**AusPAR - Voranigo - vorasidenib - Servier Laboratories (Aust) Pty Ltd - PM-2023-06126-1-4 - Type A.
Date of Finalisation: 21 May 2025. This is the Product Information that was approved with the submission described in this AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>**

▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – VORANIGO® (VORASIDENIB)

1 NAME OF THE MEDICINE

Vorasidenib

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

10 mg tablets: Each film-coated tablet contains 10 mg of vorasidenib.

40 mg tablets: Each film-coated tablet contains 40 mg of vorasidenib.

Excipient with known effect: contains lactose.

For the full list of excipients, see *section 6.1 - List of excipients*.

3 PHARMACEUTICAL FORM

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

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

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

VORANIGO is indicated for the treatment of Grade 2 astrocytoma or oligodendroglioma with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation or isocitrate dehydrogenase-2 (IDH2) mutation in adults and paediatric patients 12 years and older, who are not in need of immediate chemotherapy or radiotherapy following surgical intervention.

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment should be initiated by a physician experienced in the use of anti-cancer therapies. Prior to initiation of treatment with VORANIGO, patients with astrocytoma or oligodendroglioma must be selected based on the presence of IDH1 or IDH2 mutations in tumour samples using an appropriate diagnostic test.

Dose

The recommended dose of VORANIGO in adults and adolescents 12 years of age and older:

- 40 mg taken orally once daily for patients weighing at least 40 kg
- 20 mg taken orally once daily for patients weighing less than 40 kg

Treatment should be continued until disease progression or unacceptable toxicity.

Method of administration

VORANIGO is for oral use.

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 (see *section 5.2 - Pharmacokinetic properties*). The tablets are to be swallowed whole with a glass of water and should not be split, crushed or chewed in order to ensure the full dose is administered.

Patients should be advised not to swallow the silica gel desiccant found in the tablet bottle.

Missed or delayed doses

If a dose is missed or not taken at the usual time, it should be taken as soon as possible within 6 hours after the missed dose. The next dose should be taken at the regularly scheduled time. If a dose is missed by more than 6 hours, it should be skipped and the next dose should be taken at the regularly scheduled time.

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

Precautions to be taken prior to administration and monitoring

Assess complete blood counts and blood chemistries, including liver laboratory tests, 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 *section 4.4 - Special warnings and precautions for use*).

Dosage modifications for adverse reactions

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

Table 1: Recommended dosage reduction levels

Dosage level	Dose and schedule	Number and strength of tablets
Adult patients and Paediatric 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
Adult patients and Paediatric 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 dosage modifications and management 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 *Section 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 VORANIGO at current dose. Monitor liver laboratory tests weekly until recovery to < Grade 1.
	Grade 2 ALT or AST >3 to 5 x ULN without concurrent total bilirubin >2 x ULN	First Occurrence: withhold VORANIGO until recovery to ≤ Grade 1 or baseline. · Recovery in ≤28 days, resume VORANIGO at the same dose. · Recovery in >28 days, resume VORANIGO at reduced dose (see Table 1).

Adverse Reaction	Severity[a]	Management and Dosage Modifications
		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 *Section 4.8 - Adverse effects (Undesirable effects)*)	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.
	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

Elderly

No dosage adjustment is recommended for patients ≥ 65 years of age (see *section 5.2 - Pharmacokinetic properties*).

Renal impairment

No dosage adjustment is recommended for patients with creatinine clearance [CL_{cr}] > 40 mL/min estimated by Cockcroft-Gault[1].

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

[1] Cockcroft-Gault formula was used in the clinical trials investigating vorasidenib.

sections 4.4 - Special warnings and precautions for use and *5.2 - Pharmacokinetic properties*).

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). Vorasidenib should not be used in patients with pre-existing severe hepatic impairment (see *sections 4.4 - Special warnings and precautions for use* and *5.2 - Pharmacokinetic properties*).

Paediatric population

The safety and efficacy of VORANIGO in children under 12 years of age have not been established. No data are available. See *section 4.4 - Special warnings and precautions for use.*

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in *section 6.1 - List of excipients*.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hepatotoxicity

VORANIGO can cause hepatic transaminase elevations, which can lead to hepatic failure, hepatic necrosis and autoimmune hepatitis.

