swissmedic

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Swiss Public Assessment Report

Voranigo

International non-proprietary name:	vorasidenib as vorasidenib hemicitric acid hemihydrate
Pharmaceutical form:	film-coated tablets
Dosage strength(s):	10 mg, 40 mg
Route(s) of administration:	oral
Marketing authorisation holder:	Servier (Suisse) SA
Marketing authorisation no.:	69364
Decision and decision date:	approved on 15.11.2024

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

1L	First-line
2L	Second-line
2-HG	2-hydroxyglutarate
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BCS	Biopharmaceutics Classificatin System
BIRC	Blinded Independent Review Committee
CAS	Chemical abstracts service
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CYP	Cytochrome P450
DCO	Data Cut-off
DDI	Drug-drug interaction
DOR	Duration of response
EANO	European Association of Neuro-Oncology
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
F1/F2	Formulation 1 / formulation 2
FDA	Food and Drug Administration (USA)
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice
GSH	Gltathione
HDPE	High-density polyethylene
hERG	Human Ether-a-go-go-related Gene
HGG	High-grade glioma
HPLC	High-performance liquid chromatography
HR	Hazard ratio
IA2	Interim analysis 2
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
IDH	Isocitrate dehydrogenase
IDMC	Independent data monitoring committee
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
IUPAC	International Union of Pure and Applied Chemistry
IV	Intravenous
LoQ	List of Questions

MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
mRNA	Messenger ribonucleic acid
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NE	Not evaluable
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PCV	Procarbazine/lomustine/vincristine
PD	Pharmacodynamics
PFS	Progression-free survival
Ph.Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
PT	Preferred term
QD	Once daily
QTc	QT interval corrected for heart rate
RANO-LGG	Response Assessment in Neuro-oncology for Low-grade Gliomas
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
T_{max}	Time to reach C_{max}
TMZ	Temozolomide
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
TTNI	Time to next intervention
ULN	Upper limit of normal
WHO	World Health Organisation
WT	Wild type

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for vorasidenib as vorasidenib hemicitric acid hemihydrate in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA.
Orphan drug status was granted on 13.04.2023.

Project Orbis
The applicant requested a marketing authorisation procedure within the framework of Project Orbis. Project Orbis is coordinated by the FDA and provides a framework for concurrent submission and review of oncology products among international partners.

2.2 Indication and dosage

2.2.1 Requested indication

Voranigo is indicated for the treatment of predominantly non-enhancing astrocytoma or oligodendroglioma with a susceptible isocitrate dehydrogenase-1 (IDH1) or isocitrate dehydrogenase-2 (IDH2) mutation in adult patients following surgical intervention.

2.2.2 Approved indication

Voranigo is indicated for the treatment of adult patients with grade 2 astrocytoma or oligodendroglioma with a susceptible isocitrate dehydrogenase-1 (IDH1) or isocitrate dehydrogenase-2 (IDH2) mutation following surgical intervention and are not in immediate need of chemotherapy or radiotherapy (see section «Clinical efficacy»).

2.2.3 Requested dosage

Summary of the requested standard dosage:
IDH1 or IDH2 mutation must be confirmed by a diagnostic test.
The recommended dose of vorasidenib in adults is 40 mg taken orally once daily for patients weighing at least 40 kg.
Administer Voranigo until disease progression or unacceptable toxicity occurs.
Take Voranigo tablets at about the same time each day. Do not eat food at least 2 hours before and 1 hour after taking Voranigo. Swallow tablets whole with water, do not split, crush, or chew.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	18 January 2024
Formal control completed	29 January 2024
Preliminary decision	9 August 2024
Response to preliminary decision	6 September 2024
Final decision	15 November 2024
Decision	approval

3 Medical context

Gliomas are the most common malignant primary brain tumours in adults (Lapointe S et al. Primary brain tumours in adults. Lancet. 2018;392(10145):432–46). The classification of these tumours is made according to the World Health Organization (WHO) Classification of Central Nervous System Tumours with molecular features introduced in 2016. Based on the most recent 2021 WHO classification there are 3 main types of adult-type diffuse gliomas: IDH-mutant astrocytomas CNS WHO grade 2-4, IDH-mutant and 1p/19q-codeleted oligodendrogliomas CNS WHO grade 2-3, and IDH wildtype glioma (glioblastoma, WHO grade 4).
IDH-mutant astrocytomas have no 1p19q codeletion, whereas IDH-mutant oligodendroglioma are defined by 1p19q codeletion.

Essentially all grade 2 gliomas eventually progress to high-grade gliomas (HGG) (Claus EB et al. Survival and low-grade glioma: the emergence of genetic information. Neurosurg Focus. 2015 Jan;38(1):E6).

The WHO classification distinguishes between adult-type glioma and paediatric-type glioma, which differ in terms of incidences, tumour type, histopathology, location, molecular characteristics, treatment options, clinical course, and prognosis.

The incidence of adult-type diffuse gliomas harbouring an IDH mutation is low in paediatric and older adolescent patients. The presence of these mutations in a paediatric low-grade glioma is thought to result in “adult diffuse glioma” behaviour (Ryall et al. A comprehensive review of paediatric low-grade diffuse glioma: pathology, molecular genetics and treatment. Brain Tumor Pathol. 2017;34(2):51-61).

Surgery remains the most important first step for glioma diagnosis and management. The post-operative treatment strategy depends on the tumour type and grade. An observational approach after surgery is a treatment option for patients with grade 2 gliomas with favourable prognostic factors such as age < 40 years, gross total resection, and good neurological function. In patients with CNS WHO grade 2 astrocytoma and oligodendroglioma with less favourable prognostic factors, adjuvant radiotherapy and chemotherapy, such as PCV (procarbazine, lomustine/carmustine, vincristine) or temozolomide, is recommended. Patients with CNS WHO grade 3 glioma are usually treated with adjuvant radiotherapy and chemotherapy.
Management of recurrent or progressive tumours in patients who have been observed following initial resection of an IDH-mutant grade 2 glioma is individualised. Depending on the scenario, radiotherapy plus chemotherapy, re-resection with adjuvant radiotherapy plus chemotherapy, or participation in a clinical trial (preferred for eligible patients) are treatment options.

