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 40 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Voranigo 40 mg film-coated tablets

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

Excipient with known effect

Each film-coated tablet contains 2.52 mg lactose monohydrate (see section 4.4).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Voranigo 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 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 (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.

Select patients for the treatment of astrocytoma or oligodendroglioma with Voranigo based on the presence of IDH1 or IDH2 mutations in tumor specimens using an appropriate diagnostic test prior to initiation of treatment with vorasidenib.

Posology

The recommended dose of Voranigo in adults:
- 40 mg taken orally once daily

The recommended dose of Voranigo in 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 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 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). Manage any abnormalities promptly (see section 4.8).

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

Table 2: Recommended Voranigo 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)	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 enzymes 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 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). Recurrence: 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 *without* concurrent total bilirubin >2 x ULN	First Occurrence: 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. Recurrence: 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 *with* 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	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.

[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 m^2). The pharmacokinetics and safety of vorasidenib and metabolite AGI-69460 have not been studied in patients with eGFR ≤ 40 mL/min/1.73 m^2 or renal impairment requiring dialysis. Vorasidenib should be used with caution in patients with eGFR ≤ 40 mL/min/1.73 m^2 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 and safety of vorasidenib and AGI-69460 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 and 5.2).

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 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.

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

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

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 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).

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 3 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 3 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 3 months after the last dose.

Hepatic impairment

Vorasidenib should not be used in patients with pre-existing severe hepatic impairment (Child-Pugh class C) (see sections 4.2 and 5.2).

Renal impairment

The pharmacokinetics and safety of vorasidenib have not been studied in patients with renal impairment (eGFR ≤ 40 mL/min/1.73 m^2) or renal impairment requiring dialysis. Vorasidenib should be used with caution 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’.

Paediatric population

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). 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.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on vorasidenib

Strong or Moderate CYP1A2 inhibitors

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

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.

Concomitant use of vorasidenib with smoking tobacco may decrease vorasidenib plasma concentrations which may reduce the anti-tumor activity of vorasidenib. Consider advising that smoking tobacco should be avoided during treatment with vorasidenib.
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, pimozide, 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 3 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 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 and 4.5).

Pregnancy

There is a 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). Voranigo can cause fetal harm when administered to pregnant women.

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. No fertility studies in animals have been conducted to evaluate the effect of vorasidenib. 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, 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 (4.8%) and GGT increased (3.0%).

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

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

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

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

Tabulated list of adverse reactions

Adverse reactions reported in patients treated with vorasidenib in the INDIGO trial (Study AG881-C-004) are listed below in Table 3 by MedDRA system organ class and by frequency.

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

Table 3: Adverse drug reactions reported in patients treated with vorasidenib in the INDIGO trial (Study AG881-C-004) (N=167)

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[b]
Gastrointestinal disorders	Very common	Abdominal pain[c]
		Diarrhoea[d]
Hepatobiliary disorders	Very common	Alanine aminotransferase increased[a]
		Aspartate aminotransferase increased[a]
		Gamma-glutamyl transferase increased[a]
	Common	Alkaline phosphatase increased[a]
General disorders	Very common	Fatigue[e]

[a] Laboratory abnormality is defined as new or worsened by at least one grade from baseline, or baseline is unknown.

[b] Grouped term includes hypophosphataemia and blood phosphorus decreased.

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

[d] Grouped term includes diarrhoea, feces soft and frequent bowel movements.

[e] Grouped term includes fatigue and asthenia.

Description of selected adverse reactions

Hepatobiliary disorders
In the INDIGO clinical trial (Study AG881-C-004), 18.6% (31/167) of patients treated with Voranigo experienced ALT elevations >3 times the ULN and 8.4% (14/167) experienced AST elevations >3 times the ULN. In INDIGO, 1.2% of patients (2/167) had concurrent ALT or AST elevations >3 times the ULN and total bilirubin >2 times the ULN. Liver enzyme and bilirubin increases were transient and improved or resolved with dose modification or permanent discontinuation of treatment (see sections 4.2 and 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 Yellow Card Scheme website at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 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 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). 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.

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 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.

Efficacy results for PFS and TTNI are summarised in Table 4, Figure 1 and Figure 2.