In the INDIGO clinical trial (Study AG881-C-004), 18.6% (31/167) of patients treated with VORANIGO experienced elevations in alanine aminotransferase (ALT) > 3 times the upper limit of normal (ULN) and 8.4% (14/167) experienced elevations in aspartate aminotransferase (AST) > 3 times the ULN. Among these patients, 1.2% (2/167) had concurrent elevations in ALT or AST > 3 times the ULN and total bilirubin > 2 times the ULN (see section *4.8 - Adverse effects (Undesirable effects)*). 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, gamma-glutamyl transferase (GGT) and alkaline phosphatase) and total bilirubin prior to the start 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. 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 *section 4.2 - Dose and method of administration*).

Women of childbearing potential / contraception

Female patients

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. Women of childbearing potential should use effective non-hormonal contraception during treatment and for at least 3 months after the last dose of VORANIGO. Women who are planning to conceive a child should be advised

to seek reproductive counselling before starting treatment.

VORANIGO may decrease concentrations of hormonal contraceptives and, therefore, concomitant use of a barrier method of contraception is recommended during the treatment and for at least 3 months after the last dose (see *sections 4.5 - Interactions with other medicines and other forms of interactions* and *4.6 - Fertility, pregnancy and lactation*).

Male patients

Males with female partners of childbearing potential should use effective contraception during treatment and for at least 3 months after the last dose. Men should be advised to seek reproductive counselling before starting treatment (see *section 4.6 - Fertility, pregnancy and lactation*).

Hepatic impairment

Vorasidenib should not be used in patients with pre-existing severe hepatic impairment (Child-Pugh class C) (see *sections 4.2 - Dose and method of administration* and *5.2 - Pharmacokinetic properties*).

Renal impairment

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 *sections 4.2 - Dose and method of administration* and *5.2 - Pharmacokinetic properties*).

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.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet and can be considered as essentially ‘sodium-free’.

Use in the elderly

Of the 167 patients who were randomised 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 between patients aged 65 years or older and younger patients.

Paediatric use

Adolescents from 12 to less than 18 years of age

Only limited data are available on the safety and effectiveness of VORANIGO in adolescent patients aged 12 years to less than 18 years for IDH1 or IDH2 mutant astrocytoma or oligodendroglioma. Use of VORANIGO in this age group is supported by evidence from the INDIGO study (see *section 5.1 – Pharmacodynamic properties / Clinical trials*) of VORANIGO in adults. At the recommended doses, exposure of vorasidenib is expected to be similar between adults and adolescent patients aged 12 years and older. The course of IDH1 or IDH2 mutant astrocytoma or oligodendroglioma is sufficiently similar in adults and adolescent patients to allow extrapolation of data in adults to adolescent patients.

Children under 12 years of age

The safety and effectiveness of VORANIGO has not been established in the paediatric population under 12 years of age with predominantly non-enhancing astrocytoma or oligodendroglioma who have an IDH1 or IDH2 mutation. Use in children less than 12 years of age is not recommended.

Effects on laboratory tests

No data available.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Effect of other medicinal products on vorasidenib

Strong CYP1A2 inhibitors

Co-administration of vorasidenib with strong CYP1A2 inhibitors (such as fluvoxamine and ciprofloxacin) may increase vorasidenib plasma concentration, which may increase the risk of adverse effects. Concomitant use of strong CYP1A2 inhibitors should be avoided and consider alternative therapies that are not strong inhibitors of CYP1A2 during treatment with VORANIGO.

Moderate CYP1A2 inducers

Co-administration of vorasidenib with moderate CYP1A2 inducers (such as phenytoin and rifampicin) may decrease vorasidenib plasma concentrations, which may decrease the efficacy of VORANIGO. Consider alternative therapies that are not moderate CYP1A2 inducers during treatment with VORANIGO.

