Summary of the Risk Management Plan (RMP)

for Voranigo® (vorasidenib)

Product concerned (brand name): Voranigo®

Active substance: vorasidenib

Strength: 10 mg and 40 mg

Pharmaceutical form: film coated tablets

Version number: 0.2

Manufacturing Authorization Holder: Servier (Suisse) S.A.

Date of final sign off: 3 September 2024

Document date: 15 November 2024

Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Voranigo® is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the ”Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Voranigo® in Switzerland is the “Arzneimittelinformation / Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. Servier (Suisse) S.A. is fully responsible for the accuracy and correctness of the content of the published summary RMP of Voranigo®.

Part VI: Summary of the risk management plan

This is a summary of the risk management plan (RMP) for vorasidenib. The RMP details important risks of Voranigo, how these risks can be minimised, and how more information will be obtained about Voranigo risks and uncertainties (missing information).
Voranigo's Information for Healthcare Professionals (IHP) and its Patient Information give essential information to healthcare professionals and patients on how Voranigo should be used.
Important new concerns or changes to the current ones will be included in updates of Voranigo's RMP.

I. The medicine and what it is used for

Voranigo is authorized 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. It contains vorasidenib as the active substance and it is given by oral route.

II. Risks associated with the medicine and activities to minimise or further characterize the risks

Important risks of Voranigo, together with measures to minimize such risks for learning more about Voranigo's risks, are outlined below.
Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the Patient Information and IHP addressed to patients and healthcare professionals,
- Important advice on the medicine's packaging,
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly,
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report assessment - so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.
If important information that may affect the safe use of Voranigo is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Voranigo are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Voranigo. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information

Important identified risks	Hepatotoxicity
Important potential risks	• Use during pregnancy (embryo-foetal development toxicity) • Impairment of Fertility
Missing information	Use during breastfeeding

II.B Summary of important risks

Important identified risks: Hepatotoxicity

Evidence for linking the risk to medicine	Liver findings suggestive of hepatic enzyme induction have been observed in the pre-clinical setting. Liver enzyme elevations (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)) was added as an important identified risk of vorasidenib during the Phase 1 studies in subjects with hematologic malignancies and solid tumours including glioma. Liver enzyme elevations are among the most common adverse events reported in clinical studies, including the pivotal study. Evidence from these sources is considered to be a reliable predictor of how subjects will respond to treatment in clinical practice, by convention.
Risk factors and risk groups	Idiosyncratic drug-induced liver injury is the result of the interplay between the environment, drugs, and host (genetic, age, sex, immune factors, pre-existing diseases) (Yuan, 2013). The prevalence of DILI tends to be higher in hospitalized patients. Despite the lack of sufficient evidence that pre-existing chronic liver disease may increase the risk of DILI, DILI patients with preexisting liver diseases appear to be at increased risk for a more severe outcome (Li, 2022). Female sex may be associated with a greater risk of drug-induced acute liver failure (ALF). Similar to age, alcohol consumption is included as a risk factor in the CIOMS/RUCAM causality assessment scale and gives an extra point to patients with a known history of alcohol consumption, although no specific level of consumption has been defined (Panel, C.P.G. and European Association for the Study of the Liver, 2019). It is also suggested that patients with fatty liver disease or components of metabolic syndrome are at increased risk of DILI. In patients with DILI Diabetes mellitus has been associated with increased risk of mortality, and dyslipidaemia was associated with increased risk of chronic liver injury. Although patients with chronic liver disease may not in general have an increased risk of developing DILI, the consequences of a DILI episode in these patients might be more severe. (CIOMS DILI 2020). No specific risk factors or risk groups associated with use of vorasidenib or other IDH inhibitors are known.

Risk minimisation measures	Routine risk minimisation measures: Information for Healthcare Professionals sections "Dosage/Administration", "Warnings and precautions" and "Undesirable effects" and Patient Information sections "When is caution required when taking Voranigo?" and "Possible side effects?".

Important potential risks: Impairment of Fertility

Evidence for linking the risk to medicine	Effects on reproductive organs were seen in male and female rats during repeat-dose toxicity studies. The effects mainly consisted of loss/alteration of estrous cyclicity and atrophy (ovaries, uterus, cervix, vagina) for females. In males, degeneration of seminiferous tubules, cellular debris in the epididymides, epithelial atrophy in the prostate and seminal vesicles were observed. However, there are currently no data to understand the potential implications in human. No events of impaired fertility have been reported in vorasidenib clinical trials.
Risk factors and risk groups	Given the relatively young age of patients with glioma, including a range of adolescence in their late teens in an otherwise healthy patient population, sexually active women of childbearing potential and male patients whose partners are women of childbearing potential are at risk of possible impairment of male and female reproductive function with potential infertility.
Risk minimisation measures	Routine risk minimisation measures: Information for Healthcare Professionals section "Warnings and precautions", "Pregnancy, lactation" and Patient Information section "Can Voranigo be taken/used during pregnancy or breast-feeding?"

Important potential risk: Use during pregnancy (embryo-foetal development toxicity)

Evidence for linking the risk to medicine	In non-clinical embryo-foetal toxicity studies in rats or rabbits, vorasidenib was associated with maternal toxicity, early or late resorptions, lower foetal weights, delayed skeletal ossification and visceral malformations in rats (kidney and testis). There are no or limited amount of data from the use of vorasidenib in pregnant women. It is not known whether vorasidenib can cause foetal harm when administered to a pregnant woman.
Risk factors and risk groups	Sexually active women of childbearing potential and male patients whose partners are women of childbearing potential should use effective contraception during treatment with vorasidenib and for at least 3 months after the last dose are at risk patients treated with hormonal contraceptives not using a barrier method of contraception are also at increased risk, as vorasidenib may decrease the effectiveness of hormonal contraceptives.

Risk minimisation measures	Routine risk minimisation measures: Information for Healthcare Professionals sections "Warnings and precautions", "Interactions", "Pregnancy, lactation" and Patient Information sections “When is caution required when taking Voranigo” and "Can Voranigo be taken/used during pregnancy or breast-feeding?"

Missing information: Use during breastfeeding

Risk minimisation measures	Routine risk minimisation measures: Information for Healthcare Professionals sections "Pregnancy, lactation" and Patient Information section "Can Voranigo be taken/used during pregnancy or breast-feeding?"

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Voranigo.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Voranigo.