4 Quality aspects

4.1 Drug substance

INN: vorasidenib

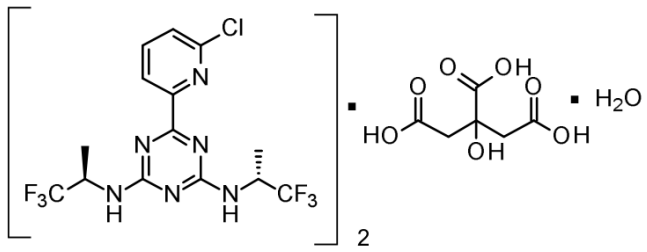
Chemical names:
CAS name:
1,3,5-Triazine-2,4-diamine, 6-(6-chloro-2-pyridinyl)-N2,N4-bis[(1R)-2,2,2 trifluoro-1-methylethyl]-, 2-hydroxy-1,2,3-propanetricarboxylate, hydrate (2:1:1)
IUPAC name:

6-(6-chloropyridin-2-yl)-N2,N4-bis[(2R)-1,1,1-trifluoropropan-2-yl]-1,3,5-triazine-2,4-diamine, 2-hydroxypropane-1,2,3-tricarboxylic acid, hydrate (2:1:1)

Molecular formula:
Free base: $C_{14}H_{13}ClF_6N_6$
Vorasidenib, citrate: $C_{14}H_{13}ClF_6N_6 \cdot 1/2\ C_6H_8O_7 \cdot 1/2\ H_2O$

Molecular mass:
Free base: 414.7 g/mol
Vorasidenib, citrate: 519.8 g/mol

Molecular structure:



Physicochemical properties:
The drug substance is a hemicitric acid, hemihydrate co-crystal.

Synthesis:
The synthesis of the drug substance has been adequately described, and the process is monitored with appropriate in-process controls and tests for isolated intermediates.

Specification:
The structure of vorasidenib has been elucidated using several spectroscopic techniques. To ensure a consistent quality, the specifications include the relevant test parameters as described in the current guidelines. Analytical methods have been described and validated according to ICH requirements.

Stability:
Appropriate stability data have been generated, resulting in a suitable packaging configuration, storage condition, and retest period.

4.2 Drug product

Description and composition:
The drug product is an immediate-release dosage form for oral administration. Vorasidenib 10 mg tablets are white to off-white, round, film-coated tablets, approximately 6 mm in diameter. The tablets are marked (imprinted) with 10 on one side and plain on the reverse. Vorasidenib 40 mg tablets are white to off-white, oblong, film-coated tablets, approximately 14.8 mm x 6.3 mm. The tablets are marked (imprinted) with 40 on one side and plain on the reverse. All excipients are widely used in pharmaceutical solid oral dosage forms. They meet the standards defined in the current Ph. Eur.

Pharmaceutical development:
The commercial formulation is the formulation used for pivotal clinical studies.

Manufacture:
The drug product is manufactured by a standard manufacturing process. Process parameters and in-process controls are defined.

Specification:
Adequate tests and acceptance criteria for release and shelf-life are established for the control of the finished product. The specifications include the parameters description, identity tests, assay, degradation products, dissolution, and uniformity of dosage units. The analytical procedures are adequately described, and non-compendial methods are validated according to the current ICH requirements. Batch analysis data have been provided. The results are within the specifications and consistent from batch to batch.

Container closure system:
Satisfactory information on the proposed container closure system has been provided. The drug product is packaged in HDPE bottles with desiccant, induction seal liner, and child-resistant closure.

Stability:
Appropriate stability data have been generated following the relevant (ICH) guidelines. Appropriate shelf-life and storage conditions were established based on the stability studies.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

5 Nonclinical aspects

5.1 Pharmacology

Vorasidenib is a potent inhibitor of mutant and wild type (WT) isocitrate dehydrogenase-1 (IDH1) and isocitrate dehydrogenase-2 (IDH2). In biochemical assays, IC_{50} values were in the low nanomolar range. Tested mutants included IDH1 R132C, IDH1 R132G, IDH1 R132H, IDH1 R132 L, IDH1 R132S, IDH2 R140Q, and IDH2 R172K (homodimer enzymes) as well as IDH1 WT/R132H, IDH2 WT/R140Q, and IDH2 WT/R172K (heterodimer enzymes). Vorasidenib inhibited 2-hydroxyglutarate (2-HG) production in cells expressing IDH1 R132C, R132G, R132H, or R132S mutations (IC_{50} values of 0.04 to 22 nM), or IDH2 R140Q (IC_{50} values of 7 to 14 nM); less potent inhibition was noted in cells expressing IDH2 R172K (IC_{50} of 130 mM). Vorasidenib was more potent than its metabolite AGI-69460 in cells with the IDH1 R132C or IDH1 R132H mutation.

In the erythroleukaemia cell line TF-1 (not fully transformed) with IDH1 R132H or IDH2 R140Q mutations, vorasidenib at concentrations that decreased 2-HG reversed the IDH-dependent block of erythroid differentiation. Furthermore, in a small study with samples from acute myeloid leukaemia (AML) patients, vorasidenib reduced 2-HG and induced myeloid differentiation in IDH1- or IDH2-mutant (IDH1 R132C, IDH2 R172K, or IDH2 R140Q) bone marrow myeloblasts.

The applicant demonstrated in various mouse xenograft models that repeated oral doses (every 12 h) of vorasidenib can reduce tumour 2-HG levels. In the orthotopic TS603 IDH1 R132H glioma model, brain tumour 2-HG levels were reduced >97% at ≥0.1 mg/kg. The applicant did not investigate the effect of vorasidenib on tumour growth.

In conclusion, the pharmacology of vorasidenib as an inhibitor of mutant IDH1 and IDH2 for the treatment of tumours with susceptible IDH1 or IDH2 mutations has been sufficiently characterised from a nonclinical perspective.

Vorasidenib did not show any off-target activity in a secondary pharmacology screen with the exception of the adenosine A3 receptor, at which vorasidenib was identified as an antagonist with an IC_{50} value of 1.5 µM (approximately 75-fold human C_{max} for unbound vorasidenib at therapeutic doses).

The safety pharmacology assessments included in the rat and monkey repeat-dose toxicity studies were limited but can be accepted for a drug under the scope of ICH S9. Vorasidenib inhibited the hERG channel current with an IC_{50} >12.3 µM (approximately 600-fold human unbound C_{max} at therapeutic doses); for the metabolite AGI-69640, the IC_{50} was >30 µM. There were no ECG changes or effects on heart rate in monkeys at exposures 80-fold human C_{max} at therapeutic doses. A marginal QTc prolongation was noted in a single male at 130-fold human C_{max} at therapeutic doses.

The safety pharmacology assessments in rats did not reveal any effects of vorasidenib on the central nervous or respiratory system at plasma concentrations approximately 150-fold human C_{max} at therapeutic doses.

5.2 Pharmacokinetics

Bioavailability after oral administration ranged from 6% in dogs to 109% in monkeys. Terminal half-life (after IV injection) was long except in dogs and ranged from 6.4 h (dogs) to 24 h (monkeys). After repeated oral doses to rats or monkeys, both C_{max} and AUC increased with the dose and accumulation occurred. There were no clear sex-related differences in exposure.

Vorasidenib is a drug with high permeability. It showed high plasma protein binding (≥95%) in humans, monkeys, dogs, rats, and mice, and remained mainly in plasma with low partitioning to red blood cells (>0.5). Brain penetration was shown in mice, rats, and monkeys. In rats, vorasidenib-derived radioactivity distributed into tissues and elimination from the body was slow. There was no significant distribution to melanin-containing tissues.