Effect of vorasidenib on CYP Enzymes

Cytochrome P450 (CYP) substrates

Concomitant use of CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4 substrates with narrow therapeutic index should be avoided in patients taking VORANIGO. Co-administration of VORANIGO with CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4 substrates with narrow therapeutic index (including, but not limited to, alfentanil, carbamazepine, ciclosporin, everolimus, fentanyl, ifosfamide, sirolimus, tacrolimus, tamoxifen) may decrease the plasma concentrations of these medicinal products.

Co-administration of VORANIGO with sensitive substrates of CYP3A4 without narrow therapeutic index (including, but not limited to, darunavir, ibrutinib, midazolam) may decrease the plasma concentrations and therapeutic effect of these medicinal products. Consider alternative therapies that are not sensitive substrates of CYP3A4 during treatment with VORANIGO.

Hormonal contraceptives

Vorasidenib may decrease concentrations of hormonal contraceptives and, therefore, concomitant use of a barrier method of contraception is recommended during treatment and for at least 3 months after the last dose (see *sections 4.4 - Special warnings and precautions for use* and *4.6 - Fertility, pregnancy and lactation*).

Drug Interaction Studies

Clinical Studies

Effect of Strong CYP1A2 Inhibitors on Vorasidenib

Co-administration of 20 mg VORANIGO with a strong CYP1A2 inhibitor (500 mg ciprofloxacin twice daily for 14 days) increased vorasidenib plasma C_{max} by 29% and AUC by 153%.

Effect of Gastric Acid Reducing Agents on Vorasidenib

No clinically significant differences in vorasidenib pharmacokinetics were observed following co-administration with the gastric acid reducing agent omeprazole.

Effect of Vorasidenib on Lamotrigine (UGT1A4 substrate)

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

Drug Transporter Systems

Effect of Transporters on Vorasidenib

Vorasidenib is not a substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), or hepatic transporters organic anion transporting polypeptide (OATP)1B1 and OATP1B3.

Effect of Vorasidenib on Transporters

In vitro data indicate that vorasidenib is an inhibitor of BCRP. Vorasidenib does not inhibit P-gp and OATP1B1. Vorasidenib may increase plasma concentrations of BCRP substrates via inhibition of intestinal efflux by BCRP.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on 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. Effects on reproductive organs were noted in repeat-dose toxicity studies after administration of vorasidenib in rats. Adverse effects in female reproductive organs included atrophy of the ovaries, uterus, cervix and vagina and oestrous cycle variations. In male rats, effects were noted on the epididymis (cellular debris), seminal vesicle/prostate (atrophy), and testis (reduced weights, tubular degeneration). These findings were observed at exposure 25-fold higher than patients' exposure at the therapeutic daily dose. 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.

Use in pregnancy

Pregnancy Category D

There are no data from the use of vorasidenib in pregnant women.

Pregnancy testing is recommended in women of childbearing potential prior to starting treatment with VORANIGO (see *section 4.4 - Special warnings and precautions for use*).

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.

Vorasidenib caused embryofetal toxicity in pregnant rats and rabbits. Higher incidences of resorptions and delayed ossification were observed in rats and rabbits at 10 and 6 mg/kg/day, respectively, resulting in systemic exposures ≥27- and 5-fold higher than the clinical exposure based on AUC. Visceral malformations (malpositioned kidney and testes) were seen in rats at 75 mg/kg/day (100-fold higher than the clinical exposure at the daily recommended dose). It is not known whether vorasidenib could cause fetal harm when administered to a pregnant woman.

Women of childbearing potential and males with female partners 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 *sections 4.4 - Special warnings and precautions for use* and *4.5 - Interaction with other medicines and other forms of interaction*).

Use in lactation

It is unknown whether vorasidenib and its metabolites are excreted in human milk. Because of the potential risk of adverse effects for the child, breast-feeding should be discontinued during treatment with

VORANIGO and for at least 2 months after the last dose.

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of safety profile

INDIGO

The safety of VORANIGO was evaluated in 330 patients with Grade 2 astrocytoma or oligodendroglioma with an IDH1 or IDH2 mutation who received at least one dose of either VORANIGO 40 mg daily (N=167) or placebo (N=163) in the INDIGO trial. Patients received VORANIGO 40 mg as a single agent, orally once daily until disease progression or unacceptable toxicity or placebo orally once daily until disease progression. Among the 167 patients who were randomised and received VORANIGO, the median duration of exposure to VORANIGO was 12.7 months (range: 1 to 30 months) with 153 patients (92%) exposed to VORANIGO for at least 6 months and 89 (53%) exposed for at least 1 year.

