

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Voranigo 10 mg film-coated tablets
Vorango 40 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Voranigo 10 mg film-coated tablets

Each film-coated tablet contains 10 mg of vorasidenib (as hemicitric acid, hemihydrate).

Excipient with known effect

Each film-coated tablet contains lactose monohydrate, equivalent to 0.60 mg lactose (see section 4.4).

Vorango 40 mg film-coated tablets

Each film-coated tablet contains 40 mg of vorasidenib (as hemicitric acid, hemihydrate).

Excipient with known effect

Each film-coated tablet contains lactose monohydrate, equivalent to 2.39 mg lactose (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Voranigo 10 mg film-coated tablets

White to off-white, round tablets with a 6 mm diameter, imprinted with '10' on one side.

Vorango 40 mg film-coated tablets

White to off-white, oblong tablets with a length of 14.8 mm and width of 6.3 mm, imprinted with '40' on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Voranigo as monotherapy is indicated for the treatment of predominantly non-enhancing Grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation in adult and adolescent patients aged 12 years and older and weighing at least 40 kg who only had surgical intervention and are not in immediate need of radiotherapy or chemotherapy (see section 5.1).

4.2 Posology and method of administration

Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.

Before taking Voranigo, patients must have confirmation of an isocitrate dehydrogenase-1 (IDH1) R132 or isocitrate dehydrogenase-2 (IDH2) R172 mutation using an appropriate diagnostic test. The presence of an IDH1 R132 or IDH2 R172 mutation should be assessed by a CE-marked *in vitro* diagnostic (IVD) with the corresponding intended purpose. If the CE-marked IVD is not available, IDH1 R132 or IDH2 R172 mutation should be assessed by an alternative validated test.

Posology

The recommended dose of Voranigo in adults and adolescents 12 years of age and older is 40 mg once daily for patients weighing at least 40 kg. No dose recommendation can be made in patients weighing less than 40 kg because of the lack of clinical data in this population.

Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.

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

Complete blood counts and blood chemistries, including liver enzymes, should be assessed prior to starting treatment, every 2 weeks during the first 2 months and then once monthly for the first 2 years of treatment, and as clinically indicated thereafter. Certain patients may require more frequent and ongoing monitoring (see section 4.4).

Dose modifications for adverse reactions

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 reduction levels

Dose level	Dose and schedule	Number and strength of tablets
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

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

Table 2: Recommended Voranigo dose modifications and management for adverse reactions

Adverse reaction	Severity ^a	Management and dose modifications
Hepatotoxicity (Elevation of ALT or AST) (see section 4.4)	Grade 1 ALT or AST increase >ULN to 3 x ULN <i>without</i> concurrent total bilirubin >2 x ULN	Continue Voranigo at current dose. Monitor liver enzymes weekly until recovery to <Grade 1.
	Grade 2 ALT or AST >3 to 5 x ULN <i>without</i> concurrent total bilirubin >2 x ULN	<u>First occurrence:</u> Withhold Voranigo and monitor liver enzymes twice per week 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). <u>Recurrence:</u> Withhold Voranigo and monitor liver enzymes twice per week 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 <i>without</i> concurrent total bilirubin >2 x ULN	<u>First occurrence:</u> Withhold Voranigo and monitor liver enzymes twice per week 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. <u>Recurrence:</u> Permanently discontinue Voranigo and monitor liver enzymes twice per week until recovery to ≤Grade 1 or baseline.
	Grade 2 or 3 Any ALT or AST >3 to 20 x ULN <i>with</i> concurrent total bilirubin >2 x ULN in absence of clear alternative explanation. ^b	Permanently discontinue Voranigo and monitor liver enzymes twice per week until recovery to ≤Grade 1 or baseline.
	Grade 4 Any ALT or AST >20 x ULN	Permanently discontinue Voranigo and monitor liver enzymes twice per week until recovery to ≤Grade 1 or baseline.
Other adverse reactions	Grade 3	<u>First occurrence:</u> Withhold Voranigo until recovery to ≤Grade 1 or baseline. Resume Voranigo at reduced dose (see Table 1). <u>Recurrence:</u> 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.

^b If an alternative aetiology is identified, consider resuming Voranigo at reduced dose (see Table 1) following resolution to Grade 1 or baseline.

Special populations

Elderly

No dose adjustment is recommended for patients ≥ 65 years of age (see section 5.2).

Renal impairment

No starting dose adjustment is recommended for patients with renal impairment (estimated glomerular filtration rate [eGFR] > 40 mL/min/1.73 m²). The pharmacokinetics of vorasidenib and metabolite AGI-69460 have not been studied in patients with eGFR ≤ 40 mL/min/1.73 m² or renal impairment requiring dialysis. Vorasidenib should not be used in patients with eGFR ≤ 40 mL/min/1.73 m² or who require dialysis (see sections 4.4 and 5.2).