Turnover of vorasidenib in hepatocytes from rats, mice, dogs, monkeys, and humans was low. Metabolism consisted of either direct hydroxylation followed by glucuronidation or de-chlorination of the chloro-pyridine ring followed or caused by GSH or cysteine conjugation. Combinations of hydroxylation, glucuronidation, and GSH/cysteine conjugation were observed as secondary metabolites. All metabolites identified in human hepatocytes were detected in animal plasma. AGI-69460 is a major circulating human metabolite that was not identified *in vitro* since it is likely formed via a combination of hepatic and extrahepatic pathways. It is the main metabolite in human plasma. Exposure to AGI-69460 was confirmed in rat, rabbit, and monkey plasma.

In rats, vorasidenib was mainly eliminated via hepatic metabolism followed by biliary/faecal excretion. There was negligible excretion of unchanged vorasidenib in rat bile and rat, dog, and monkey urine.

5.3 Toxicology

The applicant conducted a toxicology programme in line with ICH S9. The repeat-dose toxicity studies were conducted in rats and monkeys, both of which are pharmacologically relevant animal species. The major circulating human metabolite AGI-69460 was also present in rat and monkey plasma. Vorasidenib was administered orally, in line with the intended clinical route of administration. The duration of the repeat-dose toxicity studies (up to 13 weeks in rats and monkeys) is appropriate for a product intended for the treatment of advanced cancer.

Single oral doses of up to 1000 mg/kg to rats or 80 mg/kg to monkeys were well tolerated but repeated doses led to deaths at 50 mg/kg/day in rats and at 20 mg/kg/day in monkeys. The only common target organ in both rats and monkeys was the liver (hepatocellular hypertrophy, with liver enzyme elevations in monkeys only); liver enzyme elevations were observed in humans as well. Additional target organs in rats were the skin, kidney, male and female reproductive organs, and skeletal muscle. Most of these findings were fully or partially reversible. The applicant states that reproductive organs were only a target in rats; however, the testes of the monkeys in both the 28-day and 13-week studies were immature, precluding/limiting an assessment of male reproductive organs. Finally, gastro-intestinal toxicity (local irritative effects) and neutrophilic inflammatory infiltrates in the middle ear were only observed in the 28-day in rat toxicity study. The toxicological relevance of the ear findings was ruled out in a dedicated ototoxicity study. A NOEL was not identified in the 13-week rat study but 5 mg/kg/day (exposure 31-fold human AUC at therapeutic doses) were well tolerated. At the NOEL in the 13-week monkey study, exposure was 2.5-fold human AUC at therapeutic doses. These safety margins are acceptable for a product intended for the treatment of cancer.

Vorasidenib was not genotoxic. In line with ICH S9, no carcinogenicity studies were performed with vorasidenib.

The applicant did not conduct any fertility and early embryonic development or pre- and postnatal development toxicity studies, again in line with ICH S9. The repeat-dose toxicity studies revealed findings in the reproductive organs (please see above). Maternal and embryofetal toxicity were noted in pregnant rats and rabbits. The NOAEL for embryofetal toxicity was 10 mg/kg/day in rats (exposure 34-fold human AUC at therapeutic doses) and 6 mg/kg/day in rabbits (exposure 6-fold human AUC at therapeutic doses). Due to the identified embryofetal toxicity, vorasidenib is not recommended during pregnancy and in women of childbearing potential who are not using contraception.

Vorasidenib showed no phototoxicity potential *in vitro*.

There were no issues with impurities.

The applicant provided a satisfactory ERA. All relevant nonclinical safety findings are included in the nonclinical part of the safety specification of the RMP. The PIP does not include any nonclinical measures.

5.4 Nonclinical conclusions

The submitted nonclinical documentation is considered adequate to support the approval of vorasidenib in the proposed indication. All safety-relevant nonclinical data are included in the Information for healthcare professionals.

6 Clinical aspects

6.1 Clinical pharmacology

ADME

Biopharmaceutical development

Vorasidenib is a BCS-II class molecule exhibiting low solubility and high permeability. During development, the molecule was developed in two formulations: Formulation 1 (F1, uncoated tablets) and Formulation 2 (F2, film-coated tablets), with F2 being the commercial formulation. Relative bioavailability studies conducted in healthy volunteers demonstrated a 45% increase in total exposure (AUC_{0-t}) and a 65% increase in C_{max} for F2 compared to F1.

Absorption

Vorasidenib is absorbed rapidly, with a median T_{max} of 1-3 hours post-dose. The absolute bioavailability was determined to be 34.1% using a 0.1 mg IV microdose of vorasidenib under fasted conditions. Administration with a high-fat meal increased AUC by 1.29-fold and C_{max} by 3.13-fold, while a low-fat meal increased AUC by 1.34-fold and C_{max} by 2.32-fold compared to fasting conditions. Steady-state plasma concentrations were achieved by Day 14, with an accumulation factor of 3.6-5.8.

Distribution

Vorasidenib is highly protein-bound, with mean unbound fractions of 2.66%, independent of concentration. Radioactive material distributed into red blood cells, with a whole blood/plasma ratio of approximately 1.0 around T_{max}. The blood/plasma partitioning increased over time to 1.62 at the last time point measured, likely due to metabolite AGI-69460's partitioning. High brain penetration was shown in patients, with a brain tumour-to-plasma ratio for vorasidenib of 1.69. The volume of distribution was 1,110 L after IV application.

Metabolism

Vorasidenib is primarily metabolised by CYP1A2, contributing 53-90% to hepatic clearance, with negligible contributions from other CYPs and up to 30% from non-CYP pathways, as shown in *in vitro* enzyme phenotyping studies. The major metabolite, AGI-69460, was identified for the first time in the human ADME study, and is pharmacologically active. The steady-state levels of the major metabolite AGI-69640 is achieved after multiple dosing cycles (approximately 10 cycles). The metabolite-to-parent ratio was 1.17 at steady state in the pivotal clinical study.

Elimination

Vorasidenib's geometric mean plasma clearance is 24.8 L/h, based on microdose IV administration. The terminal half-life ranged from 185 to 303 hours following oral administration. Excretion was primarily faecal (84.7% of the dose) with minimal renal clearance (4.52%), as observed in a clinical ADME study.

Special populations

Population effects

Based on a population PK model, increased exposure in female patients can be expected and a 1.6-fold higher AUC at steady state was estimated.

No bodyweight-related effect was observed in the adult population with body weights ranging from 43.5 to 168 kg. The potential effect of bodyweight below 40 kg is not well understood.

Plasma concentration-time profiles, AUC, and C_{max} are generally similar between Japanese and non-Asian participants.

Hepatic impairment
In a dedicated clinical study moderate hepatic impairment resulted in a 26% increase in AUC without affecting C_{max}. The average unbound vorasidenib and AGI-64960 fractions were slightly higher in subjects with moderate hepatic impairment (2.8% for vorasidenib and 13% for AGI-64960) compared to subjects with normal hepatic function (2.2% for vorasidenib and 11% for AGI-64960). Overall, the data suggest that moderate hepatic impairment does not lead to clinically relevant changes in total or unbound vorasidenib exposure.