The demographics of patients randomised to VORANIGO were: median age 41 years (range: 21 to 71 years); 60% male, 74% White, 20% race not reported, 3% Asian, and 1.2% Black or African American; and 5% were Hispanic or Latino.

Serious adverse events occurred in 0.6% of patients who received VORANIGO. The most common serious adverse event was ALT increased (0.6%).

Permanent discontinuation of VORANIGO due to an adverse event occurred in 3% of patients. Adverse events which resulted in permanent discontinuation of VORANIGO in ≥2% of patients included ALT increased (3%).

Dosage interruptions of VORANIGO due to an adverse event occurred in 20% of patients. Adverse events which required dose interruption in ≥5% of patients included ALT increased (14%) and AST increased (6%).

Dose reductions of VORANIGO due to an adverse event occurred in 10% of patients. Adverse event which required dose reduction in ≥5% of patients included ALT increased (8%).

The most common (≥15%) adverse events were fatigue (37%), headache (28%), musculoskeletal pain (26%), diarrhea (25%), and nausea (22%).

Grade 3 or 4 (≥2%) laboratory abnormalities were ALT increased (10%), AST increased (4.8%), GGT increased (3%) and neutrophil decreased (2.4%).

Adverse events and select laboratory abnormalities reported in the INDIGO trial are shown in Table 3 and Table 4.

Table 3: Adverse Events Reported in ≥5% of Patients with Grade 2 IDH1/2 Mutant Glioma Receiving VORANIGO Compared with Placebo in the INDIGO Trial (Study AG881-C-004)

Adverse Event[a]	VORANIGO 40 mg daily (n=167)		Placebo (n=163)	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
General Disorders				
Fatigue[b]	37	0.6	36	1.2
Nervous System Disorders				
Headache[c]	28	0	29	0.6
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[d]	26	0	25	1.8
Gastrointestinal Disorders				
Diarrhoea[e]	25	0.6	17	0.6
Nausea	22	0	23	0
Abdominal pain[f]	13	0	12	0
Decreased appetite	9	0	3.7	0
Vomiting	7	0	10	0

[a] Adverse events are based on NCI CTCAE v5.0.
[b] Grouped term includes fatigue and asthenia.
[c] Grouped term includes headache, sinus headache, migraine, migraine with aura, postictal headache, ophthalmic migraine, and tension headache.
[d] Grouped term includes arthralgia, back pain, non-cardiac chest pain, pain in extremity, myalgia, neck pain, musculoskeletal chest pain, arthritis, and musculoskeletal stiffness.

Adverse Event[a]	VORANIGO 40 mg daily (n=167)		Placebo (n=163)	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)

[e] Grouped term includes diarrhoea, faeces soft and frequent bowel movements.
[f] Grouped term includes abdominal pain upper, abdominal discomfort, abdominal pain lower, abdominal tenderness, and epigastric discomfort.

Table 4: Select New or Worsened Laboratory Abnormalities ≥5% Reported in Patients with Grade 2 IDH1/2 Mutant Glioma Receiving VORANIGO in the INDIGO Trial

Parameter	VORANIGO 40 mg daily N=167		Placebo N=163	
	All Grades[a] (%[b])	Grades[a] 3 or 4 (%[b])	All Grades[a] (%[b])	Grades[a] 3 or 4 (%[b])
Chemistry				
Increased ALT	59	10	25	0
Increased AST	46	4.8	20	0
Increased Creatinine	11	0.6	7	0
Decreased Calcium	10	0	7	0
Increased Glucose[c]	10	0	4.3	0
Increased GGT	38	3	10	1.8
Decreased Phosphate[d]	8	0.6	4.9	0
Increased Potassium	23	0.6	20	0
Increased ALP	10	1.2	7	0.6
Hematology				
Increased Hemoglobin	13	0	3.1	0
Decreased Lymphocytes	11	1.8	8	0.6
Decreased Leukocytes	13	0.6	12	0.6
Decreased Neutrophils	14	2.4	12	1.8
Decreased Platelets	12	0	4.3	0

