For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only
This package insert is continually updated: Please read carefully before using a new pack.

VORANIGO®

1. GENERIC NAME

Vorasidenib film-coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Vorasidenib Immediate Release 10 mg Tablet: Each film-coated tablet contains 10 mg of vorasidenib

Vorasidenib Immediate Release 40 mg Tablet: Each film-coated tablet contains 40 mg of vorasidenib

List of excipients:
Tablet core: Microcrystalline cellulose, Croscarmellose sodium, silicified microcrystalline cellulose (contains microcrystalline cellulose and silica colloidal anhydrous), Magnesium stearate, Sodium lauryl sulfate
Tablet film-coating: Hypromellose, Titanium dioxide, Lactose monohydrate, Macrogol
Printing ink: Black iron oxide, Propylene glycol, Hypromellose

3. DOSAGE FORM AND STRENGTH

Oral Immediate release film-coated tablet
Vorasidenib Immediate Release 10 mg Tablet
Vorasidenib Immediate Release 40 mg Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Vorasidenib 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.

4.2 Posology and method of administration

Before initiating vorasidenib, evaluate blood chemistry and liver laboratory tests *(see 4.4 Special warnings and precautions for use and 4.8 Undesirable effects)*. Select patients with Grade 2 astrocytoma or oligodendroglioma for treatment with vorasidenib based on the presence of IDH1 or IDH2 mutations in tumor specimens.

Posology

The recommended dosage of vorasidenib 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.

Administer vorasidenib until disease progression or unacceptable toxicity.

Administration

Swallow vorasidenib tablets whole with water. Do not split, crush or chew vorasidenib tablets. Do not eat food at least 2 hours before and 1 hour after taking vorasidenib tablets *(see 5.3 Pharmacokinetic properties)*.

Missed Dose

Take vorasidenib tablets at about the same time each day. If a dose is missed, take the missed dose as soon as possible within 6 hours. If a dose is missed by more than 6 hours, skip the missed dose and take the next dose at the scheduled time.

Vomiting

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.

Dosage Modifications, Management and Monitoring for Adverse Reactions

Assess complete blood counts and blood chemistries, including liver enzyme tests, prior to the initiation of vorasidenib, every 2 weeks during the first 2 months of treatment and then monthly for the first 2 years, and as clinically indicated thereafter. Certain patients may require more frequent and ongoing monitoring *(see 4.4 Special warnings and precautions for use)*. Manage any abnormalities promptly *(see 4.8 Undesirable effects)*.

Dose interruption or dose reduction may be required based on individual safety and tolerability.

The recommended vorasidenib dosage reductions for adverse reactions are provided in Table 1.

Table 1: Recommended Vorasidenib Dosage Reductions for Adverse Reactions

Dosage Reduction	**Recommended Dose and Schedule**
Adults and Pediatric patients 12 years and older weighing at least 40 kg	
First	20 mg once daily
Second	10 mg once daily
Adults and Pediatric patients 12 years and older weighing less than 40 kg	
First	10 mg once daily
Permanently discontinue vorasidenib in patients unable to tolerate 10 mg once daily.	

The recommended management for adverse reactions and vorasidenib 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) *(see 4.4 Special warnings and precautions for use)*	Grade 1 ALT or AST increase >ULN to 3 x ULN *without* concurrent total bilirubin >2 x ULN	Continue vorasidenib 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 vorasidenib until recovery to ≤Grade 1 or baseline. • Recovery in ≤28 days, resume at the same dose. • Recovery in >28 days, resume vorasidenib at reduced dose *(see Table 1)*. Recurrence: Withhold vorasidenib until recovery to ≤Grade 1 or baseline, and resume vorasidenib 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 vorasidenib until recovery to ≤Grade 1 or baseline. • Recovery in ≤28 days, resume vorasidenib at reduced dose *(see Table 1)*. • If not recovered in ≤28 days, permanently discontinue vorasidenib Recurrence: Permanently discontinue vorasidenib .
	Grade 2 or 3 Any ALT or AST >3 to 20 x ULN *with* concurrent total bilirubin >2 x ULN	First Occurrence: Withhold vorasidenib until recovery to ≤Grade 1 or baseline. • Resume vorasidenib at reduced dose *(see Table 1)*. Recurrence: Permanently discontinue .
	Grade 4 Any ALT or AST >20 x ULN	Permanently discontinue vorasidenib.
Other Adverse Reactions *(see 4.8 Undesirable effects)*	Grade 3	First Occurrence: Withhold vorasidenib until recovery to ≤Grade 1 or baseline. • Resume vorasidenib at reduced dose *(see Table 1)*. Recurrence: Permanently discontinue vorasidenib .
	Grade 4	Permanently discontinue vorasidenib .