Renal impairment was not evaluated due to negligible renal elimination.

Drug-drug interactions

Effect of other drugs on vorasidenib
Vorasidenib is primarily metabolised by CYP1A2. Clinical interaction studies revealed that co-administration of vorasidenib with ciprofloxacin, a strong CYP1A2 inhibitor, increased vorasidenib C_{max} by 1.29-fold and AUC by 2.53-fold. Co-administration with omeprazole, a proton pump inhibitor, slightly decreased the C_{max} of vorasidenib by 28% but did not affect AUC.

AGI-69460 is not a substrate of major CYP450 enzymes.

Effect of vorasidenib on other drugs
No inhibition potential was detected in *in vitro* inhibition studies with recombinant CYPs. CYP induction studies were conducted *in vitro* in hepatocytes. Vorasidenib showed little to no effect on CYP1A2 activity or CYP1A2 mRNA levels but was an inducer of CYP2B6, CYP3A4, and of CYP2C8, CYP2C9, CYP2C19 (activity only), and UGT1A4 at clinically relevant concentrations.
A clinical study evaluating the effect of vorasidenib on lamotrigine, a UGT1A4 substrate, demonstrated no significant change in lamotrigine's pharmacokinetics.

Secondary pharmacology

In vitro, no IC_{50} could be established for vorasidenib and AGI-69460 towards the hERG channel. ECG assessment during clinical trials, including pivotal trials, confirmed that there is no apparent exposure-QTc relationship.

6.2 Dose finding and dose recommendation

The selection of the clinical formulation in the form of an uncoated tablet was based on preliminary safety, pharmacokinetic (PK), pharmacodynamic, and efficacy data from 2 ongoing Phase 1 studies (study AG881-C-002 and study AG120-881-C-001). The highest dose tested in study AG881-C-002 without any dose-limiting toxicities was 50 mg. This dose and the lower dose of 10 mg were selected for study AG120-881-C-001 for further evaluation. The dose-dependent reduction in tumour 2-HG was observed to be higher in patients treated with 50 mg in study AG120-881-C-001. In addition, preliminary efficacy data showed a higher overall response rate in patients treated at the higher dose level. The dose of 50 mg (uncoated formulation) was therefore chosen for the pivotal INDIGO study. The commercial formulation (film-coated tablet) was implemented in the INDIGO study with the first protocol amendment. Prior to that a relative bioavailability study was conducted to compare the 2 formulations; it showed consistent results overall.

6.3 Efficacy

INDIGO is a randomised, double-blind, placebo-controlled, multicentre, Phase 3 study to evaluate the efficacy and safety of vorasidenib compared to placebo in patients aged 12 years and older with residual or recurrent CNS WHO grade 2 glioma based on the WHO 2016 classification with an IDH1 or IDH2 mutation. The study was initiated on 8 January 2020 and data cut-off for the second interim analysis (IA2) was 6 September 2022. Subsequently the Independent Data Monitoring Committee (IDMC) decided to unblind the study since the study had met its primary endpoint.
As mentioned in the section “Dose finding”, the commercial formulation was introduced with amendment 1 in March 2020. A total of 5 patients had received the clinical formulation before switching to the commercial formulation. Overall, there were 3 global amendments which were considered acceptable.

A total of n=331 patients were randomised 1:1 to either vorasidenib (n=168) or placebo (n=163), stratified by local 1p19q status (co-deleted or not co-deleted) and baseline tumour size per local assessment.
Patients 12 years or older were eligible if they had a residual or recurrent CNS WHO grade 2 oligodendroglioma or astrocytoma per WHO 2016 criteria and a minimum expected survival time of ≥12 months. IDH1 or IDH2 mutation confirmed by central laboratory testing and 1p19q status confirmed by local testing were required for inclusion. Patients needed to have had at least 1 prior surgery for glioma (either biopsy, sub-total resection or gross-total resection) at least 1 year and not more than 5 years before the date of randomisation. Patients were not allowed “to be in need of immediate chemotherapy or radiotherapy in the opinion of the investigator” according to the study protocol. Patients undergoing biopsy only to obtain tissue for central confirmation of IDH mutation status (where tissue from previous surgery was not available) could be included without needing to wait an additional year from biopsy. Therefore, the requested treatment is intended to serve as prophylaxis against disease progression compared to a “watch and wait” strategy with treatment if (clinically relevant) progression occurs.
Patients with any prior anti-cancer therapy for glioma other than surgery were excluded from the study.
The same applied to patients with high-risk features as assessed by the investigator (brain stem involvement, clinically relevant functional or neurocognitive deficits due to the tumour, and uncontrolled seizures).

The primary endpoint was progression-free survival (PFS) defined as the time from date of randomisation to date of first documented radiographic progressive disease (as assessed by the blinded independent review committee [BIRC] per modified Response Assessment in Neuro-oncology for Low-grade Gliomas [RANO-LGG]) or date of death due to any cause, whichever occurred first.
The key secondary endpoint was time to next intervention (TTNI) defined as the time from randomisation to the initiation of the first subsequent anti-cancer therapy (including vorasidenib, for subjects randomised to placebo who subsequently crossed over) or death due to any cause.

Patients randomised to vorasidenib or matched placebo were to receive daily continuous dosing of vorasidenib or placebo until centrally confirmed disease progression, unacceptable toxicity, a need for new anti-cancer treatment (in the absence of progressive disease [PD]), pregnancy, death, or withdrawal of consent occurred. Patients from the placebo arm with PD had the option to cross over to the vorasidenib arm if BIRC-confirmed progressive disease occurred. When the study was unblinded, all patients receiving placebo were allowed to cross over to vorasidenib. This is considered critical as the benefit of vorasidenib was still unclear at the time of pre-specification and there are other guideline-recommended treatments such as radiotherapy or chemotherapy if progression occurs.

For the primary endpoint, a total of 164 PFS events were required to produce at least 90% power to detect a hazard ratio (HR) of 0.6 using a 1-sided log-rank test stratified by the randomisation

stratification factors at a significance level of 0.025, a 3-look group sequential design with a gamma family (-24) α-spending function to determine the efficacy boundaries, and a gamma family (-5) β-spending function to determine the nonbinding futility boundary.

At the time of DCO of IA2 (6 September 2022), the median follow-up duration was 13.7 months and 14.1 months in the vorasidenib and placebo arms, respectively.
Treatment was ongoing in a higher proportion of patients in the vorasidenib arm compared to the placebo arm (78.0% vs. 58.3%). The reason for discontinuation of treatment was mainly centrally confirmed disease progression. There were n=52 patients in the placebo arm who crossed over to vorasidenib following centrally confirmed disease progression.