Hepatic impairment

No starting dose adjustment is recommended for patients with mild or moderate (Child-Pugh class A or B) hepatic impairment. The pharmacokinetics of vorasidenib and AGI-69460 have not been studied in patients with severe hepatic impairment (Child-Pugh class C). Vorasidenib should be used with caution in patients with severe hepatic impairment and this patient population should be closely monitored. (see sections 4.4 and 5.2).

Paediatric population

No clinical data are available in children aged 12 years to < 18 years (see section 5.1).

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). The tablets are to be swallowed whole with a glass of water and should not be split, crushed or chewed as no data are available to confirm similar bioavailability of the drug product when tablet manipulations are applied.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Hepatotoxicity

Drug-induced hepatotoxicity, including serious cases of hepatic failure, hepatic necrosis and hepatitis acute have been reported in patients treated with vorasidenib in the pivotal clinical study or in post-marketing experience (see section 4.8).

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

Carcinogenicity risk

Animal findings may be suggestive of potential carcinogenic risk (notably in liver, see section 5.3). Carcinogenicity studies have not been conducted yet and long-term clinical safety data are insufficient. Therefore, a carcinogenicity risk in humans could not be excluded.

Women of childbearing potential / Contraception

Vorasidenib could cause foetal harm when administered to a pregnant woman. Pregnancy testing is recommended in women of childbearing potential prior to starting treatment. Women of childbearing potential should use effective contraception during treatment and for at least 2 months after the last dose. Women who are planning to conceive a child should be advised to seek reproductive counselling.

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 2 months after the last dose (see sections 4.5 and 4.6).

Male patients

Males with female partners of childbearing potential should use effective contraception during treatment and for at least 2 months after the last dose. Men should seek advice on cryo-preservation of sperm prior to treatment (see section 4.6).

Hepatic impairment

The safety and efficacy of vorasidenib have not been established in patients with severe hepatic impairment (Child-Pugh class C). Vorasidenib should be used with caution in patients with pre-existing severe hepatic impairment (Child-Pugh class C) and this patient population should be closely monitored (see sections 4.2 and 5.2).

Renal impairment

The pharmacokinetics and safety of vorasidenib have not been studied in patients with renal impairment ($\text{eGFR} \leq 40 \text{ mL/min/1.73 m}^2$) or renal impairment requiring dialysis. Vorasidenib should not be used in these patients (see sections 4.2 and 5.2).

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, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Based on *in vitro* experiments vorasidenib is a strong inducer by means of pregnane X receptor (PXR) activation and may affect the plasma exposure of co-administered medicines that are metabolised or transported by enzymes or transporters whose expression is mediated by PXR.

Effect of other medicinal products on vorasidenib

Strong CYP1A2 inhibitors

Co-administration of vorasidenib with strong CYP1A2 inhibitors (fluvoxamine and ciprofloxacin) may increase vorasidenib plasma concentration. Concomitant use of strong CYP1A2 inhibitors should be avoided and consider alternative therapies that are not strong inhibitors of CYP1A2 during treatment with vorasidenib.

In an *in vivo* drug-drug interaction study, co-administration of 20 mg vorasidenib with a strong CYP1A2 inhibitor (500 mg ciprofloxacin twice daily for 14 days) increased vorasidenib maximum plasma concentration (C_{max}) by 29% and area under the plasma time-concentration curve (AUC) by 153%.

Moderate CYP1A2 inducers

Co-administration of vorasidenib with moderate CYP1A2 inducers (phenytoin and rifampicin) may decrease vorasidenib plasma concentration. Consider alternative therapies that are not moderate CYP1A2 inducers during treatment with vorasidenib.

Gastric acid reducing agents

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

Effect of vorasidenib on other medicinal products

Cytochrome P450 (CYP) substrates with narrow therapeutic index

Co-administration of vorasidenib with CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A4 substrates with narrow therapeutic index (including, but not limited to, amitriptyline, alfentanil, carbamazepine, ciclosporin, dosulepin, everolimus, fentanyl, fosphenytoin, ifosfamide, imipramine, phenobarbital, phenytoin, pimozone, quinidine, sirolimus, tacrolimus, tamoxifen, trimipramine, valproic acid, and warfarin) may decrease the plasma concentrations of these medicinal products. Concomitant use of substrates of these enzymes with narrow therapeutic index should be avoided in patients taking vorasidenib.

Sensitive substrates of CYP enzymes without narrow therapeutic index

Co-administration of vorasidenib with sensitive substrates of CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A4 without narrow therapeutic index (including, but not limited to, bupropion, buspirone, celecoxib, darunavir, ibrutinib, midazolam, repaglinide, saquinavir, tipranavir, and triazolam) may decrease the plasma concentrations of these medicinal products. Consider alternative therapies that are not sensitive substrates of these enzymes during treatment with vorasidenib.