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.

4.3 Contraindications

None.

4.4 Special warnings and precautions for use

Hepatotoxicity

Elevations in liver enzymes, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST) >3 times the upper limit of normal (ULN), with elevation in total bilirubin >2 times the ULN have been reported in patients treated with vorasidenib *(see 4.8 Undesirable effects)*. Hepatic failure and hepatic necrosis were observed in one patient treated with vorasidenib and autoimmune hepatitis was observed in one patient treated with vorasidenib.

Monitor liver enzymes (including ALT, AST and gamma-glutamyl transferase (GGT)) and total bilirubin prior to the start of vorasidenib, every 2 weeks during the first 2 months of treatment and then monthly for the first 2 years, and as clinically indicated thereafter. Consider weekly monitoring for ALT or AST elevations ≤3 times the ULN. Withhold, reduce dose or permanently discontinue based on the severity of the liver enzyme abnormalities *(see 4.2 Posology and method of administration)*.

Embryo-Fetal Toxicity

Based on findings from animal studies, vorasidenib 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 ≥ 97-fold the maximum human therapeutic daily dose 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 at doses ≥17-fold the maximum human therapeutic daily dose of 40 mg based on AUC.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with vorasidenib and for at least 3 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with vorasidenib and for at least 3 months after the last dose *(see 4.6 Use in special populations)*.

4.5 Drug Interactions

Table 3 : Effect of Other Drugs on Vorasidenib

Strong Cytochrome P450 (CYP) 1A2 Inhibitors	
Clinical Impact	• Co-administration of vorasidenib with strong CYP1A2 inhibitors may increase vorasidenib plasma concentrations *(see 5.3 Pharmacokinetic properties)*.
Prevention or Management	• Avoid co-administration of vorasidenib with strong CYP1A2 inhibitors. • Consider alternative therapies that are not strong CYP1A2 inhibitors during treatment with vorasidenib.
Moderate CYP1A2 Inducers	

Table 3 : Effect of Other Drugs on Vorasidenib

Clinical Impact	• Co-administration of vorasidenib with moderate CYP1A2 inducers may decrease vorasidenib plasma concentrations, which may decrease the efficacy of *(see 5.3 Pharmacokinetic properties)*.
Prevention or Management	• Consider alternative therapies that are not moderate CYP1A2 inducers during treatment with vorasidenib.

Table 4 Effect of Vorasidenib on Other Drugs

CYP Substrates with Narrow Therapeutic Index	
Clinical Impact	• Co-administration of vorasidenib may decrease plasma concentrations and therapeutic effect of medications that are CYP2C19 and CYP3A4 substrates with a narrow therapeutic index.
Prevention or Management	• Avoid concomitant use of vorasidenib with CYP2C19 and CYP3A4 substrates that have a narrow therapeutic index.
Sensitive Substrates of CYP Enzymes without Narrow Therapeutic Index	
Clinical Impact	• Co-administration of vorasidenib may decrease plasma concentrations and therapeutic effect of medications that are sensitive substrates of CYP3A4 without a narrow therapeutic index.
Prevention or Management	• Consider alternative therapies that are not sensitive substrates of CYP3A4 during treatment with vorasidenib.
Hormonal Contraceptives	
Clinical Impact	• Co-administration of vorasidenib may decrease the concentrations of hormonal contraceptives.
Prevention or Management	• Consider alternative methods of contraception during treatment with vorasidenib.

4.6 Use in special populations

Pregnancy

Based on findings from animal studies, vorasidenib can cause fetal harm when administered to a pregnant woman. There is a limited amount of data on vorasidenib use in pregnant women to inform a drug-associated risk.

Lactation

There are no data on the presence of vorasidenib or its metabolites in human milk, their effects on the breastfed child, or on milk production. Because of the potential for adverse reactions in breastfed children from vorasidenib, advise women not to breastfeed during treatment with vorasidenib and for 2 months after the last dose.

Fertility

Based on findings in animals, vorasidenib may impair fertility in females and males of reproductive potential. The effects on female and male fertility were not reversible in rats *(see 6. Non-clinical Properties)*.

Verify pregnancy status in females of reproductive potential prior to starting vorasidenib.

Advise females of reproductive potential to use effective nonhormonal contraception during treatment with vorasidenib and for 3 months after the last dose. Vorasidenib can render some hormonal contraceptives ineffective *(see 4.5 Drug Interactions)*. Advise male patients with

female partners of reproductive potential to use effective contraception during treatment with vorasidenib and for 3 months after the last dose. Patients who are planning to conceive a child should be advised to seek reproductive counseling before starting treatment.