Baseline and disease characteristics were balanced overall. The median age of the study population was 39.0 years in the placebo arm and 40.5 years in the vorasidenib arm. There was only 1 patient below the age of 18 (16 years), randomised to the placebo arm. The majority of patients were male, White, and had a Karnofsky score of 100. About half of the patients had a diagnosis of astrocytoma. The median time from initial diagnosis to randomisation was 29.6 months in the placebo arm and 35.6 months in the vorasidenib arm. The majority of patients had a tumour size at baseline of ≥2 cm (placebo 84.0%; vorasidenib 82.7%) and 1 prior surgery for glioma in both arms (placebo: 82.2%; vorasidenib 75.0%). The median time from last surgery to randomisation was 2.2 years (range 0.9 – 5.0) in the placebo arm and 2.5 years (range 0.2 – 5.2) in the vorasidenib arm.
The vast majority of patients were IDH1 positive (placebo: 93.3%; vorasidenib 97.0%) compared to IDH2 positive (placebo 6.7%; vorasidenib 3.0%).

The primary endpoint PFS per the BIRC was significantly improved in the vorasidenib arm compared with the placebo arm with an HR of 0.39 (95% CI, 0.27, 0.56; P=0.000000067). The median PFS was 27.7 (95% CI, 17.0, NE) months for the vorasidenib arm and 11.1 (95% CI, 11.0, 13.7) months for the placebo arm. There were n=88 events (54.0%) in the placebo arm and n=47 events (28.0%) in the vorasidenib arm. All events were PD, and there were no death events in either treatment arm.
Based on an updated descriptive PFS analysis provided during review (DCO 7 March 2023), the median follow-up increased to 17.7 months in the vorasidenib arm. PFS was improved in the vorasidenib arm compared with the placebo arm with an HR of 0.35 (95% CI, 0.25, 0.49). 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. At 24 months, the progression-free survival rate (95% CI) was 58.8% (48.4, 67.8) for the vorasidenib arm and 26.2 (17.9, 35.3) for the placebo arm.

Subgroup analyses for PFS showed consistent results with the point estimator in favour of vorasidenib, including 1p19q co-deleted or not, number of prior surgeries, type of most recent surgery, or time from last surgery.

The key secondary endpoint TTNI was significantly improved in the vorasidenib arm compared with the placebo arm with an HR for TTNI of 0.26 (95% CI, 0.15, 0.43; P=0.000000019).
In the placebo arm, 58 patients (35.6%) had a TTNI event compared to n=19 (11.3%) in the vorasidenib arm. Median TTNI was 17.8 months (95%CI 15.0, NE) in the placebo arm and NE in the vorasidenib arm. Updated efficacy data (March 2023) showed a HR of 0.22 (95% CI: 0.14, 0.36). The median TTNI was not estimable in the vorasidenib arm (95%CI NE, NE) and 20.1 months (95%CI 17.5, 27.1) in the placebo arm.

Based on the current data, no valid conclusion is possible as to whether the benefit in PFS will result in increased overall survival or whether the same survival time will be achieved with the approach of postponing any treatment until the time of disease progression.

6.4 Safety

Safety data was presented for the vorasidenib arm without crossover and for the placebo arm pre-crossover. During review, the applicant provided updated safety data from DCO 6 September 2023 with n=174 patients in the vorasidenib arm and n=172 in the placebo arm.

The median treatment exposure in the vorasidenib arm was 22.8 months (range 1.0 – 41.9) and 14.3 months (range 0.4 – 32.4) in the placebo arm.
In the vorasidenib arm, there were n=73 (42%) patients with any dose modification and n=30 (17.2%) with any dose reduction. Treatment interruptions were reported in n=68 (39.1%) of patients, lasting for a median of 14.5 days.
In the placebo arm, n=52 (30.2%) of patients had any dose modification and n=13 (7.6%) had any dose reduction. Dose interruptions were reported in n=48 (27.9%) patients for a median number of 11 days.

Treatment emergent adverse events (TEAEs) of any grade were reported in 98.9% of patients in the vorasidenib arm and in 91.9% of patients in the placebo arm.
The most common (≥10%) TEAEs of any grade by preferred term (PT) in the vorasidenib arm were : increased alanine aminotransferase (ALT), COVID-, fatigue, increased aspartate aminotransferase (AST), increased gamma-glutamyltransferase (GGT), headache, diarrhoea, nausea, dizziness, seizure, constipation, arthralgia, insomnia, and paraesthesia.

Grade ≥3 TEAEs were reported in 28.2% of patients in the vorasidenib arm and in 15.1% of patients in the placebo arm. The most common TEAEs (≥2%) in the vorasidenib arm were increased ALT, increased AST, increased GGT, and seizure.

Serious adverse events (SAEs) were reported in 12.6% of patients in the vorasidenib arm and in 5.8% of patients in the placebo arm. Most of the events were singular events with the exception of seizure and increased ALT (1.1% vs. 0%)in the vorasidenib arm.

TEAEs leading to treatment discontinuation were reported in 5.7% of patients in the vorasidenib arm and in 1.2% in the placebo arm.

Elevated liver transaminases were defined as an adverse event of special interest (AESI). TEAEs from liver-related investigations, signs, and symptoms were reported in 52.3% of patients in the vorasidenib arm and in 23.3% of patients in the placebo arm. Grade ≥3 TEAEs were observed in 12.6% of patients in the vorasidenib arm and in 1.7% of patients in the placebo arm.
The SAE of hepatic failure (combined with a non-serious TEAE of hepatic necrosis) was reported in 1 patient in the vorasidenib arm. Another patient experienced an SAE of autoimmune hepatitis. In these 2 patients concurrent ALT or AST increase > 3 x ULN combined with total bilirubin increase > 2 x ULN in the absence of significantly increased ALP were observed. An additional 2 patients were reported in a safety update (1 in the vorasidenib arm, 1 after crossover to vorasidenib) to have experienced ALT or AST ≥3 × ULN, total bilirubin ≥2 × ULN, and ALP <2 × ULN (or missing) within 10 days of each other. The events resolved, including restoration of normal liver function, following discontinuation of the study treatment.
There were no such events in the placebo arm. Based on the liver-associated TEAEs observed under treatment with vorasidenib, hepatotoxicity is listed in the risk management plan as an important identified risk and included as a warning in the Information for healthcare professionals. Please refer to the Information for healthcare professionals for details of the dose recommendation in case of hepatotoxicity.

In addition, the applicant provided safety data from the overall glioma cohort (n=244), which included data from patients with glioma treated with doses of vorasidenib 40 mg QD in study AG881-C-004 (INDIGO) and 50 mg QD in Phase 1 studies AG881-C-002 (n=11) and AG120-881-C-001 (n=14).

Patients who crossed over to vorasidenib (n=52) in the INDIGO study were included in this safety population. There was no clinically meaningful difference between the safety results of the INDIGO study and the overall glioma cohort; therefore, the results are not presented in detail here.
Please refer to the Information for healthcare professionals for further information.
The INDIGO study is ongoing and will provide further safety updates.