Interactions with transporters

In vitro, vorasidenib is an inhibitor of breast cancer resistance protein (BCRP) (see section 5.2). Caution should be exercised when administering vorasidenib with BCRP substrates (including, but not limited to, rosuvastatin).

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 2 months after the last dose (see sections 4.4 and 4.6).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception

Pregnancy testing is recommended in women of childbearing potential prior to starting treatment with vorasidenib (see section 4.4).

Women of childbearing potential and males with female partners of childbearing potential should use effective contraception during treatment and for at least 2 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 and 4.5).

Pregnancy

There are no or limited amount of data from the use of vorasidenib in pregnant women. Studies in animals have shown embryo-foetal development toxicity (see section 5.3).

Vorasidenib should not be used during pregnancy and in women of childbearing potential not using contraception. Women of childbearing potential or male patients with female partners of childbearing potential should be advised on the potential risk to a foetus.

Breast-feeding

It is unknown whether vorasidenib and its metabolites are excreted in human milk. Breast-feeding should be discontinued during treatment and for at least 2 months after the last dose.

Fertility

There are no human data on the effect of vorasidenib on fertility. Findings on reproductive organs were observed during repeat-dose toxicity studies in female and male animals (see section 5.3). The clinical relevance of these effects is unknown. Male and female patients who are planning to conceive a child should be advised to seek reproductive counselling, and men should seek advice on cryo-preservation of sperm prior to treatment (see section 4.4).

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 diarrhoea (24.6%).

The most common grade ≥ 3 adverse reactions were ALT increased (9.6%), AST increased (4.2%) and GGT increased (3.0%).

Serious adverse reactions of hepatic failure, autoimmune hepatitis and ALT increased each occurred in 0.6% of patients who received Voranigo.

Permanent discontinuation of vorasidenib due to grade ≥ 3 ALT increased or autoimmune hepatitis was reported in 3.0% and 0.6% of patients, respectively.

Dose interruptions due to an adverse reaction occurred in 18.6% of patients 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 9.6% of patients. The most common adverse reaction requiring dose reduction was ALT increased (7.8%).

Tabulated list of adverse reactions

The adverse reactions described in this section are derived from study data (INDIGO study [N=167]) and post-marketing experience with Voranigo.

The adverse reactions reported in patients treated with vorasidenib are listed below in Table 3 by MedDRA system organ class and by frequency.

Frequencies are defined as very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\ 000$ to $< 1/100$), rare ($\geq 1/10\ 000$ 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 3: Adverse drug reactions reported in patients treated with vorasidenib

System organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Very common	Platelet count decreased ^a
Metabolism and nutrition disorders	Common	Hyperglycaemia
		Decreased appetite
		Hypophosphataemia
Nervous system disorders	Very common	Dizziness
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea
Gastrointestinal disorders	Very common	Diarrhoea
	Common	Abdominal pain
		Gastro-oesophageal reflux disease
Hepatobiliary disorders	Very common	Alanine aminotransferase increased ^a
		Aspartate aminotransferase increased ^a
		Gamma-glutamyl transferase increased ^a
	Common	Alkaline phosphatase increased ^a
		Blood bilirubin increased ^a
	Uncommon	Hepatic failure
		Autoimmune hepatitis
		Hepatic necrosis
	Not known	Drug-induced liver injury*
		Hepatitis acute*
General disorders and administration site conditions	Very common	Fatigue

*Identified during post-approval use.

^aLaboratory abnormality is defined as new or worsened by at least one grade from baseline, or baseline is unknown.

Description of selected adverse reactions

Hepatotoxicity

In the INDIGO study, of the 167 patients treated with vorasidenib, 18.6% experienced elevations in ALT > 3 times the ULN and 8.4% experienced elevations in AST > 3 times the ULN. Among these patients, 1.2% had concurrent elevations in ALT or AST > 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 (see sections 4.2 and 4.4). The median time to first event onset for AST and ALT increased (any grade) was 85.0 days (range: 14 – 451 days) and 57.0 days (range: 1 – 506 days). Each of the following adverse reactions, hepatic failure, hepatic necrosis and autoimmune hepatitis, was reported once with vorasidenib in the INDIGO study (see section 4.4).

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 via the national reporting system listed in [Appendix V](#).

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). Patients should be closely monitored and provided with appropriate supportive care (see sections 4.2 and 4.4). There is no specific antidote for vorasidenib overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Vorasidenib is an 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 contributing to oncogenesis. Inhibition of the IDH1- and IDH2-mutated proteins by vorasidenib inhibits the abnormal production of 2-HG leading to differentiation of malignant cells and a reduction in their proliferation. Pre-clinical studies investigating the ability of vorasidenib to decrease tumour size were not performed.

