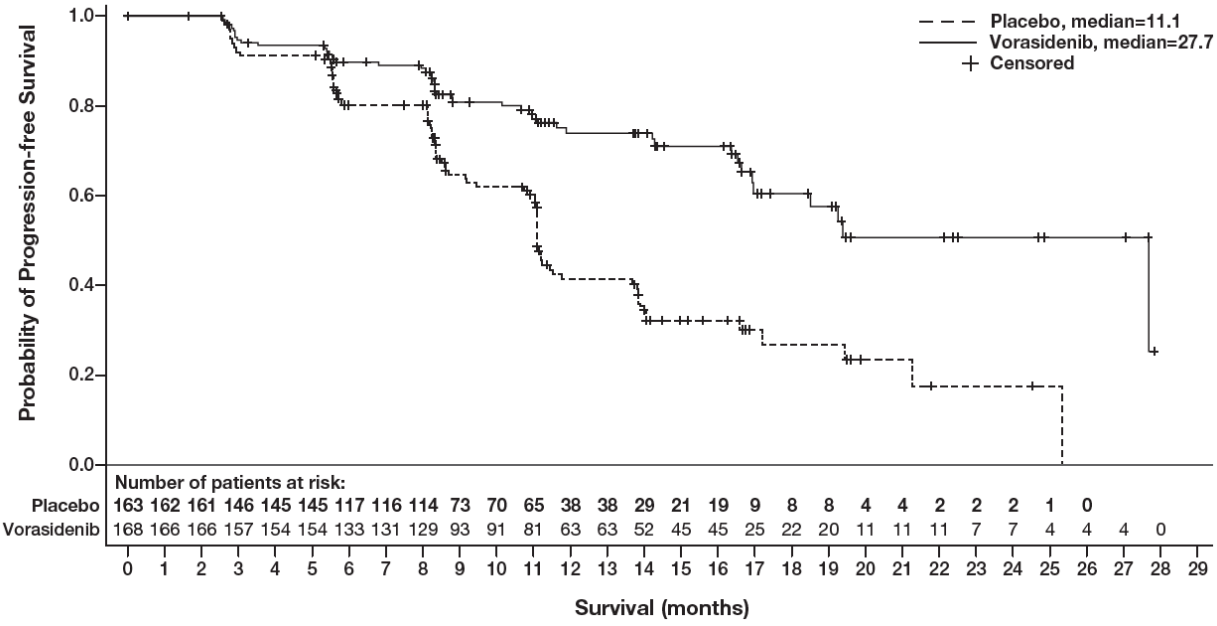
[b] The 95% confidence interval for the median was calculated using the Brookmeyer and Crowley method.

[c] Estimated with Cox proportional hazard model adjusted by the following stratification factors: 1p19q status and baseline tumour size.

[d] Based on one-sided stratified log-rank test compared to the pre-specified α of 0.000359 (one-sided).

[e] Based on one-sided stratified log-rank test compared to the pre-specified α of 0.00000048 (one-sided).

Figure 1: Kaplan-Meier Curve for Progression-Free Survival per BIRC Review in INDIGO Trial



15. MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

In repeat-dose studies, vorasidenib was administered orally in Sprague Dawley rats (both sexes) for 13 weeks at daily doses of 5, 15 and 50 mg/kg (up to 176-fold the MRHD of 40 mg based on AUC), and

in cynomolgus monkeys (both sexes) for 13 weeks at daily doses of 2, 6 and 20 mg/kg (up to 73-fold the MRHD of 40 mg based on AUC).

The following adverse effects in rats and monkeys were considered related to vorasidenib. Hepatocellular hypertrophy, increase in liver weight and changes in liver enzymes (AST, ALT, GGT, sorbitol dehydrogenase (SDH) and ALP) were observed in both sexes of rats (at least 5 mg/kg/day; at least 29-fold the MRHD of 40 mg based on AUC) and of monkeys (at least 6 mg/kg/day; at least 9-fold the MRHD of 40 mg based on AUC). Effects on neuromuscular system such as tremor, ataxia, head tilt, decrease in muscle tone, effects on skin such as desquamation, redness and hyperplasia, and effects on the kidneys such as mixed inflammatory cell infiltrates, tubular degeneration and decrease in kidney weight were observed in the high dose groups of both species. Reversible changes in erythrocyte and reticulocyte counts, red blood cell distribution, hemoglobin, platelets and fibrinogen levels were observed in both sexes of rats (at least 15 mg/kg/day; at least 77-fold the MRHD of 40 mg based on AUC) and in monkeys (at least 6 mg/kg/day; at least 9-fold the MHRD of 40 mg based on AUC).

Other effects such as decrease in body weight and food consumption as well as effects on gastrointestinal tract were mainly observed in high dose groups of rats.

After a recovery phase of four weeks, the effects in the liver and the changes in the liver enzymes either persisted or partially resolved in both rats and monkeys, depending on the dose level. Partial recovery was noted for skin hyperplasia in rats.

Carcinogenicity: No long-term animal studies have been performed to evaluate the carcinogenic potential of vorasidenib.

