25 July 2025
EMA/OD/0000159477
EMADOC-360526170-2529813
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Voranigo (vorasidenib)
Treatment of glioma
EU/3/22/2737

Sponsor: Les Laboratoires Servier

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Product and administrative information

Product	
Designated active substance	Vorasidenib hemicitrate hemihydrate
Other name	Vorasidenib hemicitric acid, hemihydrate
International Non-Proprietary Name	Vorasidenib
Tradename	Voranigo
Orphan condition	Treatment of glioma
Sponsor's details:	Les Laboratoires Servier 50 Rue Carnot 92284 Suresnes Cedex France
Orphan medicinal product designation procedural history	
Sponsor/applicant	Les Laboratoires Servier
COMP opinion	8 December 2022
EC decision	13 January 2023
EC registration number	EU/3/22/2737
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Alexandre Moreau / Peter Mol
Applicant	Les Laboratoires Servier
Application submission	4 January 2024
Procedure start	25 January 2024
Procedure number	EMA/H/C/0006284
Invented name	Voranigo
Therapeutic indication	Voranigo as monotherapy is indicated for the treatment of recurrent or residual predominantly non enhancing Grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation in adult and adolescent patients aged 12 years and older and weighing at least 40 kg who only had surgical intervention and are not in immediate need of radiotherapy or chemotherapy. Further information on Voranigo can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/voranigo
CHMP opinion	24 July 2025
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	Elisabeth Johanne Rook / Bozenna Dembowska-Baginska
Sponsor's report submission	30 January 2024
COMP discussion	21-23 January 2025
COMP opinion (adoption via written procedure)	25 July 2025

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2023 was based on the following grounds:

"Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing vorasidenib hemicitrate hemihydrate was considered justified based on non-clinical studies in a valid model of the condition showing reduction in tumour growth as well as preliminary clinical data, in patients with glioma responding to treatment;
- the condition is chronically debilitating due to symptoms caused by the tumour compressing the surrounding brain tissue including headache, anorexia, nausea, vomiting, seizures, neurological deficits, personality changes and cognitive decline. The condition is also life-threatening, with a limited median overall survival;
- the condition was estimated to be affecting approximately 2.6 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing vorasidenib hemicitrate hemihydrate will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that showed responses in relapsed patients previously treated with temozolomide and/or radiotherapy. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are cumulatively fulfilled. The COMP therefore recommends the designation of this medicinal product, containing vorasidenib hemicitrate hemihydrate as an orphan medicinal product for the orphan condition: treatment of glioma".

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Gliomas are tumours that originate in the glial cells of the central nervous system (CNS), such as astrocytes, oligodendrocytes and ependymal cells, and are therefore located in the brain or the spinal cord. This heterogeneous group of tumours makes up about 30% of all brain and CNS tumours, and 80% of all malignant brain tumours. The three most common types of glioma are ependymomas, oligodendrogliomas, and astrocytomas, classified based on their phenotypic cell characteristics and molecular markers. Glioblastoma multiforme (grade 4 astrocytomas) is the most common and aggressive subtype of glioma, accounting for up to 50% of all primary brain gliomas (Zhang et al., 2012).

The aetiology of gliomas remains largely unknown. Several occupations, environmental carcinogens, dietary factors, and viruses have been reported to be associated with an elevated glioma risk. However, the only environmental factor that is unequivocally associated with an increased risk of brain tumours, including gliomas, is X-irradiation of the brain in the context of treatment for another disease. The majority of gliomas occur sporadically: familial gliomas account for approximately 5% of malignant gliomas, and less than 1% of gliomas are associated with inherited mutations of highly penetrant genes related with rare syndromes.

The fifth edition of WHO CNS classifies 'Gliomas', 'Glioneuronal Tumours', and 'Neuronal Tumours' into 6 different families: (1) 'Adult-type diffuse gliomas' (the majority of primary brain tumours in adults); (2) 'Paediatric-type diffuse low-grade gliomas' (expected to have good prognoses); (3) 'Paediatric-type diffuse high-grade gliomas' (expected to behave aggressively); (4) 'Circumscribed astrocytic gliomas' ("circumscribed" referring to their more solid growth pattern, as opposed to the inherently "diffuse" tumours in groups 1, 2, and 3); (5) 'Glioneuronal and neuronal tumours' (a diverse group of tumours, featuring neuronal differentiation); and (6) 'Ependymomas' (Louis et al., 2021).