Pharmacodynamic effects

A therapeutic daily dose of vorasidenib was observed to decrease 2-HG tumour concentrations in subjects with IDH1 or IDH2 mutated glioma.

Clinical efficacy and safety

The efficacy and safety of vorasidenib were evaluated in the INDIGO trial, 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 as defined by 2016 WHO criteria with an IDH1 R132 mutation or IDH2 R172 mutation, had surgery including biopsy, sub-total resection, or gross-total resection as their only treatment and were not in immediate need of chemotherapy or radiotherapy in the opinion of the investigator. Patients who had MRI-evaluable, measurable, non-enhancing disease, as confirmed by the blinded independent review committee (BIRC) were enrolled. Patients with centrally-confirmed enhancing disease were permitted to enrol provided that the enhancement was minimal, non-nodular, non-measurable and had not changed between the 2 most recent scans. 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 vorasidenib 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 vorasidenib after documented radiographic disease progression provided that they were not in need of immediate chemotherapy or radiotherapy in the opinion of the investigator.

The primary efficacy outcome measure was radiographic progression-free survival (PFS) as evaluated by a BIRC according to modified response assessment in neuro-oncology for low grade glioma (RANO-LGG) criteria (radiographic progression only).

Patient demographics and disease characteristics were balanced between the treatment arms. Among the 168 patients randomised to vorasidenib, the median age was 41 years (range: 21 to 71 years), with 98.8% aged 18-64 years. A single paediatric patient aged 16 years was randomised to placebo, and no patient under the age of 18 was randomised to vorasidenib. 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, 45.8% had a KPS score of 90-80, and 0.6% had a KPS score of 70-60. 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.

Efficacy results for PFS are summarised in Table 4 and Figure 1.

Table 4: Efficacy results for the INDIGO trial (Study AG881-C-004)

Efficacy parameter	Voranigo 40 mg daily (n=168)	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)^a	27.7 (17.0, NE)	11.1 (11.0, 13.7)
Hazard ratio (95% CI)^b	0.39 (0.27, 0.56)	
p-value^c	0.000000067	

Abbreviations: CI = Confidence interval; NE = Not estimable

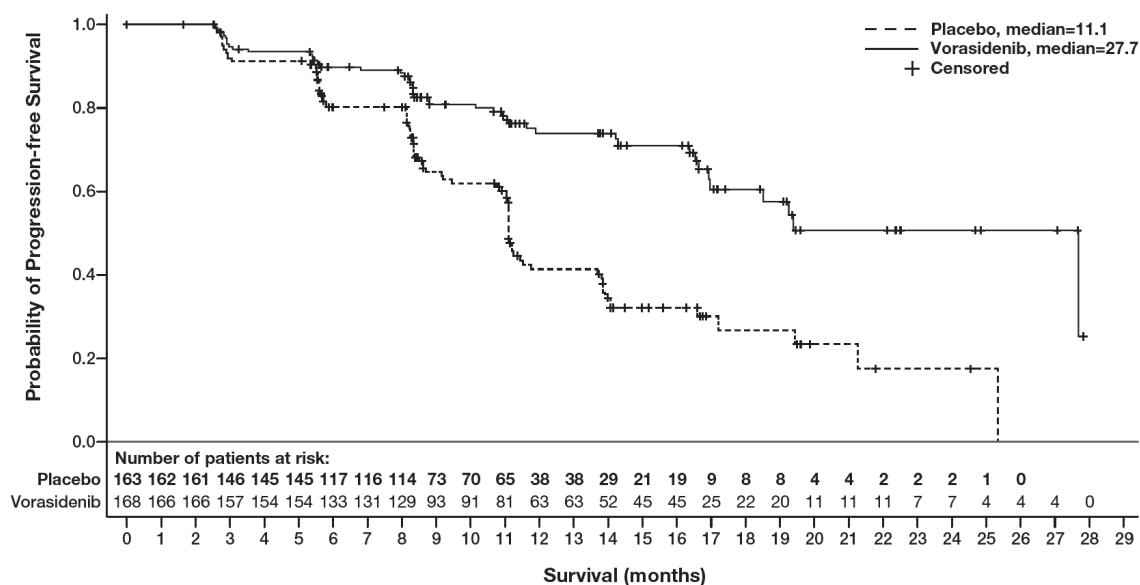
The full analysis set included all patients who had undergone randomisation.

^a The 95% confidence interval for the median was calculated using the Brookmeyer and Crowley method.

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

^c Estimated from one-sided stratified log-rank test. PFS was tested at a one-sided efficacy α -level of 0.000359, based on an updated efficacy boundary corresponding to the 82% information fraction.

Figure 1: Kaplan-Meier curve for progression-free survival per BIRC review 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 vorasidenib 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 vorasidenib arm and was 11.4 (95% CI: 11.1, 13.9) months for the placebo arm.