Pediatric

The safety and effectiveness of vorasidenib have been established in pediatric patients aged 12 years and older for the treatment of Grade 2 IDH1- or IDH2-mutant astrocytoma or oligodendroglioma. Use of vorasidenib for this indication in this age group is supported by evidence from an adequate and well-controlled study of vorasidenib in adult and pediatric patients with additional population pharmacokinetic data demonstrating that age had no clinically meaningful effect on the pharmacokinetics of vorasidenib. In addition, the course of IDH1- or IDH2-mutant astrocytoma or oligodendroglioma is sufficiently similar between adults and pediatric patients to allow extrapolation of pharmacokinetic data in adults to pediatric patients *(see 4.8 Undesirable effects, 5.3 Pharmacokinetic properties and Clinical Studies)*.

The exposure of vorasidenib in pediatric patients 12 years and older is predicted to be within range of exposure observed in adults at the recommended dosages *(see 5.3 Pharmacokinetic properties)*.

The safety and effectiveness of vorasidenib have not been established in pediatric patients younger than 12 years of age for any indication.

Geriatric Use

Of the 167 patients who were randomized and received vorasidenib 40 mg once daily in the INDIGO trial, 1.2% (2 patients) were 65 years or older. Clinical studies of vorasidenib did not include sufficient numbers of patients aged ≥65 to determine whether they respond differently from younger subjects.

Renal Impairment

No dosage adjustment is recommended for patients with creatinine clearance (CL_{cr}) >40 mL/min.

The pharmacokinetics and safety of vorasidenib in patients with $CL_{cr} \leq 40$ mL/min or renal impairment requiring dialysis have not been studied *(see 5.3 Pharmacokinetic properties)*. For patients with $CL_{cr} \leq 40$ mL/min or who require dialysis, monitor for increased adverse reactions and modify the dosage for adverse reactions as recommended *(see 4.2 Posology and method of administration and 5.3 Pharmacokinetic properties)*.

Hepatic Impairment

No dosage adjustment is recommended for patients with mild or moderate (Child-Pugh Class A or B) hepatic impairment *(see 5.3 Pharmacokinetic properties)*.

The pharmacokinetics and safety of vorasidenib in patients with severe hepatic impairment (Child-Pugh Class C) have not been studied. Vorasidenib should not be used in patients with pre-existing severe hepatic impairment *(see 5.3 Pharmacokinetic properties)*.

4.7 Effects on ability to drive and use machines

Vorasidenib has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of safety profile

The most common adverse reactions, including laboratory abnormalities, were ALT increased (59.3%), AST increased (45.5%), GGT increased (37.7%), fatigue (36.5%), and diarrhea (24.6%).

The most common grade 3 or 4 adverse reactions were ALT increased (9.6%), AST increased (4.8%) and GGT increased (3.0%).

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

Permanent discontinuation of vorasidenib due to an adverse reaction was reported in 5 of 167 patients (3.0%). The most common grade 3 or 4 adverse reactions leading to permanent discontinuation was ALT increased (3.0%).

Dose interruptions due to an adverse reaction occurred in 32 of 167 patients (19.2%) treated with vorasidenib. The most common adverse reactions requiring dose interruption were ALT increased (14.4%) and AST increased (6.0%).

Dose reductions of vorasidenib due to an adverse reaction occurred in 16 of 167 patients (9.6%). The most common adverse reaction requiring dose reduction was ALT increased (7.8%).

Tabulated list of adverse reactions

Adverse reactions reported in patients treated with vorasidenib in the INDIGO trial (Study AG881-C-004) are listed below in Table 5 by MedDRA system organ class and by frequency.

Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 5: Adverse Drug Reactions Reported in Patients Treated with Vorasidenib in the INDIGO Trial (Study AG881-C-004) (N=167)

System organ class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Very common	Platelet count decreased[a]
Metabolism and nutrition disorders	Common	Hyperglycemia
		Decreased appetite
		Hypophosphatemia[b]
Gastrointestinal disorders	Very common	Abdominal pain[c]
		Diarrhea[d]
Hepatobiliary disorders	Very common	Alanine aminotransferase increased[a]
		Aspartate aminotransferase increased[a]
		Gamma-glutamyl transferase increased[a]
	Common	Alkaline phosphatase increased[a]
General disorders	Very common	Fatigue[e]

[a] Laboratory abnormality is defined as new or worsened by at least one grade from baseline, or baseline is unknown.
[b] Grouped term includes hypophosphatemia and blood phosphorus decreased.
[c] Grouped term includes abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, epigastric discomfort, and abdominal tenderness.
[d] Grouped term includes diarrhea, feces soft and frequent bowel movements.