6.5 Final clinical benefit-risk assessment

The INDIGO study showed a statistically significant improvement in the primary endpoint progression-free survival (PFS) with consistent results in prespecified subgroup analyses. The key secondary endpoint time to next intervention (TTNI) was also significantly improved in the vorasidenib arm compared to placebo.
Safety risks were adequately presented in the Information for healthcare professionals and considered manageable.

The overall benefit-risk assessment is positive for adult patients with residual or recurrent grade 2 IDH-positive astrocytoma and oligodendroglioma after initial surgery who are not in need of immediate adjuvant treatment after surgery.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Voranigo, film-coated tablets was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ 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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Voranigo

Composition

Active substances

Vorasidenib as vorasidenib hemicitric acid hemihydrate

Excipients

Voranigo 10 mg:
Tablet core: microcrystalline cellulose, croscarmellose sodium, silicified microcrystalline cellulose (contains microcrystalline cellulose and silica colloidal anhydrous), magnesium stearate, sodium lauryl sulfate (E487)
Tablet film-coating: hypromellose, titanium dioxide (E171), lactose monohydrate (0.63 mg), macrogol
Printing ink: black iron oxide, propylene glycol (E1520), hypromellose
Contains a maximum of 0.51 mg sodium per film-coated tablet.

Voranigo 40 mg:
Tablet core: microcrystalline cellulose, croscarmellose sodium, silicified microcrystalline cellulose (contains microcrystalline cellulose and silica colloidal anhydrous), magnesium stearate, sodium lauryl sulfate (E487)
Tablet film-coating: hypromellose, titanium dioxide (E171), lactose monohydrate (2.52 mg), macrogol
Printing ink: black iron oxide, propylene glycol (E1520), hypromellose
Contains a maximum of 2.1 mg sodium per film-coated tablet.

Pharmaceutical form and active substance quantity per unit

10 mg film-coated tablets
Each film-coated tablet contains 10 mg of vorasidenib (as 12.5 mg of vorasidenib hemicitric acid, hemihydrate). White to off-white, round, film-coated tablets, with a "10" printed in black on one side.
40 mg film-coated tablets
Each film-coated tablet contains 40 mg of vorasidenib (as 50.1 mg of vorasidenib hemicitric acid, hemihydrate). White to off-white, oblong, film-coated tablets, with a "40" printed in black on one side.

Indications/Uses

Voranigo is indicated for the treatment of adult patients with Grade 2 astrocytoma or oligodendroglioma with a susceptible isocitrate dehydrogenase-1 (IDH1) or isocitrate dehydrogenase-2 (IDH2) mutation

following surgical intervention and are not in immediate need of chemotherapy or radiotherapy (see section «Clinical efficacy»).

Dosage/Administration

Treatment should be initiated under the supervision of a physician experienced in the use of anti-cancer medicinal products.
The presence of an IDH1 or IDH2 mutation must be confirmed using an appropriate diagnostic test prior to initiation of treatment with vorasidenib.

Usual dosage

The recommended dose of vorasidenib in adults is 40 mg taken orally once daily for patients weighing at least 40 kg

Duration of treatment

Treatment should be continued until disease progression 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 the initiation of 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 «Warnings and precautions»).

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

Table 1: 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 «Warnings and precautions»)	Grade 1 ALT or AST increase >ULN to 3 x ULN *without* concurrent total bilirubin >2 x ULN	Continue Voranigo at current dose. Monitor liver laboratory tests weekly until recovery to <Grade 1.
	Grade 2 ALT or AST >3 to 5 x ULN *without* concurrent total bilirubin >2 x ULN	First Occurrence: Withhold Voranigo until recovery to ≤Grade 1 or baseline. • Recovery in ≤28 days, resume Voranigo at the same dose. • Recovery in >28 days, resume Voranigo at reduced dose (see Table 1). Recurrence: Withhold Voranigo until recovery to ≤Grade 1 or baseline, and resume Voranigo at reduced dose (see Table 1).
	Grade 3 ALT or AST >5 to 20 x ULN *without* concurrent total bilirubin >2 x ULN	First Occurrence: Withhold Voranigo until recovery to ≤Grade 1 or baseline. • Recovery in ≤28 days, resume Voranigo at reduced dose (see Table 1).

		• If not recovered in ≤28 days, permanently discontinue Voranigo. Recurrence: Permanently discontinue Voranigo.
	Grade 2 or 3 Any ALT or AST >3 to 20 x ULN *with* concurrent total bilirubin >2 x ULN	First Occurrence: Withhold Voranigo until recovery to ≤Grade 1 or baseline. • Resume Voranigo at reduced dose (see Table 1). Recurrence: Permanently discontinue Voranigo.
	Grade 4 Any ALT or AST >20 x ULN	Permanently discontinue Voranigo.
Other Adverse Reactions	Grade 3	First Occurrence: Withhold Voranigo until recovery to ≤Grade 1 or baseline. • Resume Voranigo at reduced dose (see Table 1). Recurrence: Permanently discontinue Voranigo.
	Grade 4	Permanently discontinue Voranigo.

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

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

Special populations

Elderly patients

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

Patients with renal disorders

No starting dose adjustment is recommended for patients with renal impairment (creatinine clearance [CL_{cr}] > 40 mL/min estimated by Cockcroft-Gault). The pharmacokinetics and safety of vorasidenib have not been studied in patients with CL_{cr} ≤ 40 mL/min or renal impairment requiring dialysis. Voranigo should be used with caution in patients with CL_{cr} ≤ 40 mL/min or who require dialysis (see sections «Warnings and precautions» and «Pharmacokinetics»).

Patients with hepatic disorders

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 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 «Warnings and precautions» and «Pharmacokinetics»).

Paediatric population

Voranigo is not authorised for use in the paediatric population.

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 vorasidenib (see section «Pharmacokinetics»). The tablets are to be swallowed whole with a glass of water and should not be split, crushed or chewed in order to ensure the full dose is administered.
Patients should be advised not to swallow the silica gel desiccant found in the tablet bottle.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section «Composition».

Warnings and precautions

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 Voranigo (see section «Undesirable effects»). Hepatic failure and hepatic necrosis were observed in one patient treated with Voranigo and autoimmune hepatitis was observed in one patient treated with Voranigo.

Liver enzymes (including ALT, AST, gamma-glutamyl transferase (GGT)) and total bilirubin must be monitored prior to starting Voranigo, 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 Voranigo based on the severity of the liver enzyme abnormalities (see section «Dosage/Administration»).

Women of childbearing potential / contraception for women and men

Voranigo could cause foetal harm when administered to a pregnant woman. Pregnancy testing is recommended in women of childbearing potential prior to starting treatment with Voranigo. Women of childbearing potential and males with female partners of childbearing potential should use effective contraception during treatment and for at least 3 months after the last dose of Voranigo.

Voranigo may decrease concentrations of hormonal contraceptives and, therefore, concomitant use of a barrier method of contraception is recommended during the treatment and for at least 3 months after the last dose (see sections «Interactions» and «Pregnancy, lactation»).