Paediatric population

Adolescents from 12 to less than 18 years of age

Use of vorasidenib in patients aged 12 years to less than 18 years with IDH1 or IDH2 mutant astrocytoma or oligodendroglioma is supported by pharmacokinetic data demonstrating that age had no clinically meaningful effect on the pharmacokinetics of vorasidenib (see section 5.2).

5.2 Pharmacokinetic properties

The pharmacokinetics of vorasidenib have been characterised in patients with low-grade glioma with an IDH1 or IDH2 mutation and in healthy subjects. The pharmacokinetic profile of vorasidenib is similar between patients with low-grade glioma and 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). In most patients, a second plasma concentration peak occurred within 24 hours after drug administration but was lower than the observed C_{max} at 2 hours post-dose. Although absolute bioavailability has not been directly determined, the absorption of vorasidenib is estimated to be moderate to high for the 40 mg film-coated tablets.

Accumulation ratios were approximately 3.8 for C_{max} and 4.4 for AUC. Steady-state plasma levels were reached after 2 to 3 weeks of once-daily dosing.

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).

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 bound plasma protein fraction for vorasidenib and AGI-69460 was 97% and 87%, respectively. Both vorasidenib and AGI-69460 exhibit preferential binding to serum albumin over alpha-1 acid glycoprotein. Vorasidenib blood to plasma ratio is 0.87, AGI-69460 blood to plasma ratio is 1.38, and vorasidenib brain tumour to plasma concentration ratio is 1.6.

Biotransformation

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.

AGI-69460 is a downstream active metabolite of vorasidenib. After a single 40 mg vorasidenib oral dose, the observed T_{max} for metabolite AGI-69460 was 336 hours, the observed geometric mean C_{max} was 3.32 ng/mL (CV%: 55.6), and the geometric mean AUC_{0-t} was 1,172 hr*ng/mL (CV%: 61). At steady-state, geometric mean AGI-69460 $C_{min,ss}$ was 111 ng/mL (CV%: 58) and geometric mean AUC_{0-4} at cycle 2 day 1 was 190 hr*ng/mL (CV%: 90).

Interactions

In vitro, vorasidenib has a strong induction effect on sensitive CYP3A4 substrates and a moderate induction effect on sensitive CYP2B6 and CYP2C19 substrates (see section 4.5).

In vitro data indicate that vorasidenib is an inhibitor of BCRP. Vorasidenib does not inhibit P-glycoprotein (P-gp) and hepatic transporter organic anion transporting polypeptide (OATP)1B1. *In vitro*, AGI-69460 is an inhibitor of BCRP and OATP1B3.

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

Elimination

Approximately 89% of the administered vorasidenib radioactive dose, using a powder-in-capsule formulation with an absolute bioavailability of < 34%, 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), the effective half-life is 63.2 hours (CV%: 75) and the mean apparent clearance is 14.0 L/h (CV%: 56).

Linearity/non-linearity

Following administration of Voranigo, vorasidenib C_{max} and AUC increases in a proportional manner between 10 and 40 mg.

Special populations

Elderly

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

Renal impairment

Renal impairment (eGFR > 40 mL/min/1.73 m²) had no clinically significant effect on the pharmacokinetics of vorasidenib. The pharmacokinetics of vorasidenib in patients with eGFR ≤ 40 mL/min/1.73 m² or renal impairment requiring dialysis are unknown.

Hepatic impairment

Moderate hepatic impairment (Child-Pugh class B) had no clinically significant effects on vorasidenib and AGI-69460 pharmacokinetics. There were no clinically relevant changes in total or free (unbound) vorasidenib concentrations (similar vorasidenib C_{max} values and an increase of 26.0% in vorasidenib AUC_{0-t} were observed, while decreased AGI-69460 exposure was observed) in patients with moderate hepatic impairment following a single oral dose of 20 mg vorasidenib. The pharmacokinetics of vorasidenib and AGI-69460 in patients with severe hepatic impairment (Child-Pugh class C) are unknown (see sections 4.2 and 4.4).

Other

No clinically significant effects on the pharmacokinetics of vorasidenib were observed based on age (16 to 75 years), race, ethnicity and body weight (43.5 to 168 kg). Female patients were observed to have a 1.6-fold higher vorasidenib exposure as compared to male patients.

Paediatric population

Pharmacokinetic data demonstrated that age had no clinically meaningful effect on the pharmacokinetics of vorasidenib. The exposure of vorasidenib is expected to be similar between adults and adolescent patients aged 12 years and older.

5.3 Preclinical safety data

The main target toxicities identified during repeat-dose toxicity studies concern liver, gastrointestinal tract, skin, kidney, skeletal muscle, reproductive organs and mammary gland.