Table 4: 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)		
Number of Events, n (%) Progressive disease Death	47 (28.0) 0	88 (54.0) 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 Crossover to VORANIGO	19 (11.3) 0	6 (3.7) 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**

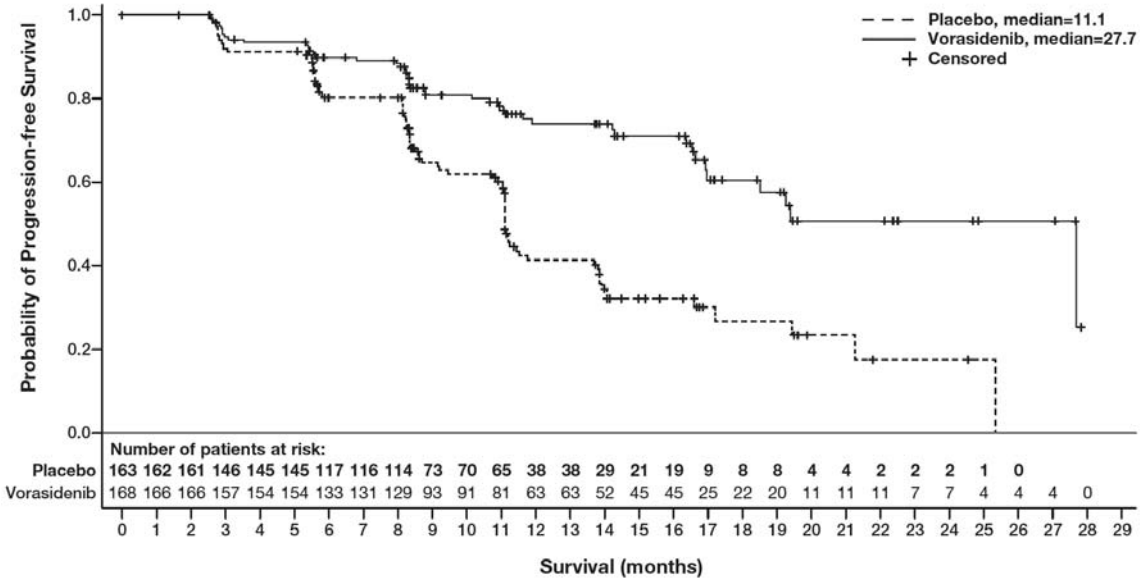
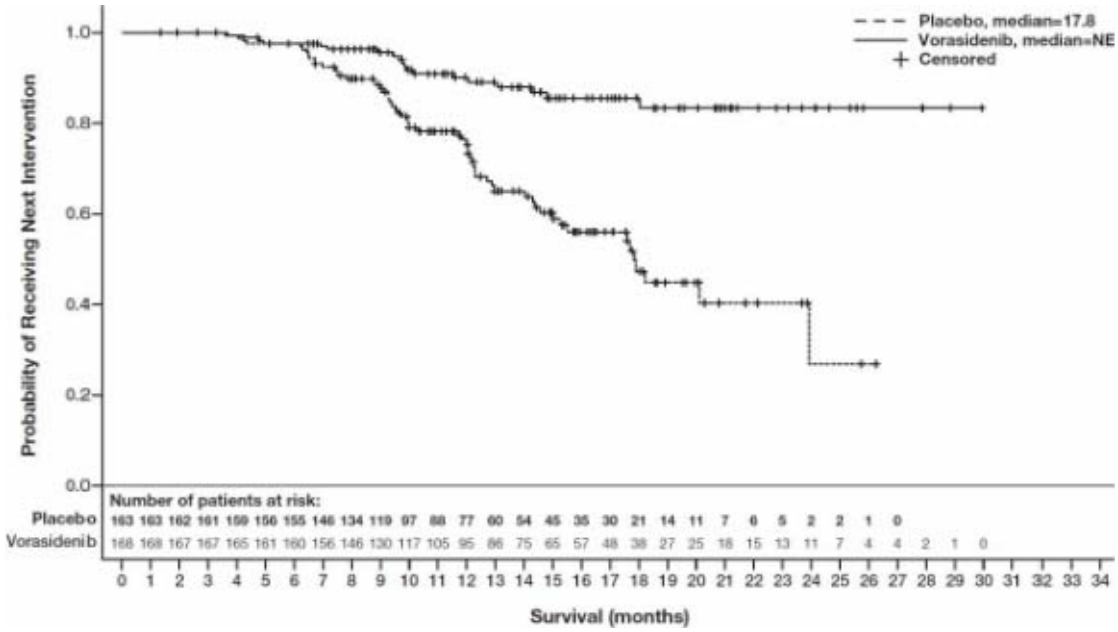


Figure 2: Kaplan-Meier Curve for Time to Next Intervention in INDIGO Trial



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.