[e] Grouped term includes fatigue and asthenia.

Description of selected adverse reactions

Hepatobiliary disorders

In the INDIGO clinical trial (Study AG881-C-004), 18.6% (31/167) of patients treated with vorasidenib experienced ALT elevations >3 times the ULN and 8.4% (14/167) experienced AST elevations >3 times the ULN. In INDIGO, 1.2% of patients (2/167) had concurrent ALT or AST elevations >3 times the ULN and total bilirubin >2 times the ULN. Liver enzyme and bilirubin increases were transient and improved or resolved with dose modification or permanent discontinuation of treatment.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to Servier.India.PV@servier.com.

4.9 Overdose

In the event of overdose, toxicity is likely to manifest as exacerbation of the adverse reactions associated with vorasidenib *(see 4.8 Undesirable effects)*. Patients should be closely monitored and provided with appropriate supportive care *(see 4.2 Posology and method of administration and 4.4 Special warnings and precautions for use)*. There is no specific antidote for vorasidenib overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of action

Vorasidenib is a small molecule dual inhibitor that targets the mutant IDH1 and IDH2 enzymes. In patients with astrocytoma or oligodendroglioma, IDH1 and IDH2 mutations lead to overproduction of the oncogenic metabolite 2-hydroxyglutarate (2-HG), resulting in impaired cellular differentiation and increased cellular proliferation contributing to oncogenesis. Direct inhibition of the gain-of-function activity of the IDH1- and IDH2-mutated proteins by vorasidenib inhibits the abnormal production of 2-HG through the differentiation of the malignant cells and reduction of cellular proliferation.

5.2 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents; other antineoplastic agents
ATC code: L01XM04

Exposure-Response Relationships
A therapeutic daily dose of vorasidenib decreases 2-HG tumor concentrations in subjects with IDH1 or IDH2 mutated glioma. The posterior median percentage reduction (95% credible interval) in tumor 2-HG was 92.6% (76.1%, 97.6%) in tumors from subjects treated with vorasidenib, relative to tumors from subjects in the untreated group.

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

5.3 Pharmacokinetic properties

Vorasidenib maximum plasma concentration (C_{max}) and AUC increased approximately proportionally over the dose range of 10 to 200 mg following once daily administration of single and multiple doses. At the highest approved recommended dosage, steady state mean (CV%) C_{max} is 133 ng/ml (73%) and AUC is 1,988 h•ng/ml (95%). Steady state is achieved within 28 days of once daily dosing and the mean accumulation ratio of AUC is 4.4.

Absorption

The median (minimum, maximum) time to maximum plasma concentrations (t_{max}) at steady state is 2 hours (0.5 to 4 hours). The mean absolute bioavailability of vorasidenib is 34%.

Food Effect

A high-fat and high-calorie (total 800-1,000 calories, of which 500-600 from fat) meal increased vorasidenib C_{max} 3.1-fold and AUC 1.4-fold, compared to the fasting conditions. A low-fat and low-calorie (total 400-500 calories, of which 100-125 from fat) meal increased vorasidenib C_{max} 2.3-fold and AUC 1.4-fold, compared to the fasting conditions.

Distribution

The mean (CV%) volume of distribution at steady state of vorasidenib is 3,930 L (40%). The protein binding is 97% in human plasma independent of vorasidenib concentrations in vitro. The brain tumor-to-plasma concentration ratio is 1.6.

Elimination

The mean (CV%) steady state terminal half-life is 10 days (57%) and oral clearance is 14 L/h (56%).

Metabolism

Vorasidenib is primarily metabolized by CYP1A2 with minor contributions from CYP286, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A. Non-CYP pathways may contribute up to 30% of its metabolism.

Excretion

Following a single oral radiolabeled dose of vorasidenib, 85% of the dose was recovered in feces (56% unchanged) and 4.5% was recovered in urine

Specific Populations

No clinically significant effects on the pharmacokinetics of vorasidenib were observed based on age (16 to 75 years), sex, race (White, Black or African American, Asian, American Indian/Alaskan Native, Native Hawaiian or Other Pacific Islander), ethnicity (Hispanic and non-Hispanic), body weight (43.5 to 168 kg), mild or moderate hepatic impairment (Child-Pugh Class A or B) or CL_{cr} > 40 mL/min (as Cockcroft-Gault). The pharmacokinetics of vorasidenib has not been studied in patients with severe hepatic impairment (Child-Pugh Class C), in patients with $CL_{cr} \leq 40$ mL/min or in patients with renal impairment who require dialysis.