Genotoxicity: Vorasidenib was not genotoxic at maximum tested limits. Vorasidenib was not mutagenic in an in vitro bacterial reverse mutation assay in five bacteria strains. Vorasidenib was not clastogenic or aneugenic in an in vitro chromosomal aberration assay in cultured human peripheral blood lymphocytes, nor in an in vivo micronucleus assay in bone marrow of rats treated with oral doses up to 2000 mg/kg.

Reproductive and Developmental Toxicology:

Fertility

No fertility animal studies have been performed to evaluate whether vorasidenib affects fertility in males or females. In a 13-week repeat-dose study, male and female rats were administered vorasidenib orally at daily doses of 5, 15 and 50 mg/kg (exposure up to 176-fold the MRHD of 40 mg based on AUC). Adverse effects in female and male reproductive organs were observed from a dose of 5 mg/kg/day (approximately 29-fold the MRHD based on AUC). Adverse effects in females included atrophy of the ovaries, hyperplasia in the epithelia of uterus, cervix and vagina, uterine squamous metaplasia, decreased numbers of corpora lutea and estrous cycle variations. Adverse effects in males included degeneration of seminiferous tubules with germ loss and/or exfoliation into tubular lumen, cellular debris in the epididymis, atrophy of the testis, the epididymis, the prostate (with mixed cell inflammation) and seminal vesicles. After a recovery phase of 4 weeks, partial recovery was observed in both sexes at doses of at least 15 mg/kg/day (at least 77-fold the MRHD of 40 mg based on AUC).

Embryo-fetal Development

Embryo-fetal development was evaluated in female rats administered vorasidenib orally during organogenesis (gestation days 6 to 17) at daily doses of 10, 25 and 75 mg/kg (exposure up to 118-fold the MRHD of 40 mg based on AUC). At daily dose of 75 mg/kg (118-fold the MRHD based on AUC), increases in early and late resorptions and post-implantation losses, higher incidences of visceral

abnormalities were observed, and fetal body weights were 20% lower than concurrent controls. Higher incidences of skeletal abnormalities were observed at all dose levels (at least 31-fold the MRHD based on AUC).

Embryo-fetal development was evaluated in pregnant rabbits administered vorasidenib orally during organogenesis (gestation days 6 to 19) at daily doses of 2, 6 and 18 mg/kg resulting in clinically relevant exposures at the daily MRHD of 40 mg based on AUC. At daily dose of 18 mg/kg (exposure of 12-fold the MRHD of 40 mg based on AUC), increases in embryo-fetal resorptions and post-implantation losses were observed, and fetal body weights were 8% lower than concurrent controls. Higher incidences of delayed ossification and other skeletal variations were observed at daily doses of at least 6 mg/kg/day (exposure of at least 5-fold the MRHD based on AUC).

In both species, dose-dependent decreases in maternal food intake and body weight gain were observed during gestation.

Special Toxicology: The 28-day administration of vorasidenib at or more than 3 mg/kg/day in male and female rats (at least 8-fold the MRHD of 40 mg based on AUC) caused a reversible and minimal neutrophil infiltration of the epithelial lining of the middle ear and Eustachian tube (otitis media) in both sexes.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr] VORANIGO®

Vorasidenib tablets

Read this carefully before you start taking **VORANIGO** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **VORANIGO**.

What is VORANIGO used for?

VORANIGO is used to treat adults and adolescents (12 years of age and older) with certain types of cancers of the brain called low grade astrocytoma or oligodendroglioma following surgery, who have an abnormal gene called “IDH1” or “IDH2”.

Your healthcare professional will test your cancer for abnormal isocitrate dehydrogenase-1 (IDH1) or isocitrate dehydrogenase-2 (IDH2) protein to make sure that VORANIGO is right for you.

How does VORANIGO work?

VORANIGO is a cancer medicine that contains the active drug vorasidenib. It is used to treat specific cancers of the brain with changed (mutated) genes that make proteins known as IDH1 or IDH2. VORANIGO blocks the mutated form of the IDH1 or IDH2 protein and helps to slow or stop the brain cancer from growing.

What are the ingredients in VORANIGO?

Medicinal ingredients: vorasidenib

Non-medicinal ingredients: croscarmellose sodium, hypromellose, lactose monohydrate, macrogol, magnesium stearate, microcrystalline cellulose, pharmaceutical ink, silicified microcrystalline cellulose, sodium lauryl sulfate, titanium dioxide

VORANIGO comes in the following dosage forms:

Tablets: 10 mg and 40 mg.

Do not use VORANIGO if:

- you are allergic to vorasidenib or any of the other ingredients of this medicine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take VORANIGO. Talk about any health conditions or problems you may have, including if you:

- have kidney problems
- have liver problems
- are a smoker

- are intolerant to lactose. This is because VORANIGO contains lactose.