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. AGI-69460, its major circulating metabolite, was not genotoxic in the Ames assay, the *in vitro* human lymphocyte micronucleus assay, and the *in vivo* rat bone marrow micronucleus and Comet assays.

In the 13-week study in monkeys, Kupffer cell hyperplasia were observed at primary necropsy and worsened after recovery period at 8-fold the clinical exposure. In addition, findings from rat toxicity studies suggested hormonal perturbation. Such findings may be suggestive of potential carcinogenic risk. Carcinogenicity studies have not been conducted yet with vorasidenib.

Fertility studies in animals have not been conducted with vorasidenib. Effects on reproductive organs were noted during 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 (weights, tubular degeneration). These findings were observed at the lowest tested dose of 5 mg/kg/day in the 13-week rat study, resulting in an exposure level 26-fold higher than the human exposure at 50 mg daily dose.

Vorasidenib caused embryo-foetal toxicity in pregnant rats and rabbits (higher incidence of resorptions, delayed ossification, visceral malformations for kidney and testes in rats). These effects occurred at doses that were higher compared to patients receiving the therapeutic daily dose. The exposure ratios at the NOAEL for embryo-foetal development in rats and rabbits were 8.0 to 28.5 and 1.1 to 4.9, respectively, on gestation days 6 and 17 for rat and 6 and 19 for rabbit.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose (E460)

Croscarmellose sodium

Silicified microcrystalline cellulose (contains microcrystalline cellulose and silica colloidal anhydrous)

Magnesium stearate (E470b)

Sodium lauryl sulfate (E487)

Tablet film-coating

Hypromellose

Titanium dioxide (E171)

Lactose monohydrate

Macrogol (E1521)

Printing ink

Black iron oxide (E172)

Propylene glycol (E1520)

Hypromellose (E464)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

White HDPE bottle with a polypropylene (PP) child-resistant closure and polyethylene (PE) faced induction heat seal liner including three silica gel desiccants in HDPE canisters. Pack-size of 30 film-coated tablets.

6.6 Special precautions for disposal

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

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Les Laboratoires Servier

50, rue Carnot
92284 Suresnes cedex
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1912/001

EU/1/25/1912/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 September 2025

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Servier (Ireland) Industries Ltd.

Gorey Road

Arklow

Co. Wicklow

Y14 E284

Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Voranigo 10 mg film-coated tablets
vorasidenib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 10 mg of vorasidenib (as hemicitric acid, hemihydrate).

3. LIST OF EXCIPIENTS

Contains lactose. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not swallow the desiccant.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
--

Discard unused contents appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex
France

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/25/1912/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Voranigo 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**BOTTLE LABEL****1. NAME OF THE MEDICINAL PRODUCT**

Voranigo 10 mg film-coated tablets
vorasidenib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 10 mg of vorasidenib (as hemicitric acid, hemihydrate).

3. LIST OF EXCIPIENTS

Contains lactose. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not swallow the desiccant.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
--

Discard unused contents appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Les Laboratoires Servier

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/25/1912/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Voranigo 40 mg film-coated tablets
vorasidenib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 40 mg of vorasidenib (as hemicitric acid, hemihydrate).

3. LIST OF EXCIPIENTS

Contains lactose. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not swallow the desiccant.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
--

Discard unused contents appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex
France

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/25/1912/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Voranigo 40 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**BOTTLE LABEL****1. NAME OF THE MEDICINAL PRODUCT**

Voranigo 40 mg film-coated tablets
vorasidenib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 40 mg of vorasidenib (as hemicitric acid, hemihydrate).

3. LIST OF EXCIPIENTS

Contains lactose. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not swallow the desiccant.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
--

Discard unused contents appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Les Laboratoires Servier

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/25/1912/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Voranigo 10 mg film-coated tablets

Voranigo 40 mg film-coated tablets

vorasidenib

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Voranigo is and what it is used for
2. What you need to know before you take Voranigo
3. How to take Voranigo
4. Possible side effects
5. How to store Voranigo
6. Contents of the pack and other information

1. What Voranigo is and what it is used for

What Voranigo is and how it works

Voranigo is a cancer medicine that contains the active substance vorasidenib.

It is used as treatment for cancers of the brain called astrocytoma or oligodendroglioma in adults and adolescents from 12 years of age and older who weigh at least 40 kg, who have had surgery as their only treatment and who do not need other treatments such as radiotherapy or chemotherapy immediately.

This medicine is only used when the cancer cells have changes in the genes (mutations) that make proteins known as IDH1 and IDH2. The doctor will have a test performed to check if the cells have this mutation before treatment starts. The IDH1 and IDH2 proteins play an important role in making energy for cells and when the *IDH1* gene or *IDH2* gene is mutated, these proteins are changed and do not function properly. This results in changes in the cells that can lead to the development of cancer.