Abbreviations: AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transferase; ALP: Alkaline phosphatase
[a] Based on NCI CTCAE v5.0
[b] The denominator used to calculate percentages is N, the number of subjects in the Safety Analysis Set within each treatment group.
[c] Increased glucose is based on the treatment-emergent adverse event incidence and not laboratory values. In the INDIGO trial, glucose high does not have a corresponding CTCAE grading.
[d] Grouped term includes hypophosphatemia and blood phosphorus decreased. In the INDIGO trial, decreased phosphate does not have a corresponding CTCAE grading.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

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.

Pharmacodynamic effects

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

Clinical trials

The efficacy of VORANIGO was evaluated in the INDIGO trial (Study AG881-C-004), a phase 3, randomised (1:1), multicentre, double-blind, placebo-controlled study of 331 adults and adolescents ≥ 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 for glioma. Patients with non-enhancing tumours or minimal tumour enhancement, including non-nodular or non-measurable lesions, were permitted to enrol. 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 randomised to receive either VORANIGO 40 mg orally once daily or matched placebo until radiographic disease progression or unacceptable toxicity. Randomisation 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 randomised to placebo were allowed to cross over to receive VORANIGO after documented radiographic disease progression.

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 randomisation to the initiation of first subsequent anticancer therapy or death due to any cause, was a key secondary outcome measure. Tumour Growth Rate (TGR), another secondary endpoint, was defined as the on-treatment percentage change in tumour volume every 6 months.

VORANIGO demonstrated a statistically significant and clinically meaningful improvement in the primary endpoint of PFS (HR=0.39; 95% CI: 0.27, 0.56; 1-sided P= 0.000000067) reflecting a 61% reduction in the risk of progression or death compared with placebo. The improvement in PFS was further supported by a statistically significant improvement in the key secondary endpoint of TTNI, which was significantly improved in the VORANIGO group compared with the placebo group (HR= 0.26; 95% CI: 0.15 to 0.43; P=0.000000019). Both PFS and TTNI showed consistent results across all prespecified subgroups and illustrated the clinical relevance of delaying disease progression. The post-treatment tumour volume decreased in subjects randomised to VORANIGO by a mean of 2.5% every 6 months (TGR of -2.5%; 95% CI: -4.7 to -0.2), while tumour 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.

Patient demographics and disease characteristics were balanced between the treatment arms. Among the 168 patients randomised to VORANIGO, the median age was 41 years (range: 21 to 71 years), with 98.8% aged 18-64 years. 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 at least 1 prior surgery for glioma (75%) and 25% had ≥ 2 prior surgeries. Across both arms, 95% of patients had an IDH1 R132 mutation and 5% had an IDH2 R172 mutation. 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%).

Efficacy results for PFS and TTNI are summarised in Table 5, Figure 1 and Figure 2.

Table 5: Efficacy Results for the INDIGO Trial (Study AG881-C-004)

Efficacy parameter	VORANIGO 40 mg daily (n=168)[a]	Placebo (n=163)
Progression-free survival (PFS) by IRC		
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)
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 full analysis set included all patients who had undergone randomisation.