Pediatric Patients

The exposure of vorasidenib in pediatric patients ≥12 years of age is predicted to be within range of that observed in adults at the approved recommended dosage.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Effect of Other Drugs on Vorasidenib

Strong and Moderate CYP1A2 Inhibitors: Concomitant use of ciprofloxacin (moderate CYP1A2 inhibitor) increased vorasidenib plasma C_{max} 1.3-fold and AUC 2.5-fold.

Concomitant use with fluvoxamine (strong CYP1A2 inhibitor) is predicted to increase vorasidenib C_{max} and AUC by ≥5-fold.

Moderate CYP1A2 Inducers: Concomitant use with phenytoin or rifampicin (moderate CYP1A2 inducers) is predicted to decrease vorasidenib steady-state C_{max} by 30% and AUC by 40%.

Gastric Acid Reducing Agents: No clinically significant difference in vorasidenib pharmacokinetics was observed following concomitant use with omeprazole (an acid-reducing agent).

Effect of Vorasidenib on Other Drugs

CYP3A Substrates: Concomitant use of multiple doses of vorasidenib with CYP3A substrates is predicted to decrease the concentrations of these substrates.

UGT1A4 Substrate: No clinically significant difference in lamotrigine pharmacokinetics was observed following the administration of lamotrigine with multiple doses of vorasidenib.

P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP) Substrates: No clinically significant difference in the pharmacokinetics of digoxin (P-gp substrate) or rosuvastatin (BCRP substrate) is predicted when used concomitantly with vorasidenib.

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

Vorasidenib is not a substrate of P-gp, BCRP, or organic anion transporting polypeptide (OATP)1B1 and OATP1B3.

Vorasidenib is an inhibitor of BCRP. Vorasidenib does not inhibit P-gp and OATP1B1.

6. NON-CLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

In repeat-dose toxicity studies, oral administration of vorasidenib to rats for 28 days led to ototoxicity findings of reversible neutrophil infiltration of the epithelial lining of the middle ear and Eustachian tube at doses >3 mg/kg/day (>12-times the human exposure based on the AUC at the highest recommended dose). Additional findings in a 28-day ototoxicity study included edema in the tympanic cavity at doses >30 mg/kg/day. In addition, oral administration of vorasidenib to monkeys for 13 weeks resulted in dilated cardiomyopathy and secondary congestive heart failure at a dose of 20 mg/kg/day (105 times the human exposure based on the AUC at the highest recommended dose). Skeletal muscle was a target organ in the repeat dose toxicology studies in rats and monkeys at doses ≥13 times the AUC in patients at the highest recommended dose. Findings included decreased hind limb muscle tone, abnormal gait with limited hind limb usage, and low carriage, associated with small size and atrophy of the muscle in rats and necrosis and mononuclear/mixed cell infiltrates in the muscle in monkeys.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with vorasidenib. Vorasidenib and its major circulating metabolite, AGI-69460, were not mutagenic in an in vitro bacterial reverse mutation

(Ames) assay. Vorasidenib was not clastogenic in an in vitro human lymphocyte micronucleus assay, or an in vivo rat bone marrow micronucleus assay.

Fertility studies in animals have not been conducted with vorasidenib. In repeat-dose toxicity studies up to 13 weeks in duration with oral administration of vorasidenib in rats, adverse effects in female reproductive organs included atrophy, decreased/absent corpora lutea, increased atretic follicles, and interstitial cell vacuolation of the ovaries, atrophy, hypertrophy, and metaplasia of the uterus, hyperplasia of the cervix, atrophy, hyperplasia, and mucification of the vagina, and estrous cycle variations at doses ≥3 mg/kg/day (≥12 times the exposure based on AUC in humans at the highest recommended dose). Adverse effects in male reproductive organs in rats included tubular degeneration and atrophy of the testes, degeneration of seminiferous tubules, cellular debris in the epididymides, epithelial atrophy and inflammation in the prostate, and atrophy in the seminal vesicles at doses ≥3 mg/kg/day (≥12 times the exposure based on AUC in humans at the highest recommended dose). Findings in the male rats were not reversible. In the 4-week repeat-dose toxicity studies in monkeys, oral administration of vorasidenib led to adverse effects in male and female reproductive organs including fibrotic hypoplasia of the testes in males at doses ≥10 mg/kg/day (approximately 17 times the exposure based on AUC in humans at the highest recommended dose) and decreased uterine weights in females at doses ≥10 mg/kg/day (approximately 22 times the exposure based on AUC in humans at the highest recommended dose). Findings in male and female monkeys were reversible.

In animal embryo-fetal development studies, oral administration of vorasidenib to pregnant rats and rabbits during the period of organogenesis caused embryo-fetal toxicity at ≥8 times the human exposure based on the AUC at the highest recommended dose.