The active substance in Voranigo, vorasidenib, blocks the abnormal IDH1 and IDH2 proteins. In patients with astrocytoma or oligodendroglioma brain cancers, these proteins are not working properly, causing the overproduction of a substance called 2-hydroxyglutarate (2-HG) that plays a part in the process of normal cells turning into cancer cells. By blocking these proteins, vorasidenib stops the abnormal production of 2-HG which helps to slow or stop the cancer from growing.

2. What you need to know before you take Voranigo

Do not take Voranigo

- if you are allergic to vorasidenib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Voranigo:

- if you have kidney problems
- if you have liver problems

Monitoring of liver function

Voranigo may affect how well your liver functions. Your doctor will carry out blood tests to check how well your liver is working before you are treated with Voranigo, and as necessary during the treatment. If necessary, your doctor may lower your dose or temporarily or permanently stop your treatment.

Tell your doctor, pharmacist or nurse right away if you develop any of the following, which may be signs and symptoms of liver problems:

- yellowing of your skin or the white part of your eyes (jaundice)
- dark “tea-coloured” urine
- loss of appetite
- pain on the upper right side of your stomach area
- feeling weak or very tired

Pregnancy and birth control

This medicine may cause harm to the baby during pregnancy. Women who are able to become pregnant should use effective birth control during treatment and for at least 2 months after treatment has stopped.

Men who are using Voranigo should also use effective birth control during treatment and for at least 2 months after treatment has stopped if they have a partner who is able to become pregnant (see "Contraception in women and men").

Children

Do not give this medicine to children under 12 years old. It has not been studied in this age group.

Other medicines and Voranigo

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because Voranigo can affect the way some other medicines work and some other medicines can affect the way Voranigo works.

In particular, tell your doctor or pharmacist if you are taking any of the following medicines listed below.

The following medicines may increase the risk of side effects with Voranigo by increasing the amount of Voranigo in the blood:

- **Ciprofloxacin** (used to treat bacterial infections)
- **Fluvoxamine** (used to treat depression)

The following medicines may decrease the effectiveness of Voranigo by decreasing the amount of Voranigo in the blood:

- **Rifampicin** (used to treat tuberculosis or certain other infections)
- **Phenytoin** (used to treat epilepsy)

Voranigo may decrease the effectiveness of the following medicines by decreasing the amount of these medicines in the blood:

- **Alfentanil** (used for anaesthesia in surgery)
- **Carbamazepine, fosphenytoin, phenobarbital, phenytoin** (used to treat seizures)

- **Ciclosporin, everolimus, sirolimus, tacrolimus** (medicines used after organ transplants to help control your body's immune response)
- **Fentanyl** (used for severe pain)
- **Pimozide** (used to treat abnormal thoughts and feelings)
- **Quinidine** (used to treat abnormal heartbeat)
- **Ibrutinib, ifosfamide, tamoxifen** (used to treat certain cancers)
- **Buspirone** (used to treat nervous system disorders and/or relieve anxiety)
- **Darunavir, saquinavir, tipranavir** (medicines used to treat HIV infection)
- **Midazolam, triazolam** (used to help you sleep and/or relieve anxiety)
- **Amitriptyline, dosulepin, imipramine, trimipramine** (used to treat depression)
- **Bupropion** (used to help you stop smoking)
- **Celecoxib** (used to treat arthritis)
- **Repaglinide** (used to treat diabetes)
- **Rosuvastatin** (used to lower blood cholesterol)
- **Valproic acid** (used to treat epilepsy)
- **Warfarin** (used to treat blood clots)
- **Hormonal contraceptive medicines** (medicines used to prevent pregnancy, such as birth control pills). See “Contraception in women and men” section below.

The medicines listed here may not be the only ones that could interact with Voranigo. Ask your doctor or pharmacist for advice before taking any medicine.

Pregnancy

Voranigo should not be used during pregnancy as it could harm the unborn baby. If you are a woman able to have children, your doctor should perform a pregnancy test before you start treatment.

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or nurse for advice before taking this medicine. Contact your doctor or nurse right away if you become pregnant while taking Voranigo.

Contraception in women and men

Voranigo should not be used in pregnancy as it could harm the unborn baby. Women who can become pregnant or men with partners who can become pregnant must use effective contraception to avoid pregnancy during treatment with Voranigo and for at least 2 months after the last dose. Voranigo may stop hormonal contraceptives (such as birth control pills, contraceptive patches or implants) from working properly. If you or your partner use a hormonal contraceptive, you must also use a barrier method (such as condoms or a diaphragm) to avoid pregnancy.

Talk to your doctor or nurse about the right methods of contraception for you and your partner.

Breast-feeding

It is not known if Voranigo passes into breast milk. Do not breast-feed while taking Voranigo and for at least 2 months after the last dose.

