Report VORANIGO® - Vorasidenib

Product & Mechanism of action

Substance: Vorasidenib

Brand Name: Voranigo

Originator/licensee: Les Laboratoires Servier

Classification: NCE

ATC code: C10AX

Orphan Status:
Eu: Yes
Us: Yes

Mechanism of action: Vorasidenib, an antineoplastic agent, is an inhibitor that targets the mutant IDH1 and IDH2 enzymes. In pts. with astrocytoma or oligodendroglioma, IDH1 and IDH2 mutations lead to overproduction of the oncogenic metabolite 2-hydroxyglutarate, which results in impaired cellular differentiation contributing to oncogenesis. By inhibiting the IDH1 and IDH2 mutated proteins, vorasidenib inhibits the abnormal production of 2-HG thereby leading to differentiation of malignant cells and a reduction in their proliferation [1].

Authorized indications Licensing status

Authorized Indication:
EMA: Vorasidenib as monotherapy is indicated for the treatment of predominantly non-enhancing Grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation in adult and adolescent pts aged ≥12 years and weighing ≥40 kg who only had surgical intervention and are not in immediate need of radiotherapy or chemotherapy [1].

FDA: Vorasidenib is indicated for the treatment of adult and paediatric pts ≥12 years with Grade 2 astrocytoma or oligodendroglioma with a susceptible IDH1 or IDH2 mutation following surgery including biopsy, sub-total resection, or gross total resection [2].

Route of administration: OS

Licensing status
EU CHMP P.O. date: 24/07/2025
FDA M.A. date: 06/08/2024

EU Speed Approval Pathway: No
FDA Speed Approval Pathway: Yes

ABBREVIATIONS:
AE: Adverse Event
CHMP: Committee for Medicinal Products for Human Use
CI: Confidential Interval
ECOG: Eastern Cooperative Oncology Group
HR: Hazard Ratio
IDH1: Isocitrate dehydrogenase-1
IDH2: Isocitrate dehydrogenase-2
ITT: Intention to treat
M.A.: Marketing Authorization
PFS: Progression free survival
P.O.: Positive Opinion
PS: Performance Status
Pts: Patients
WHO: World Health Organization

Essential therapeutic features

Summary of clinical EFFICACY:
INDIGO (NCT04164901) was an international, double-blind, placebo-controlled, phase 3 trial to assess efficacy and safety of vorasidenib therapy in pts. with residual or recurrent grade 2 IDH-mutant glioma.

Eligible pts. were ≥12 years of age, had residual or recurrent histologically confirmed grade 2 oligodendroglioma or astrocytoma, according to WHO 2016 criteria, with centrally confirmed IDH1 and IDH2 mutation status.
Pts. had to have a Karnofsky of ≥80, ≥1 previous surgery (most recent surgery occurring between one year and fine years before randomization). Other anticancer treatment for glioma and/or use of glucocorticoids were not allowed.

Pts. (n=331) were randomly assigned in a 1:1 ratio to receive vorasidenib (n=168) or placebo (n=163). Vorasidenib was administered orally at the dose of 40 mg daily.

The primary endpoint was PFS in the ITT population [3].

Results are provided in table 1.

Table 1: primary endpoint

	Vorasidenib (n=168)	Placebo (n=163)
Median Progression-Free Survival (PFS)	27.7 months	11.1 months
Number of Events, n (%)		
Progressive disease	47 (28)	88 (54)
Death	0	0
HR (95% IC)	0.39 (0.27, 0.56)	
p-value	<0.0001	

Summary of clinical SAFETY:
Most common grade ≥3 AEs are summarized in table 2 [3].

Table 2: most common grade ≥3 AEs

Grade ≥3 AEs	Vorasidenib (n=167)	Placebo (n=163)
	n. (%)	
Any adverse event	38 (22.8)	22 (13.5)
Increased alanine aminotransferase	16 (9.6)	0
Increased aspartate aminotransferase	7 (4.2)	0
Increased γ-glutamyltransferase	5 (3.0)	2 (1.2)
Seizure	7 (4.2)	4 (2.5)
Fatigue	1 (0.6)	2 (1.2)
Diarrhoea	1 (0.6)	1 (0.6)

Ongoing studies:
- ***For the same indication:*** Yes
- ***For other indications:*** No

Discontinued studies (for the same indication): No

References:

[1] https://www.ema.europa.eu/en/medicines/human/EPAR/voranigo
[2] https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/218784s000lbl.pdf
[3] https://www.nejm.org/doi/pdf/10.1056/NEJMoa2304194
[4] https://www.researchgate.net/publication/221730949_Epidemiology_of_glial_and_non-glial_brain_tumours_in_Europe
[5] https://pmc.ncbi.nlm.nih.gov/articles/PMC4109985/

NHS impact

Cost of therapy:
Not available yet.

Epidemiology:
In Europe, the annual incidence of gliomas is approximately of 6 cases/100,000 people [4]. Most gliomas are astrocytic (70%) or oligodendroglia tumours (9%) [5].

POSSIBLE PLACE IN THERAPY:
The combination of radiation and chemotherapy is the standard of care for the postoperative treatment of pts. with IDH-mutant grade 3 gliomas and high risk for early disease progression IDH-mutant grade 2 gliomas. However, treatment is not curative and it is associated with potential long-term toxic effects. To delay these potential long-term toxic effects, a watch-and-wait period is considerable for pts with IDH-mutant grade 2 gliomas [3].

The addition of Vorasidenib to the above regimens could represent a new opportunity for these pts.

OTHER INDICATIONS IN DEVELOPMENT: -

SAME INDICATION IN EARLIER LINE(S) OF TREATMENT: -

OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION: - .

*Service reorganization: No
*Possible off label use: Yes