In an embryo-fetal development study, vorasidenib was administered to pregnant rats via oral gavage at dose levels of 10, 25, and 75 mg/kg/day during the period of organogenesis (gestation days 6 to 17). Embryo-fetal toxicity (higher incidence of early resorptions, and visceral malformations of kidney and testes) occurred in rats at the maternally toxic dose of 75 mg/kg/day (approximately 170 times the human exposure based on the AUC at the highest recommended dose). Malformation of heart occurred in a rat at a dose of 25 mg/kg (approximately 97 times the human exposure based on the AUC at the highest recommended dose). Dose-related delayed ossification of bones and short ribs associated with decreased fetal body weights was observed at 10 and 25 mg/kg/day in the absence of maternal toxicity and at 75 mg/kg/day. The dose of 10 mg/kg/day is ≥45 times the human exposure based on the AUC at the highest recommended dose.

In an embryo-fetal development study, oral administration of vorasidenib to pregnant rabbits at dose levels of 2, 6, and 18 mg/kg/day during the period of organogenesis (gestation days 6 to 19) resulted in maternal toxicity at all doses (≥1.5 times the human exposure based on the AUC at the highest recommended dose) and caused higher incidence of late resorptions at 18 mg/kg/day as well as decreased fetal weights and delayed ossification at doses ≥6 mg/kg/day (≥8 times the human exposure based on the AUC at the highest recommended dose).

Clinical Studies

The efficacy of vorasidenib was evaluated in the INDIGO trial (Study AG881-C-004), a randomized, multicenter, double-blind, placebo-controlled study of 331 patients (NCT04164901). Eligible patients were required to have IDH1- or IDH2-mutant Grade 2 astrocytoma or oligodendroglioma with prior surgery including biopsy, sub-total resection, or gross total resection. Patients were required to have measurable, non-enhancing disease; patients with centrally confirmed minimal, non-nodular, nonmeasurable enhancement were eligible. Patients who received prior anti-cancer treatment, including chemotherapy or radiation therapy were excluded. Patients were randomized to receive either vorasidenib 40 mg orally once daily or placebo orally once daily until disease progression or unacceptable toxicity. IDH1 or IDH2 mutation status was prospectively determined by the Life Technologies Corporation Oncomine Dx Target Test.

Randomization was stratified by local 1p19q status (co-deleted or not co-deleted) and baseline tumor size (diameter ≥2 cm or <2 cm). Patients who were randomized to placebo were allowed to cross over to receive vorasidenib after documented radiographic disease progression. Tumor assessments were performed every 12 weeks.

A total of 331 patients were randomized, 168 to the vorasidenib arm and 163 to the placebo arm. The median age was 40 years (range: 16 to 71); 57% were male; 78% were White, 4% were Asian, 1% were Black or African American and 16% had race not reported; 78% were not Hispanic or Latino; 52% oligodendroglioma and 48% astrocytoma; 79% had one prior surgery and 21% had ≥2 prior surgeries. In the vorasidenib arm, 14% of patients had biopsy, 48% had sub-total resection and 51% had gross-total resection. The majority of IDH1 mutations consisted of R132H (87%). The other alleles were reported as follows: R132C (5%), R132G (3%), R132L (1%), and R132S (1%). IDH2 mutations consisted of R172K (2%) and R172G (1%).

The major efficacy outcome was progression-free survival (PFS) as evaluated by a blinded independent review committee (BIRC) per 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 a key secondary outcome measure. Tumor growth rate (TGR), another secondary endpoint, was defined as the on-treatment percentage change in tumor volume every 6 months.

Efficacy results for PFS and TTNI are summarized in Table 6, Figure 1 and Figure 2.

Table 6 Efficacy Results for the INDIGO Trial (Study AG881-C-004)

Efficacy Parameter	**VORASIDENIB 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 vorasidenib	0	52 (31.9)
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[d]	0.000000019	

Abbreviations: CI = Confidence Interval; NE = Not estimable

[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 tumor size.

[d] Estimated from one-sided stratified log-rank test.