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

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

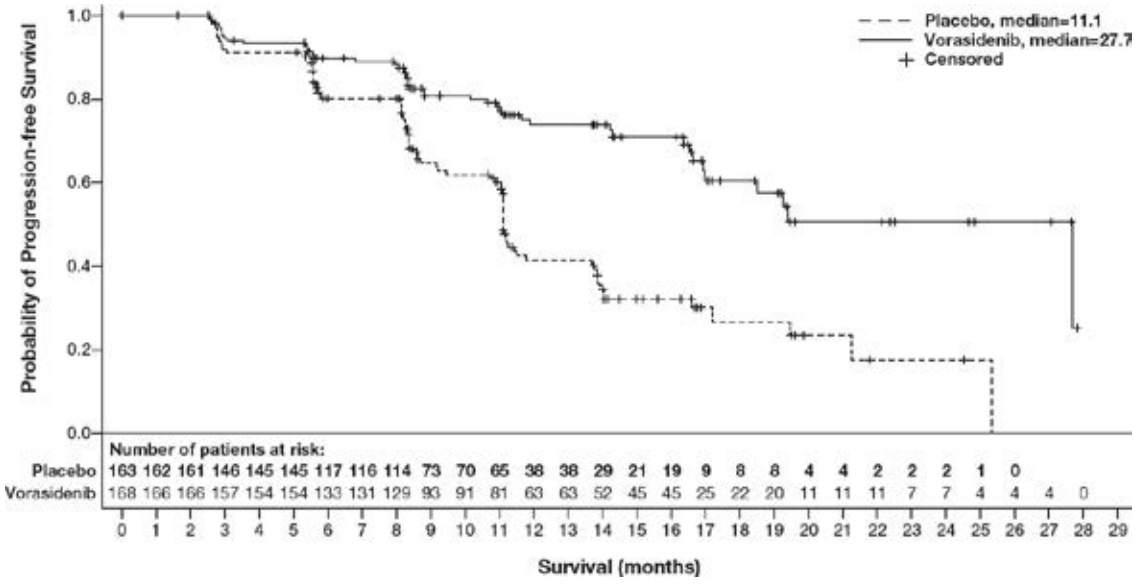
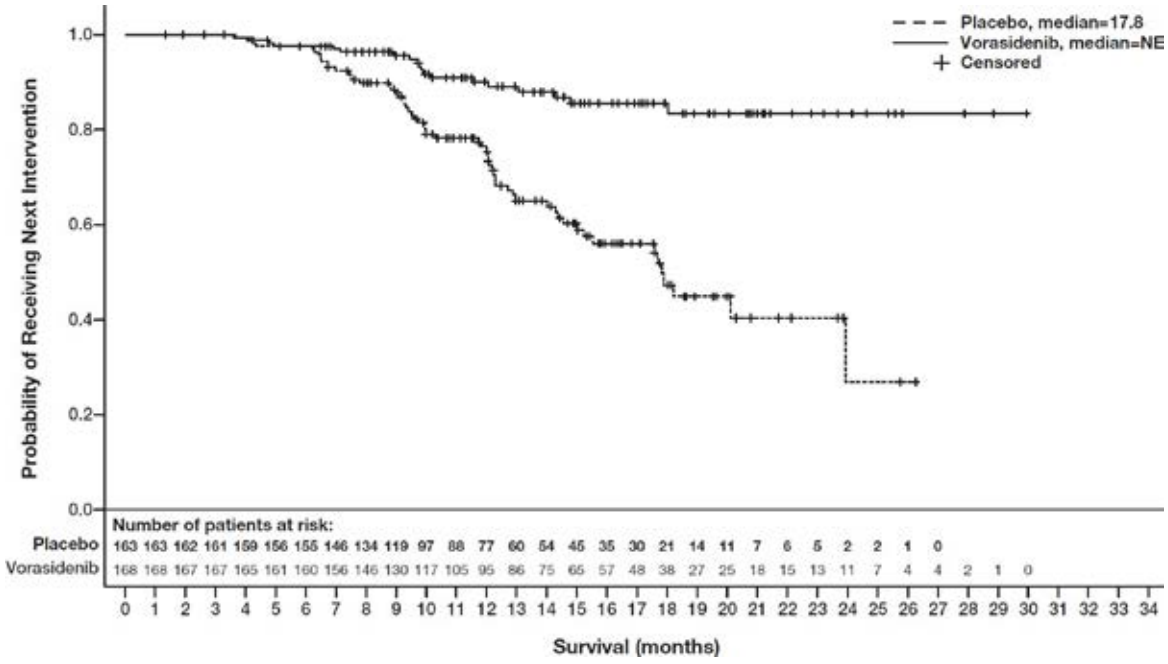


Figure 2: Kaplan-Meier Curve for Time to Next Intervention in INDIGO Trial



5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of vorasidenib have been characterised in patients with IDH1- or IDH2-mutated glioma and in healthy subjects.