Patients with hepatic disorders

Vorasidenib should not be used in patients with pre-existing severe hepatic impairment (Child-Pugh class C) (see sections «Dosage/Administration» and «Pharmacokinetics»).

Patients with renal disorders

The pharmacokinetics and safety of vorasidenib have not been studied in patients with renal impairment (CLcr ≤ 40 mL/min) or renal impairment requiring dialysis. Voranigo should be used with caution in these patients (see sections «Dosage/Administration» and «Pharmacokinetics»).

Lactose

Voranigo contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose galactose malabsorption (rare hereditary diseases) 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’.

Interactions

Effect of other agents on the pharmacokinetics of 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 Voranigo.

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 Voranigo.

Other interactions

Gastric acid reducing agents

Multiple-dose administration of omeprazole (40 mg QD) did not affect plasma vorasidenib AUC and lowered vorasidenib C_{max} (28%).

Effect of vorasidenib on the pharmacokinetics of other agents

Cytochrome P450 (CYP) substrates with narrow therapeutic index

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

Sensitive substrates of CYP enzymes without narrow therapeutic index

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

Hormonal contraceptives

Vorasidenib may decrease concentrations of hormonal contraceptives and, therefore, concomitant use of a barrier method of contraception is recommended during the treatment and for at least 3 months after the last dose (see sections «Warning and precautions» and «Pregnancy, lactation»).

Other interactions

UGT1A4 Substrate

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

In vitro CYP studies

In vitro, vorasidenib has a strong induction effect on sensitive CYP3A4 substrates and a moderate induction effect on sensitive CYP2B6 and CYP2C19 substrates.

Interactions with transporters

In vitro data indicate that vorasidenib is an inhibitor of breast cancer resistance protein (BCRP). Vorasidenib does not inhibit P-glycoprotein (P-gp) and 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 OATP1B1 and OATP1B3

Pregnancy, lactation

Women of childbearing potential / contraception for women and men

Pregnancy testing is recommended in women of childbearing potential prior to starting treatment with Voranigo (see section «Warnings and precautions»).

Women of childbearing potential and males with female partners of childbearing potential should use effective contraception during treatment with Voranigo and for at least 3 months after the last dose. Since the effect of vorasidenib on the metabolism and efficacy of systemically acting hormonal contraceptives has not been investigated, barrier methods should be applied as a second form of contraception to avoid pregnancy (see sections «Warnings and precautions» and «Interactions»).

Pregnancy

There are no or limited amount of data from the use of vorasidenib in pregnant women. Studies in animals have shown reproductive toxicity (see section «Preclinical data»).

Voranigo is not recommended 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.

Lactation

It is unknown whether vorasidenib or its metabolites are excreted in breast milk. Breast-feeding should be discontinued during treatment with Voranigo 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 (see section «Preclinical data»). The clinical relevance of these

effects is unknown. Patients who are planning to conceive a child should be advised to seek reproductive counselling.

Effects on ability to drive and use machines

Vorasidenib has negligible influence on the ability to drive and use machines.

Undesirable effects

Summary of the safety profile

The description of adverse events is based on n=244 patients with Grade 2 astrocytoma or oligodendroglioma treated with vorasidenib 40 mg once daily.
The most common adverse reactions, including laboratory abnormalities, were ALT increased (57.4%), AST increased (43.4%), fatigue (33.2%), GGT increased (32.8%) and diarrhoea (20.9%).
The most common grade ≥ 3 adverse reactions were ALT increased (8.6%), AST increased (4.5%) and GGT increased (2.0%).
Serious adverse reactions were reported in 3 of 244 patients (1.2%) who received Voranigo. The most common serious adverse reaction was ALT increased (1.2%).
Permanent discontinuation of Voranigo was reported in 7 of 244 patients (2.9%). The most common grade ≥ 3 adverse reactions leading to permanent discontinuation was ALT increased (2.9%).
Dose interruptions due to an adverse reaction occurred in 42 of 244 patients (17.2%) treated with Voranigo. The most common adverse reactions requiring dose interrruption were ALT increased (13.9%) and AST increased (5.7%).
Dose reductions of Voranigo due to an adverse reaction occurred in 20 of 244 patients (8.2%). The most common adverse reaction requiring dose reduction was ALT increased (7.0%).

List of adverse reactions

Adverse reactions reported in patients with Grade 2 astrocytoma or oligodendroglioma treated with vorasidenib 40 mg once daily are listed below in Table 3 by MedDRA system organ class and by frequency.
The adverse reactions observed during the use of vorasidenib are arranged according to MedDRA system organ classes and the conventional frequencies as follows: “very common” (≥1/10), “common” (≥1/100, <1/10), “uncommon” (≥1/1 000, <1/100), “rare” (≥1/10 000, <1/1 000), “very rare” (<1/10 000), “not known” (frequency cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3: Adverse drug reactions reported in patients with Grade 2 astrocytoma or oligodendroglioma treated with vorasidenib 40 mg once daily (N=244)

System organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Very common	Platelet count decreased[a] (10.7%)
Metabolism and nutrition disorders	Common	Hyperglycaemia
		Hypophosphataemia[b]
		Decreased appetite
Gastrointestinal disorders	Very common	Diarrhoea[c] (20.9%)
		Abdominal pain[d] (11.9%)
Hepatobiliary disorders	Very common	Alanine aminotransferase increased[a] (57.4%)
		Aspartate aminotransferase increased[a] (43.4%)
		Gamma-glutamyl transferase increased[a] (32.8%)
	Common	Alkaline phosphatase increased[a]
General disorders and administration site conditions	Very common	Fatigue[e] (33.2%)

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

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Description of specific adverse reactions and additional information

Hepatobiliary disorders

Of the 244 patients treated with vorasidenib, 17.6% experienced elevations in ALT > 3 times the ULN and 7.8% experienced elevations in AST > 3 times the ULN. Among these patients, 0.8% 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 «Dosage/Administration» and «Warnings and precautions»).

Overdose

In the event of overdose, toxicity is likely to manifest as exacerbation of the adverse reactions associated with vorasidenib (see section «Undesirable effects»). Patients should be closely monitored and provided with appropriate supportive care (see sections «Dosage/Administration» and «Warnings and precautions»). There is no specific antidote for vorasidenib overdose.

Properties/Effects

ATC code

L01XM04

Mechanism of action

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

Pharmacodynamics

A therapeutic daily dose of vorasidenib was observed to decrease 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 vorasidenib, relative to tumours from subjects in the untreated group.