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

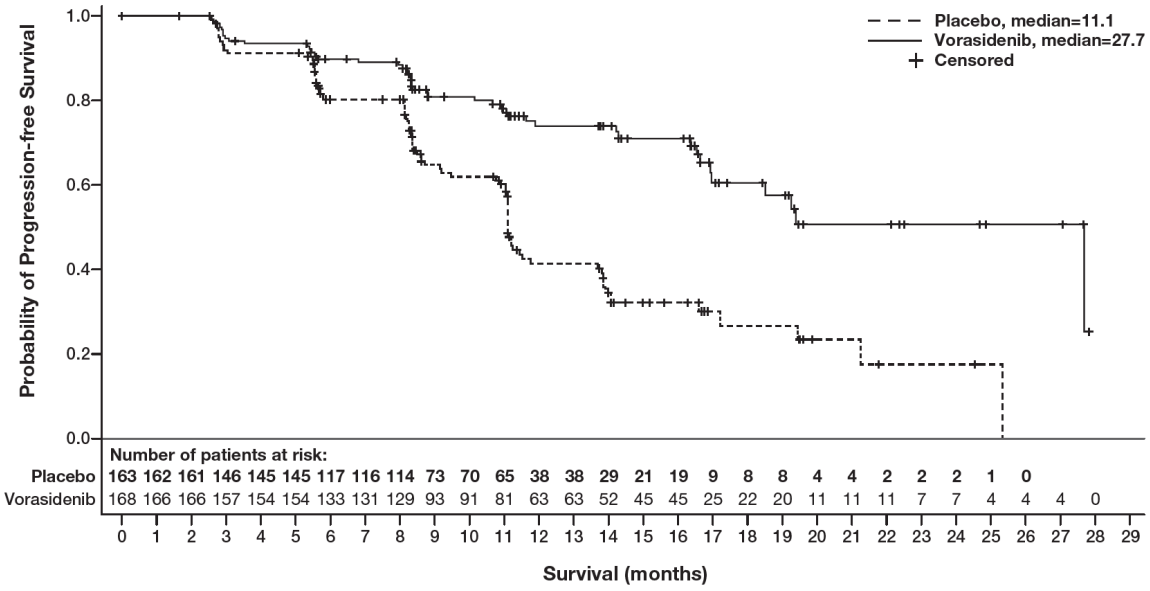
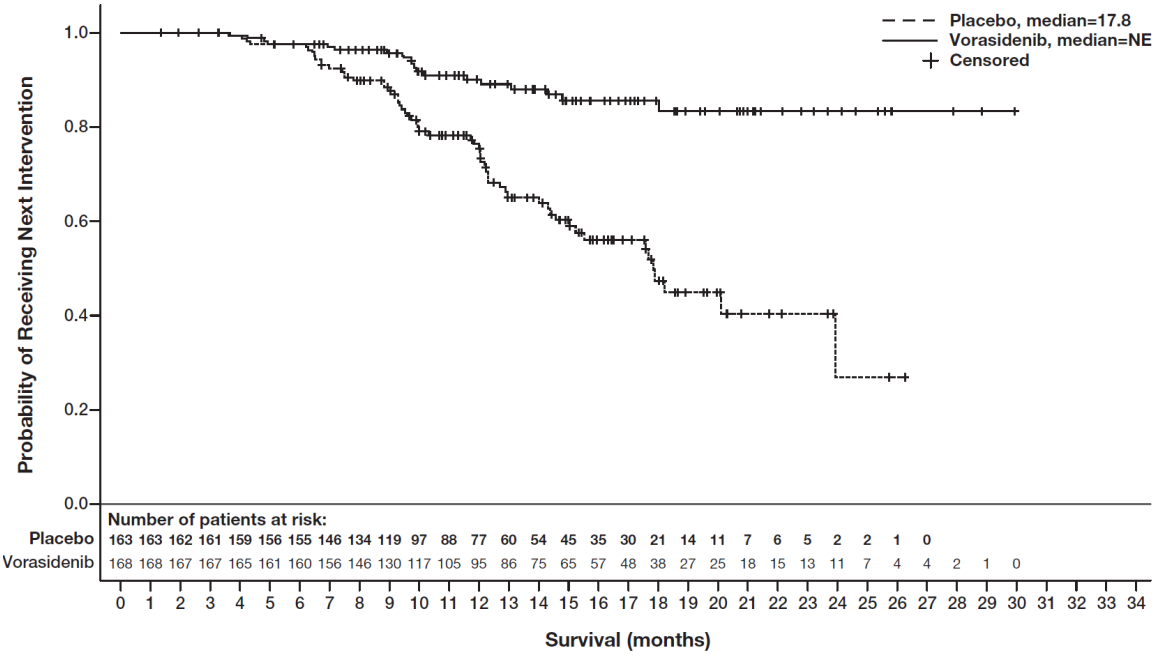


Figure 2: Kaplan-Meier Curve for Time to Next Intervention in INDIGO Trial



An updated PFS by BIRC analysis, carried out at 96% (N = 158) of events, confirmed the benefit of vorasidenib compared to placebo (hazard ratio: 0.35 [95% CI: 0.25, 0.49]). At 24 months, the progression-free survival rate was 59% (95% CI: 48.4, 67.8) in the arm and 26% (95% CI: 17.9, 35.3) in the placebo arm. The median PFS was not estimable (95% CI: 22.1, NE) for the arm and was 11.4 (95% CI: 11.1, 13.9) months for the placebo arm.