Absorption

After a single 40 mg oral dose, the median time to C_{max} (T_{max}) for vorasidenib was 2.0 hours, the geometric mean C_{max} was 75.4 ng/mL (CV%: 44), and the geometric mean AUC was 2,860 hr·ng/mL (CV%: 56). At steady-state, vorasidenib geometric mean C_{max} was 133 ng/mL (CV%: 73) and geometric mean AUC was 1,988 hr·ng/mL (CV%: 95). Following administration of VORANIGO, vorasidenib C_{max} and AUC increases in a proportional manner between 10 and 50 mg.

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. The mean absolute bioavailability of vorasidenib is 34%.

The mean C_{max} and AUC of vorasidenib 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 vorasidenib C_{max} and AUC of 2.3- and 1.4-fold, respectively (see *section 4.2 - Dose and method of administration*).

Distribution

Vorasidenib has a mean apparent volume of distribution of 3,930 L (CV%: 40). The vorasidenib volume of distribution following a single 0.1 mg IV microdose is 1,110 L. The mean plasma protein binding of vorasidenib is approximately 97% and is independent of concentration *in vitro*. Vorasidenib blood to plasma ratio is 0.87 and brain tumour to plasma ratio is 1.6.

Metabolism

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

Interactions

Vorasidenib is predicted to have a strong induction effect on sensitive CYP3A4 substrates; weak induction effect on sensitive CYP2B6 and CYP2C19 substrates; and no relevant induction effect on sensitive CYP2C8 and CYP2C9 substrates (see *section 4.5 - Interaction with other medicines and other forms of interaction*).

Co-administration of strong inhibitors of CYP1A2 (fluvoxamine) is predicted to result in a ≥ 5-fold increase in vorasidenib exposure, whilst co-administration with moderate CYP1A2 inducers (phenytoin and rifampicin) is predicted to have a weak induction effect on vorasidenib exposure (see *section 4.5 - Interaction with other medicines and other forms of interaction*).

In vitro data indicate that vorasidenib is an inhibitor of breast cancer resistance protein (BCRP). Vorasidenib does not inhibit P-glycoprotein (P-gp) and hepatic transporter organic anion transporting polypeptide (OATP)1B1. Vorasidenib is predicted to have no relevant impact on sensitive P-gp and BCRP substrates.

Vorasidenib is not a substrate of P-gp, BCRP, or hepatic transporters OATP1B1 and OATP1B3.

Elimination

Approximately 89% of a single radiolabelled vorasidenib dose was recovered over 44 days, with 85% in faeces and 4.5% in urine. Most of the administered radioactivity that was recovered in faeces was unchanged vorasidenib (55%) while no unchanged vorasidenib was detected in urine.

The mean terminal half-life of vorasidenib is 238 hours (CV%: 57) and the mean apparent clearance is 14.0 L/h (CV%: 56).

Special populations

No clinically significant effects on the pharmacokinetics of vorasidenib were observed based on age (16 to 75 years), sex, race, ethnicity or body weight (43.5 to 168 kg).

Elderly

No clinically meaningful effects on the pharmacokinetics of vorasidenib were observed in older patients up to 75 years (see *section 4.2 - Dose and method of administration*).

Renal impairment

Renal impairment (CL_{cr} > 40 mL/min) had no clinically significant effect on the pharmacokinetics of vorasidenib. The pharmacokinetics of vorasidenib in patients with CL_{cr} ≤ 40 mL/min or renal impairment requiring dialysis are unknown (see *sections 4.2 - Dose and method of administration* and *4.4 - Special warnings and precautions for use*).

Hepatic impairment

Mild to moderate hepatic impairment (Child-Pugh class A or B) had no clinically significant effects on vorasidenib pharmacokinetics. The pharmacokinetics of vorasidenib in patients with severe hepatic impairment (Child-Pugh class C) is unknown (see *sections 4.2 - Dose and method of administration* and *4.4 - Special warnings and precautions for use*).

Paediatric population

A VORANIGO dose of 20 mg in adolescent patients weighing < 40 kg is predicted to provide vorasidenib plasma exposure similar to that provided by a 40 mg dose in adults weighing ≥ 40 kg (see *section 4.2 - Dose and method of administration*).