IDH1/2 mutations (which includes the proposed target population for vorasidenib) occur early in the course of the disease and are preserved through progression. IDH mutation results in accumulation of 2-HG, an oncometabolite that induces epigenetic changes that impair cellular differentiation and gliomagenesis. IDH1 and IDH2 mutations occur early in gliomagenesis and IDH1 mutations are the most frequent genetic events in Grade 2 and 3 diffuse gliomas, occurring in approximately 80% of cases, while IDH2 mutations are far less frequent (approximately 4%) (Cohen et al, 2013).

The approved therapeutic indication "*Voranigo as monotherapy is indicated for the treatment of recurrent or residual predominantly non enhancing Grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation in adult and adolescent patients aged 12 years and older and weighing at least 40 kg who only had surgical intervention and are not in immediate need of radiotherapy or chemotherapy* (see section 5.1)" falls within the scope of the designated orphan condition "treatment of glioma".

Intention to diagnose, prevent or treat

The medical plausibility is confirmed by the positive benefit/risk assessment of the CHMP.

Chronically debilitating and/or life-threatening nature

The sponsor claimed that there have been no significant changes to the chronically debilitating or life-threatening nature of IDH mutant glioma since the grant of the orphan designation for vorasidenib in January 2023.

The sponsor discussed the chronically debilitating nature of the condition with multiple tumour- or treatment-related symptoms including seizures, headaches, fatigue, memory changes, cognitive decline, or other neurological dysfunctions depending on the tumour location. Many of these symptoms worsen over time due to diffuse infiltrative glioma growth or because of adverse effects from treatments such as surgery, radiation therapy (RT), chemotherapy, and antiepileptic medications (Dietrich and Wen, 2022; van den Bent and Loeffler, 2022).

The sponsor also discussed the life-threatening nature of the condition with an estimated median overall survival (OS) for Grade 2/3 diffuse gliomas ranging from 3 years to 14 years (Buckner et al, 2016; Lassman et al, 2022; van den Bent et al, 2021).

The COMP has previously accepted the condition is chronically debilitating due to symptoms caused by the tumour compressing the surrounding brain tissue including headache, anorexia, nausea, vomiting, seizures, neurological deficits, personality changes and cognitive decline. The condition is also life-threatening, with a limited median overall survival.

This view is still retained by the COMP for this procedure.

Number of people affected or at risk

At the time of orphan designation in 2023, the prevalence was agreed to be 2.6 in 10,000 by the COMP and the sponsor argued that there have been no significant changes to this previously adopted figure.

The sponsor calculated the prevalence based on the prevalence reported for brain and central nervous system (CNS) cancers from cancer registries in Germany, NORDCAN countries, Netherlands and Spain.

Table 1. European cancer registry incidence and prevalence of brain and CNS cancer (excluding endocrine tumours)

Country/ Region	Reporting Period	Incidence	Prevalence (cases/prevalence)	Population †	Reference
Germany	2019	Men: 3838 7.1** Women: 2968 5.1**	5-year* n=13163 1.6/10 000 20 years* n=30,174 3.6/10,000	83,019,213	German Centre for Cancer Registry Data ZfKD – accessed on 15 December 2023

Country/ Region	Reporting Period	Incidence	Prevalence (cases/prevalence)	Population †	Reference
Nether-lands (Brain only)	2022	Total cases: 1392 5.98/100 000**	5-year* n=2173 1.23/10,000 20 year* 4457 2.5/10,000	17,590,672	Netherlands Cancer Registry (NCR) accessed on 07 December 2023
Spain	2023 for incidence 2020 for prevalence	Total cases:4072 6.3/100 000**	5 Year* n=6897 1.46/10,000 Total prevalence n=12 952 2.74/10 000	47,332,614	Redecan incidence – accessed on 15 December 2023 Redecan prevalence – accessed on 15 December 2023

*based on individuals diagnosed within the last 5 years, 10 years, 20 years.
**per 100,000 age standardised according to the old european standard population.
† population extracted from eurostat for the reporting year.