Updated analysis for TTNI also showed improved results for the vorasidenib arm compared with the placebo arm (hazard ratio: 0.22 [95% CI: 0.14, 0.36]). At 24 months, the likelihood of survival without an intervention was 85% (95% CI: 77.3, 89.6) in the vorasidenib arm and 41% (31.0, 51.5) in the placebo arm. The median TTNI was not estimable (95% CI: NE, NE) in the arm and was 20.1 (95% CI: 17.5, 27.1) months in the placebo arm.

The post-treatment tumor volume decreased in subjects randomized to vorasidenib by a mean of 2.5% every 6 months (TGR of -2.5%; 95% CI: -4.7 to -0.2), while tumor volume increased by a mean of 13.9% every 6 months (TGR of 13.9%; 95% CI: 11.1 to 16.8) for the placebo arm.

7. DESCRIPTION

10 mg strength: white to off-white, round tablets with a 6 mm diameter, imprinted with “10” on one side

40 mg strength: white to off-white, oblong tablets with length of 14.8 mm and width of 6.3 mm, imprinted with “40” on one side

Tablet core: Microcrystalline cellulose, Croscarmellose sodium, Silicified microcrystalline cellulose (contains microcrystalline cellulose and silica colloidal anhydrous), Magnesium stearate, Sodium lauryl sulfate

Tablet film-coating: Hypromellose, Titanium dioxide, Lactose monohydrate, Macrogol

Printing ink: Black iron oxide, Propylene glycol, Hypromellose

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

Not applicable

8.2 Shelf life

Refer to outer carton for more details.

8.3 Packaging information

Vorasidenib10 mg and 40 mg tablets are available 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 desiccant canister(s). The bottles are packaged in a cardboard box. Each box contains 1 bottle.

8.4 Storage and handling

Store at a temperature not exceeding 30°C

9. Patient counselling information

Hepatotoxicity

Inform patients of the risk of hepatotoxicity and to promptly report any signs or symptoms of hepatotoxicity to their healthcare provider *(see 4.4 Special warnings and precautions for use)*.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *(see 4.4 Special warnings and precautions for use and 4.6 Use in special populations)*.

Advise females of reproductive potential to use effective nonhormonal contraception during treatment with vorasidenib and for 3 months after the last dose *(see 4.6 Use in special populations)* since vorasidenib can render some hormonal contraceptives ineffective *(see 4.5 Drug Interactions)*.

Advise males with female partners of reproductive potential to use effective contraception during treatment with vorasidenib and for 3 months after the last dose *(see 4.6 Use in special populations).*

Lactation

Advise women not to breastfeed during treatment with vorasidenib and for 2 months after the last dose *(see 4.6 Use in special populations)*.

Infertility

Advise females and males of reproductive potential that vorasidenib may impair fertility *(see 4.6 Use in special populations and 6. Non-clinical Properties)*.

Drug Interactions

Advise patients and caregivers to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins and herbal products *(see 4.5 Drug Interactions)*.

Instructions for Taking Vorasidenib
Advise patients to swallow tablets whole with a glass of water and to not split, crush or chew vorasidenib tablets. Do not eat food at least 2 hours before and 1 hour after taking *(see 4.2 Posology and method of administration)*.

If a patient misses a dose by less than 6 hours, instruct patients to take the missed dose right away. If a patient misses a dose by 6 or more hours, instruct patients to skip the dose for that day. Advise patients to take the next dose at the usual time *(see 4.2 Posology and method of administration)*.

If a patient vomits a dose, instruct patients not to take another dose. Advise patients to take the next dose at the usual time *(see 4.2 Posology and method of administration)*.

10. Details of manufacturer

Servier (Ireland) Industries Limited, Gorey Road, Arklow, Co. Wicklow, Y14 E284, Ireland

11. Date of permission or licence number with date

Permission Number: - IMP-ND-46/2025 dated 15-Oct-2025

Imported and marketed by

Servier India Private Limited
1703, 17th Floor, Crescenzo Business District, 'B' Wing, Plot Nos. C38/39, G Block, Behind MCA, BKC, Bandra (East), Mumbai 400 051, India.

12. Date of revision

Version 1 dated 15 Oct 2025

User of Regd. trademark.
Under Licence from: ®LES LABORATOIRES SERVIER, FRANCE

13. SOURCE

US PI dated 06th Aug 2024, CCDS version 01 dated 28th Oct 2024