Fertility

Voranigo may affect your ability to have a baby. Talk to your doctor for advice before using it.

Driving and using machines

Voranigo is not expected to affect your ability to drive or use machines.

Voranigo contains lactose

This medicine contains lactose (found in milk or dairy products). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Voranigo contains sodium

This medicine contains less than 1 mmol of sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Voranigo

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose for adults and adolescents (12 years of age and older) is:

- For patients who weigh at least 40 kg, take **40 mg (one 40 mg tablet)** once a day.
- Patients who weigh less than 40 kg should not take Voranigo.

If you get certain side effects while you are taking Voranigo (see section 4 "Possible side effects"), your doctor may lower your dose or temporarily or permanently stop your treatment. Do not change your dose or stop taking Voranigo without talking to your doctor first.

How and when to take Voranigo

- Voranigo is taken by mouth once a day. You should try to take the medicine at the same time each day.
- Swallow the tablet whole with a glass of water. Do not split, crush or chew the tablet; you may not get the full dose you need unless you swallow a whole tablet.
- Do not eat food for 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 swallow the desiccant package found in the bottle.

If you take more Voranigo than you should

If you accidentally take too many tablets, tell your doctor, pharmacist or nurse right away. You may require urgent medical attention.

If you forget to take Voranigo

Take care not to miss a dose of Voranigo. If you miss a dose by less than 6 hours, take it as soon as you remember, and then take the next dose at your scheduled time. If you miss a dose by more than 6 hours, you should skip the dose and wait to take the next dose at your scheduled time.

If you stop taking Voranigo

Do not stop taking Voranigo unless your doctor tells you to. It is important to take Voranigo every day for as long as your doctor prescribes it to you.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Tell your doctor, pharmacist or nurse if you notice any of the following side effects:

Serious side effects

If you experience any serious side effects, stop taking this medicine and tell your doctor right away. Your doctor may lower your dose, pause treatment or stop treatment completely.

Very common (may affect more than 1 in 10 people):

- Increased amount of liver enzymes, as measured in blood tests (see section 2, “Monitoring of liver function”)

Uncommon (may affect up to 1 in 100 people)

- A condition where your body’s immune system attacks the liver by mistake (autoimmune hepatitis); this can lead to liver damage
- Death of liver cells (hepatic necrosis)
- Inability of the liver to work properly (hepatic failure)

Not known (frequency cannot be estimated from the available data):

- Signs and symptoms of liver injury from the medicine (see section 2, “Monitoring of liver function”)
- Sudden liver inflammation (acute hepatitis)

Other side effects

Very common (may affect more than 1 in 10 people):

- Abdominal pain (belly pain)
- Diarrhoea
- Decreased amount of blood platelets, components that help the blood to clot, as measured in blood tests; this can cause bleeding and bruising
- Tiredness
- Dizziness (lightheadedness)

Common (may affect up to 1 in 10 people):

- Increased blood level of bilirubin, a yellow breakdown substance of the blood pigment (see section 2, “Monitoring of liver function”)
- Increased blood sugar levels (hyperglycaemia)
- Decreased appetite
- Low blood phosphate levels as measured in blood tests (hypophosphataemia); this can cause confusion or muscle weakness
- Difficulty breathing
- Disease where stomach acid rises up into the oesophagus

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Voranigo

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle label and carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Voranigo contains

The active substance is vorasidenib.

- Voranigo 10 mg: Each film-coated tablet contains 10 mg of vorasidenib (as hemicitric acid, hemihydrate).
- Voranigo 40 mg: Each film-coated tablet contains 40 mg of vorasidenib (as hemicitric acid, hemihydrate).

The other ingredients are:

- Tablet core: microcrystalline cellulose (E460), croscarmellose sodium, silicified microcrystalline cellulose, magnesium stearate (E470b) and sodium lauryl sulfate (E487)
- Film-coating: hypromellose, titanium dioxide (E171), lactose monohydrate and macrogol (E1521)
- Printing ink: black iron oxide (E172), propylene glycol (E1520) and hypromellose (E464)

See section 2 “Voranigo contains lactose” and “Voranigo contains sodium”.

What Voranigo looks like and contents of the pack

10 mg film-coated tablets

- White to off-white, round tablets, imprinted with ‘10’ on one side.

40 mg film-coated tablets

- White to off-white, oblong tablets, imprinted with ‘40’ on one side.

Voranigo is available in a plastic bottle with child-resistant closure containing 30 film-coated tablets and 3 desiccant canisters. The bottles are packaged in a cardboard box. Each box contains 1 bottle.

Marketing Authorisation Holder

Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex
France

Manufacturer

Servier (Ireland) Industries Ltd.
Gorey Road
Arklow
Co. Wicklow

Y14 E284
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien

S.A. Servier Benelux N.V.
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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<https://www.ema.europa.eu>.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.