PDL DRUG REVIEW

Proprietary Name: Voranigo®
Common Name: vorasidenib
PDL Category: Antineoplastics

Pharmacology/Usage: Vorasidenib, the active ingredient of Voranigo®, is an isocitrate dehydrogenase-1 (IDH1) and isocitrate dehydrogenase-2 (IDH2) inhibitor. It is a small molecule inhibitor that targets IDH1 and IDH2 enzymes. In cell-based and in vivo tumor models expressing IDH1 or IDH2 mutated proteins, vorasidenib decreased production of 2-hydroxyglutarate (2-HG) and partially restored cellular differentiation.

Indication: For the treatment of adult and pediatric patients 12 years and older with Grade 2 astrocytoma or oligodendroglioma with a susceptible isocitrate dehydrogenase-1 (IDH1) or isocitrate dehydrogenase-2 (IDH2) mutation following surgery including biopsy, sub-total resection, or gross total resection.

There is no pregnancy category for this medication; however, the risk summary indicates that based on findings from animal studies and its mechanism of action, Voranigo® can cause fetal harm when administered to a pregnant woman. There are no available data on use in pregnant women to inform a drug-associated risk. Advise pregnant women of the potential risk to a fetus. Verify pregnancy status in females of reproductive potential prior to starting Voranigo®. In addition, advise females of reproductive potential to use effective nonhormonal contraception during treatment and for 3 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose. The safety and efficacy of use have not been established in the pediatric population younger than 12 years.

Dosage Form: Film-Coated Tablets: 10mg and 40mg.

Swallow tablets whole with water; do not split, crush, or chew.

Recommended Dosage: Before starting Voranigo®, assess blood chemistry and liver laboratory tests.

Select patients with Grade 2 astrocytoma or oligodendroglioma for treatment with Voranigo® based on the presence of IDH1 or IDH2 mutations in tumor specimens. An FDA-approved test for detection of IDH1 or IDH2 mutations in Grade 2 astrocytoma or oligodendroglioma for selecting patients for treatment with Voranigo® is not available.

The recommended dosage in adult patients is 40mg PO QD until disease progression or unacceptable toxicity.

The recommended dosage in pediatric patients 12 years and older is based on body weight:

- Patients weighing ≥40kg: 40mg PO QD.
- Patients weighing <40kg: 20mg PO QD.

Continue treatment with Voranigo® until disease progression or unacceptable toxicity.

Take tablets with or without food. Take Voranigo® tablets at about the same time each day. If a dose is missed, take the missed dose as soon as possible within 6 hours. If a dose is missed by more than 6 hours, skip the missed dose and take the next dose at the scheduled time. If vomiting occurs after taking a dose, do not take a replacement dose, and take the next dose at the scheduled time on the following day.

Refer to the prescribing information for information on dosage modifications, management, and monitoring for adverse reactions.

Dose adjustments are not recommended for patients with creatinine clearance (CL-cr) >40ml/min. The pharmacokinetics and safety of vorasidenib in patients with CL-cr ≤40ml/min or renal impairment requiring dialysis have not been studied. For patients with CL-cr ≤40ml/min or who require dialysis, monitor for increased adverse reactions and modify the dosage for adverse reactions as recommended. Dose adjustments are not recommended for patients with mild or moderate hepatic impairment. The pharmacokinetics and safety of vorasidenib in patients with severe hepatic impairment have not been studied. For patients with severe hepatic impairment, monitor for increased adverse reactions and modify the dosage for adverse reactions as recommended.

Drug Interactions: Avoid concomitant use of Voranigo® with strong and moderate CYP1A2 inhibitors. If concomitant use of moderate CYP1A2 inhibitors cannot be avoided, monitor for increased adverse reactions and modify the dosage for adverse reactions as recommended.

Avoid concomitant use of Voranigo® with moderate CYP1A2 inducers and smoking tobacco.

Avoid concomitant use of Voranigo® with CYP3A substrates, where a minimal concentration change may lead to reduced therapeutic effect.