In addition, the most recent Global Cancer Observatory (GLOBOCAN) dataset released in 2020 estimate that 129,465 people are affected by brain and central nervous system cancer in the EU 27, corresponding to a 5-year prevalence of 2.91/10 000 (Cancer 2020). Considering that glioma accounts for 84% (Girardi, Rous et al. 2021) of malignant brain tumours, the prevalence of gliomas can be estimated at 2.44 cases per 10,000 persons.

Last update of Orphanet data (July 2023 available at Orphadata) reported 2.6 in 10,000 persons for glioma prevalence. A targeted literature search using Pubmed was conducted to identify the recent published literature and update data on glioma provided in the initial submission. However, no recent data allowing to revise the initial estimate of glioma prevalence data were found.

In addition to these glioma data, the sponsor identified two publications focusing on relevant histology (astrocytoma and oligodendroglioma) and eventually IDH mutation status.

One of the publications referenced in the original submission (Crocetti, Trama et al. 2012), provides prevalence of Glial tumour in EU 27, including the detail per type of brain tumour. Based on data from several populations - based on cancer registries across Europe – the complete prevalence in EU27 of astrocytic tumours was estimated to be 20.4/ 100 000 and 2.7/100 000 for Oligodendroglial tumours (Crocetti, Trama et al. 2012). This represents a total prevalence of 2.31/10 000 for astrocytoma and oligodendroglioma glioma types as targeted in the proposed therapeutic indication.

A recent publication providing incidence data according to full molecular status and using national registry cancer in Belgium was identified. Details are provided in Table 2.

Table 2. Full molecular status using the Belgium national registry cancer:

Country /Region	Reporting Period	Incidence	Estimated Prevalence Rate/10 000	Population †	Registry	Reference
Belgium	2017-2019	Diffuse Adult type glioma: 8,55 per 100.000 persons year WHO Grade 4 lesions regardless IDHm status: 6,75 per 100.000 person years* Astrocytoma grade 2: 0,6 per 100.000 person years Astrocytoma grade 3: 0.48 per 100.000 person years Oligodendroglioma: 0,52 per 100.000 person years	Diffuse Adult type glioma: 4.16 Grade 4: 3.29 Astrocytoma grade 2:0.25 Astrocytoma grade 3: 0.20 Oligodendroglioma: 0.35	11,697,557	Belgian Cancer Registry (BCR)	Pinson et al. 2024 (data transformed into the 2021 WHO classification)

The prevalence data provided in this table are estimated prevalence. If prevalence is not available, crude approximation based on incidence could be used. As done in the initial submission, prevalence could be estimated using the estimated average duration of 4.87 years for glioma. A corresponding duration was calculated for astrocytoma (estimated duration = Prevalence (20.4)/incidence rate (4.8) = 4.25 years) and oligodendroglioma (estimated duration = Prevalence (2.7)/incidence rate (0.4) = 6.75 years).

Based on the above data presented the COMP considered that the prevalence for glioma has not changed since the initial orphan designation and the figure of 2.6 in 10,000 persons is acceptable.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

The sponsor presented a list of medicinal products authorized for the treatment of glioma in paediatric and adult patients in at least 1 EU member state.

Table 3. List of medicinal products authorised in at least 1 EU member state for the treatment of glioma in paediatric and adult patients