Clinical efficacy

The efficacy of Voranigo was evaluated in the INDIGO trial (Study AG881-C-004), a phase 3, randomised (1:1), multicentre, double-blind, placebo-controlled study of 331 adults and adolescents ≥ 12 years old weighing ≥ 40 kg. Eligible patients were required to have Grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 mutation or IDH2 R172 mutation and prior surgery for glioma including biopsy, sub-total resection, or gross total resection and were not in immediate need of chemotherapy or radiotherapy in the opinion of the investigator. Patients enrolled in this study had their most recent surgery at least 1 year and not more than 5 years before randomisation. Patients with non-enhancing tumours or minimal tumour enhancement, including non-nodular or non-measurable lesions, were permitted to enrol. The INDIGO trial excluded patients who received prior anti-cancer treatment, including chemotherapy or radiation therapy. IDH1 or IDH2 mutation status was prospectively determined using the Oncomine Dx Target Test.

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

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

Patient demographics and disease characteristics were balanced between the treatment arms. Among the 168 patients randomized to Voranigo, the median age was 41 years (range: 21 to 71 years), with 98.8% aged 18-64 years. A majority of patients were male (60.1%), 74.4% were White, 3.0% Asian, 1.2% Black, 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. In the Voranigo arm, 14% of patients had biopsy, 48% had sub-total resection and 51% had gross-total resection. The median time from the last surgery to randomization was 2.5 years. 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 summarized in Table 4. No events resulting in death occurred at the time of the analysis.

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 vorasidenib	 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.

Children from birth to less than 12 years of age

The European Medicines Agency has waived the obligation to conduct studies with Voranigo in a subset of the paediatric population from birth to less than 12 years of age for the treatment of low-grade glioma (see section «Dosage/Administration» for information on paediatric use).

Pharmacokinetics

The pharmacokinetics of vorasidenib have been characterized in patients with low-grade glioma with an IDH1 or IDH2 mutation and in healthy subjects.

Absorption

After a single 40 mg oral dose, the median time to C_{max} (T_{max}) was 2.0 hours, the mean C_{max} was 75.4 ng/mL (CV%: 44), and the mean AUC was 2,860 hr·ng/mL (CV%: 56). At steady-state, vorasidenib C_{max} was 133 ng/mL (CV%: 73) and AUC was 1,988 hr·ng/mL (CV%: 95).
Accumulation ratios were approximately 3.83 for C_{max} and 4.43 for AUC. Steady-state plasma levels were reached after 14 days of once-daily dosing.
The mean C_{max} and AUC increased by 3.1-fold and 1.4-fold, respectively, when vorasidenib was administered with a high-fat meal. Administration of vorasidenib with a low-fat meal resulted in increases in C_{max} and AUC of 2.3- and 1.4-fold, respectively (see section «Dosage/Administration»).

The mean absolute bioavailability of vorasidenib is 34%.

Distribution

Vorasidenib has a mean apparent volume of distribution of 3,930 L (CV%: 40). The mean plasma protein binding of vorasidenib is approximately 97% and is independent of concentration *in vitro*.

Metabolism

Vorasidenib is primarily metabolized 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.
Vorasidenib is predicted to have a strong induction effect on sensitive CYP3A4 substrates; weak induction effect on sensitive CYP2B6 and CYP2C19 substrates; and no relevant induction effect on sensitive CYP2C8 and CYP2C9 substrates (see section «Interactions»).
Co-administration of strong inhibitors of CYP1A2 (fluvoxamine) is predicted to result in a ≥ 5-fold increase in vorasidenib exposure, whilst co-administration with moderate CYP1A2 inducers (phenytoin and rifampicin) is predicted to have a weak induction effect on vorasidenib exposure (see section «Interactions»).
In vitro data indicate that vorasidenib is an inhibitor of BCRP. Vorasidenib does not inhibit P-gp and OATP1B1. Vorasidenib is predicted to have no relevant impact on sensitive P-gp and BCRP substrates. Vorasidenib is not a substrate of P-gp, BCRP, or OATP1B1 and OATP1B3 (see section «Interactions»).

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). The geometric mean metabolite to parent molar ratio is 1.17.

Elimination

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

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

Linearity/non-linearity

Vorasidenib C_{max} and AUC increases in a proportional manner between 10 and 200 mg.

Kinetics in specific patient groups

Elderly patients

Based on population pharmacokinetic modelling, no clinically meaningful effects on the pharmacokinetics of vorasidenib were observed in older patients up to 75 years (see section «Dosage/Administration»).

Patients with renal disorders

Based on population pharmacokinetic modelling, renal impairment (CL_{cr} > 40 mL/min) had no clinically significant effect on the pharmacokinetics of vorasidenib. The pharmacokinetics of vorasidenib in patients with CL_{cr} ≤ 40 mL/min or renal impairment requiring dialysis are unknown (see sections «Dosage/Administration» and «Warnings and precautions»).

Patients with hepatic disorders

Mild to moderate hepatic impairment (Child-Pugh class A or 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, 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 in patients with severe hepatic impairment (Child-Pugh class C) are unknown (see sections «Dosage/Administration» and «Warnings and precautions»).

Special patient groups

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

Gender

Based on population pharmacokinetic modelling, female patients were observed to have a 1.6-fold higher vorasidenib exposure as compared to male patients. No dose adjustment is needed.

Preclinical data

Repeated dose toxicity

The main target toxicities identified during repeat-dose toxicity studies concern liver, gastrointestinal tract, skin, kidney, muscle and reproductive organs. The margins of exposures for target organ toxicity relative to the human exposure were up to 26-fold and up to 8-fold (based on AUC) in rats and monkeys respectively compared to the human exposure at the 50 mg daily dose.

Genotoxicity

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

Carcinogenicity

Carcinogenicity studies have not been conducted with vorasidenib.

Reproductive toxicity

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 the ovaries (atrophy, interstitial cell vacuolation, decreased numbers of corpora lutea and/or higher numbers of large atretic follicles), uterus (epithelial hypertrophy and squamous metaplasia), cervix (epithelial hyperplasia) and vagina (epithelial hyperplasia and mucification), and estrous cycle variations. In male rats, effects were noted on the epididymis (cellular debris), seminal vesicle (atrophy), prostate (atrophy and inflammation) and testis (tubular degeneration and atrophy). These findings were observed at exposures that were higher (approximately 26-fold based on AUC) than patients' exposure at the 50 mg daily dose.

Vorasidenib caused embryo-foetal toxicity in pregnant rats and rabbits (higher incidence of resorptions, delayed ossification, reduced fetal weights, and visceral malformations for kidney and testes in rats). These effects occurred at exposures that were higher (61-fold (rats) and 11-fold (rabbits) based on AUC) compared to patients receiving the 50 mg daily dose.

Other information

Shelf life

Do not use this medicine after the expiry date marked as "EXP" on the pack.

Shelf life after opening

Once opened, the medicinal product should be used within 60 days.

Special precautions for storage

Keep out of the reach of children.
Do not store above 30°C.

Disposal

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

Authorisation number

69364 (Swissmedic)

Packs

Voranigo 10 mg: 30 film-coated tablets [A]
Voranigo 40 mg: 30 film-coated tablets [A]

Marketing authorisation holder

Servier (Suisse) S.A., 1202 Genève

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