Other warnings you should know about:

- **Pregnancy and breastfeeding**
  Female patients
  - If you are pregnant or plan to be pregnant during treatment with VORANIGO, there are important risks you should discuss with your healthcare professional.
  - Do NOT become pregnant during treatment with VORANIGO. It may harm your unborn baby.
  - If you are able to become pregnant:
    - Your healthcare professional should perform a pregnancy test before you start treatment.
    - Avoid becoming pregnant by using an effective barrier (non-hormonal) method of birth control during treatment and for at least 3 months after the last dose of VORANIGO.
      - If you are taking hormonal birth control methods (such as birth control pills, contraceptive patches or implants), you must also use a barrier method (such as condoms or a diaphragm) to avoid pregnancy.
      - Talk to your healthcare professional about birth control methods that may be right for you.
    - Tell your healthcare professional right away if you become pregnant while taking VORANIGO.

  Breastfeeding
  - Do NOT breastfeed while taking VORANIGO and for at least 2 months after the last dose. It is not known if VORANIGO passes into breast milk.
  - Talk to your healthcare professional about the best way to feed your baby during treatment with VORANIGO.

  Male patients
  - Do NOT father a child during treatment with VORANIGO.
  - If you have a partner who is able to become pregnant:
    - Use an effective barrier method of birth control during treatment and for at least 3 months after the last dose. Hormonal birth control may be used by your partner as well to prevent pregnancy.
    - Talk to your healthcare professional about birth control methods that may be right for you.
    - Tell your healthcare professional right away if your partner becomes pregnant during your treatment with VORANIGO.

- **Fertility**
  VORANIGO may affect fertility. Talk to your healthcare professional if this is a concern for you.

- **Children**
  - Children under 12 years of age should not be given VORANIGO. It is not known if VORANIGO is safe and effective in children below 12 years of age.
  - Children (12 to 18 years of age) may be at a higher risk of side effects.

- **Check-ups and testing**
  - You will have regular visits with your healthcare professional during treatment with VORANIGO. They will:
    - Do blood tests before you start treatment with VORANIGO, and as necessary during treatment. This is to check how well your liver is working and check your blood counts.
    - Check for signs of side effects.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with VORANIGO:

- Alfentanil (used for anaesthesia in surgery)
- Carbamazepine, phenytoin (used to treat seizures)
- Ciprofloxacin (used to treat bacterial infections)
- Cyclosporine, everolimus, sirolimus, tacrolimus (medicines used after organ transplants to help control your body's immune response)
- Fentanyl (used for severe pain)
- Fluvoxamine (used to treat depression)
- Hormonal contraceptive medicines (medicines used to prevent pregnancy, such as birth control pills)
- Ifosfamide, tamoxifen (used to treat certain cancers)
- Pimozide (used to treat abnormal thoughts and feelings)
- Quinidine (used to treat abnormal heartbeat)
- Rifampicin (used to treat tuberculosis or certain other infections)
- Smoking cigarettes

How to take VORANIGO:

- Always take this medicine exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.
- Take VORANIGO by mouth. Swallow the tablet whole with a glass of water. Do not split, crush or chew the tablet.
- Do NOT eat food at least 2 hours before and 1 hour after you take the tablet.
- If you vomit after taking your usual dose, do not take an extra dose. Take the next dose at your scheduled time.
- Do not stop taking VORANIGO unless your healthcare professional tells you to. It is important to take VORANIGO for as long as your doctor prescribes it to you.

Usual dose:

- The recommended dose for adults and adolescents (12 years of age and older) depends on your weight:
  - For patients who weigh **at least 40 kg**: take 40 mg (one 40 mg tablet) by mouth once a day at approximately the same time each day.
  - For patients who weigh **less than 40 kg**: take 20 mg (two 10 mg tablets) by mouth once a day at approximately the same time each day.
- If necessary, your healthcare provider may lower your dose or have you temporarily or permanently stop treatment.

Overdose:

If you think you, or a person you are caring for, have taken too much VORANIGO, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take VORANIGO by:

- **less than** 6 hours, take it as soon as you remember. You can take your next dose at your usual scheduled time.
- **more than** 6 hours, skip the missed dose. Wait to take your next dose at the scheduled time. Do NOT take double the dose to make up for a dose you have missed.

What are possible side effects from using VORANIGO?

These are not all the possible side effects you may have when taking VORANIGO. If you experience any side effects not listed here, tell your healthcare professional.

- decreased appetite
- stomach pain
- acid reflux or indigestion
- fatigue

VORANIGO may cause abnormal blood test results. Your health professional will tell you if your blood test results are abnormal and if you need treatment to correct these side effects.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Diarrhea	X		
Increased amount of liver enzymes in blood (alanine aminotransferase increased, aspartate aminotransferase increased and gamma-glutamyl transferase increased): 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 and feeling very tired or weak		X	X

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store at room temperature (15°C to 30°C).
- Do not use this medicine after the expiry date which is stated on the bottle label and box.
- Keep out of reach and sight of children.
- Once opened, this medicine should be used within 60 days.

If you want more information about VORANIGO:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website (www.servier.ca), or by calling 1-800-363-6093.

This leaflet was prepared by Servier Canada Inc.

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