Active Substance or INN (invented name)	**Indication**	**Satisfactory method**
Temozolomide (Temodal) + various generics:	Treatment of: • adult patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and subsequently as monotherapy treatment. • children from the age of 3 years, adolescents, and adult patients with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy.	No: Voranigo is indicated for recurrent or residual predominantly non enhancing Grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation while Temozolomide is for the glioblastoma multiforme which is Grade 4 or anaplastic astrocytoma which is Grade 3.
Carmustine (Carmustine Medac - previously Carmustine Obvius) + various generics	Treatment of: • the following malignant neoplasms as a single agent or in combination with other antineoplastic agents and/or other therapeutic measures (radiotherapy, surgery) in adults for – Brain tumors (glioblastoma, brain-stem gliomas, medulloblastoma, astrocytoma and ependymoma), brain metastases – […]	No: Voranigo is indicated for adolescents from the age of 12 years
Dabrafenib (Finlee)	Treatment of: • Low-grade glioma: in combination with trametinib for the treatment of paediatric patients aged 1 year and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy. • - High-grade glioma: in combination with trametinib for the treatment of paediatric patients aged 1 year and older with high-grade glioma (HGG) with a BRAF V600E mutation who have received at least one prior radiation and/or chemotherapy treatment.	No: Voranigo is indicated for the treatment of recurrent or residual predominantly non enhancing Grade 2 astrocytoma or oligodendroglioma with an IDH1-R132 mutation or IDH2-R172 mutation who are not in immediate need of radiotherapy or chemotherapy.

Active Substance or INN (invented name)	**Indication**	**Satisfactory method**
Trametinib (Spexotras)	Treatment of: • Low-grade glioma: in combination with dabrafenib for the treatment of paediatric patients aged 1 year and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy. • High-grade glioma: in combination with dabrafenib for the treatment of paediatric patients aged 1 year and older with high-grade glioma (HGG) with a BRAF V600E mutation who have received at least one prior radiation and/or chemotherapy treatment.	No: Voranigo is indicated for the treatment of recurrent or residual predominantly non enhancing Grade 2 astrocytoma or oligodendroglioma with an IDH1-R132 mutation or IDH2-R172 mutation who are not in immediate need of radiotherapy or chemotherapy.
Carmustine (Gliadel, implant)	Indicated for: • the treatment of adult patients with newly diagnosed high-grade malignant glioma as an adjunct to surgery and radiation. As an adjunct to surgery for the treatment of adult patients with recurrent histologically proved glioblastoma multiforme and for whom surgical resection is indicated.	No: Voranigo is indicated for adolescents from the age of 12 years.
Carmustine (Carmustine Creative Pharma Solutions)	Indicated in adults as palliative therapy as a single agent or in established combination therapy with other approved chemotherapeutic agents in the following: • brain tumours - glioblastoma, medulloblastoma, astrocytoma and metastatic brain tumours.	No: Voranigo is indicated for adolescents from the age of 12 years
Lomustine (lomustine "Medac")	As palliative or supplementary treatment, usually in combination with radiotherapy and/or surgery as part of multiple drug regimens in: • brain tumours (primary or metastatic) All paediatric age groups	No: the indication of Voranigo is not limited to cases of "*palliative or supplementary treatment, usually in combination with radiotherapy and/or surgery as part of multiple drug regimens*".

Abbreviations: EU = European Union; INN = International Non-proprietary Name.

The therapeutic indication for Voranigo is "Voranigo as monotherapy is indicated for the treatment of recurrent or residual predominantly non enhancing Grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation in adult and adolescent patients aged 12 years and older and

weighing at least 40 kg who only had surgical intervention and are not in immediate need of radiotherapy or chemotherapy (see section 5.1)".

Voranigo is indicated for patients with glioma who are not candidates for immediate chemotherapy and radiotherapy after resection of the tumour. There are no other therapies authorized in this very specific setting, and therefore significant benefit does not have to be assessed.

Significant benefit

Not applicable.

4. COMP position adopted on 25 July 2025

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of glioma (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 2.6 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to symptoms caused by the tumour compressing the surrounding brain tissue including headache, anorexia, nausea, vomiting, seizures, neurological deficits, personality changes and cognitive decline. The condition is also life-threatening, with reduced life expectancy;
- at present, no satisfactory method has been authorised in the European Union for the treatment of the entirety of patients covered by the therapeutic indication of Voranigo.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Voranigo, vorasidenib hemicitrate hemihydrate, vorasidenib for treatment of glioma (EU/3/22/2737) is not removed from the Community Register of Orphan Medicinal Products.