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

The post-treatment tumour volume decreased in subjects randomized to vorasidenib by a mean of 2.5% every 6 months (TGR of -2.5%; 95% CI: -4.7 to -0.2), while 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.

The preliminary efficacy and safety of vorasidenib was evaluated in a phase 1, multicenter, open label dose-escalation study in subjects with advanced solid tumours, including IDH1- and IDH2-mutant gliomas, in a total of 93 subjects across 6 dose levels. For all subjects with glioma (N=52), the objective response rate (ORR) was 11.5% (95% CI: 4.35%, 23.44%). The ORR in subjects with non-enhancing glioma (n=22) was 22.7% and in subjects with enhancing glioma (n=30) the ORR was 3.3%. The median PFS for all glioma subjects (N=52) was 7.5 (95% CI: 3.7, 12.9) months with 75% of events reported. Among the 22 subjects with non-enhancing gliomas, the median PFS was 36.8 (95% CI:14.9, 60.2) months with 63.6% of events reported. Of the 30 subjects with enhancing gliomas, the median PFS was 3.6 (95% CI:1.9, 7.5) months with 83.3% of events reported.

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 an 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). 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.

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. Following multiple daily doses of vorasidenib 40 mg, the mean plasma trough concentrations (Ctrough) of AGI-69460 appear to reach steady-state by Cycle 3, Day 1. 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 an *in vivo* drug-drug interaction study, co administration of 20 mg vorasidenib with a moderate 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%.

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

In vitro, vorasidenib has a strong induction effect on sensitive CYP3A4 substrates and a moderate induction effect on sensitive CYP2B6, CYP2C8, and CYP2C19 substrates (see section 4.5).

In vitro data indicate that vorasidenib is an inhibitor of BCRP. Vorasidenib did not inhibit P-glycoprotein (P-gp) and hepatic transporter organic anion transporting polypeptide (OATP)1B1. However, the inhibiting effect of vorasidenib on gut P-gp at drug concentrations higher than those assessed in the initial *in vitro* study is unknown. *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

Clinical studies of vorasidenib did not include sufficient numbers of patients aged ≥65 (n=2) to determine the effects of age on the pharmacokinetics of vorasidenib, and no data are available in patients aged >75 years.

Renal impairment

Renal impairment (eGFR > 40 mL/min/1.73 m^2) had no clinically significant effect on the pharmacokinetics of vorasidenib. The pharmacokinetics of vorasidenib in patients with eGFR ≤ 40 mL/min/1.73 m^2 or renal impairment requiring dialysis are unknown.

Hepatic impairment

Moderate hepatic impairment (Child-Pugh class B) had no clinically significant effects on vorasidenib 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) in patients with moderate hepatic impairment following a single oral dose of 20 mg vorasidenib. The pharmacokinetics of vorasidenib 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 (18 to 75 years), race, ethnicity and body weight (43.5 to 168 kg). There are limited clinical data available in non- Caucasian or non-Asian populations. Female patients were observed to have a 1.6 fold higher vorasidenib exposure as compared to male patients.

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). 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 (see section 4.2).

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.

Carcinogenicity studies have not been conducted with vorasidenib. 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.

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 estrous 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 exposure higher than patients' exposure at the therapeutic daily dose. At the lowest tested dose of 5 mg/kg/day (13-week study), the findings were observed at an exposure 42-fold higher compared to human exposure at the 40 mg daily dose.

Vorasidenib caused embryo-fetal 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-fetal development in rats and rabbits were 13 to 45 and 1.7 to 7.8, 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
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92284 Suresnes cedex
France

8 MARKETING AUTHORISATION NUMBER(S)

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10 DATE OF REVISION OF THE TEXT

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