In vitro Studies and PBPK Model-Based Approaches

Effect of Other Strong CYP1A2 Inhibitors on Vorasidenib

Co-administration with strong inhibitors of CYP1A2 (fluvoxamine) is predicted to result in a ≥5-fold increase in vorasidenib exposure.

Effect of Moderate CYP1A2 inducers on Vorasidenib

Co-administration with moderate CYP1A2 inducers (phenytoin and rifampicin) is predicted to decrease vorasidenib steady-state C_{max} and AUC by 30 to 40%.

Effect of Vorasidenib on CYP Enzymes

Vorasidenib is predicted to decrease exposure of sensitive substrates of CYP3A4 by approximately 80%, CYP2C19 by 30 to 35%, CYP2B6 by approximately 20%, and no relevant induction effect on sensitive CYP2C8 and CYP2C9 substrates.

5.3 PRECLINICAL SAFETY DATA

Rats treated with vorasidenib for up to 28 days developed mild inflammation of the middle ear and Eustachian tube, characterised by a neutrophil infiltration of the epithelial lining, presence of macrophages, and luminal exudate in the tympanic cavity. These findings may be related to the pharmacology of vorasidenib. Patients should be monitored for any signs of adverse effects on the middle ear.

Genotoxicity

Vorasidenib was not genotoxic in the *in vitro* bacterial reverse mutation (Ames) assay, *in vitro* human lymphocyte micronucleus and *in vivo* rat bone marrow micronucleus assays.

Carcinogenicity

Carcinogenicity studies have not been conducted with vorasidenib.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- Microcrystalline cellulose
- Croscarmellose sodium
- Silicified microcrystalline cellulose
- Magnesium stearate
- Sodium lauryl sulfate
- Hypromellose
- Titanium dioxide
- Macrogol 400
- Lactose monohydrate

Printing Ink:

- OPACODE WB monogramming ink NS-78-17821 BLACK (Proprietary Ingredient No.: 12156)

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Once opened, VORANIGO should be used within 60 days.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Keep the bottle tightly closed.

6.5 NATURE AND CONTENTS OF CONTAINER

White, high-density polyethylene (HDPE) bottle with polypropylene (PP) child resistant closure and polyethylene (PE) faced induction heat seal liner. Each bottle contains 30 film-coated tablets and a silica gel desiccant in HDPE canister(s). The bottles are packaged in a cardboard box; each box contains 1 bottle.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

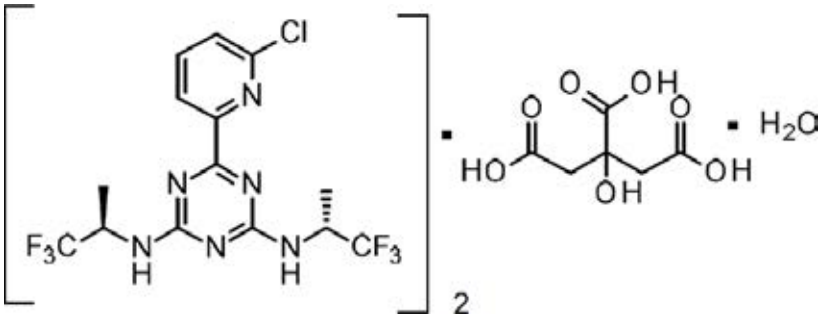
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

VORANIGO is comprised of vorasidenib (as hemicitric acid, hemihydrate) with the 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). 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. Vorasidenib is practically insoluble in aqueous solutions between pH 1.2 to 6.8.

Chemical structure

The chemical structure of vorasidenib (the hemicitric acid, hemihydrate of vorasidenib) drug substance:



CAS number

2316810-02-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription only medicine

8 SPONSOR

Servier Laboratories (Aust.) Pty. Ltd.
www.servier.com.au
Level 4, Building 9
588A Swan Street
Burnley, 3121, Victoria

9 DATE OF FIRST APPROVAL

To be advised

10 DATE OF REVISION

Not applicable

SUMMARY TABLE OF CHANGES

Section(s) Changed	Summary of new information