Concomitant use of Voranigo® may decrease the concentrations of hormonal contraceptives, which may lead to contraception failure and/or an increase in breakthrough bleeding. If concomitant use cannot be avoided, use with nonhormonal contraception methods.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Voranigo®) minus reported % incidence for placebo for all grades. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included fatigue (1%), COVID-19 (4%), seizure (1%), musculoskeletal pain (1%), diarrhea (8%), constipation (1%), abdominal pain (1%), and decreased appetite (5.3%).

Laboratory abnormalities included increased ALT (34%), increased AST (26%), increased creatinine (4%), decreased calcium (3%), increased glucose (5.7%), increased GGT (28%), decreased phosphate (3.1%), increased potassium (3%), increased ALP (3%), increased hemoglobin (9.9%), decreased lymphocytes (3%), decreased leukocytes (1%), decreased neutrophils (2%), and decreased platelets (7.7%).

Voranigo® can cause hepatic transaminase elevations, which can lead to hepatic failure, hepatic necrosis, and autoimmune hepatitis. Monitor liver laboratory tests (ALT, AST, GGT, total bilirubin, and alkaline phosphatase) prior to the start of Voranigo®, every 2 weeks during the first 2 months of treatment, then monthly for the first 2 years of treatment, and as clinically indicated, with more frequent testing in patients who develop transaminase elevations. Reduce the dose, withhold, or permanently discontinue Voranigo® based on severity.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Servier Pharmaceutical LLC

Analysis: The efficacy of Voranigo® was assessed in the INDIGO trial, a randomized, multicenter, double-blind, placebo-controlled study that included patients (N=331) who were required to have IDH1- or IDH2-mutant Grade 2 astrocytoma or oligodendroglioma with prior surgery including biopsy, sub-total resection, or gross total resection. Patients were required to have measurable, non-enhancing disease; patients with centrally confirmed minimal, non-nodular, non-measurable enhancement were eligible.

Patients were randomized to receive either Voranigo® 40mg or placebo until disease progression or unacceptable toxicity. IDH1 or IDH2 mutation status was prospectively determined by the Life Technologies Corporation Oncomine Dx Target Test. Patients who were randomized to placebo were

allowed to cross over to receive Voranigo® after documented radiographic disease progression. Tumor assessments were performed every 12 weeks. The median age of included patients was 40 years (range 16 to 71), while 57% were male, 78% were white, 52% with oligodendroglioma, and 48% with astrocytoma. In addition, 79% had one prior surgery and 21% had ≥2 prior surgeries.

The major efficacy outcome was progression-free survival (PFS) as evaluated by a blinded independent review committee (BIRC) per modified Response Assessment in Neuro-Oncology for Low Grade Glioma (RANO-LGG) criteria. Efficacy results are presented in the table below, which was adapted from the prescribing information.

	Voranigo® (N=168)	Placebo (N=163)
Progression-free survival (PFS)		
Number of events, n (%)		
Progressive Disease	47 (28%)	88 (54%)
Death	0	0
Hazard ratio; p-value	0.39; p<0.0001	

The major efficacy analyses are supported by a prospectively defined key secondary outcome measure time to next intervention (defined as the time from randomization to the initiation of the first subsequent anti-cancer therapy or death due to any cause). The median time to next intervention was not reached for patients in the Voranigo® arm and 17.8 months for patients in the placebo arm (HR 0.26, p<0.0001).

Place in Therapy: Voranigo® is an isocitrate dehydrogenase-1 (IDH1) and IDH2 inhibitor indicated for the treatment of adult and pediatric patients 12 years and older with Grade 2 astrocytoma or oligodendroglioma with a susceptible IDH1 or IDH2 mutation following surgery including biopsy, sub-total resection, or gross total resection. Before starting treatment, assess blood chemistry and liver laboratory tests. The efficacy of Voranigo® was assessed in a randomized, double-blind, placebo-controlled study that included patients required to have IDH1- or IDH2-mutant Grade 2 astrocytoma or oligodendroglioma with prior surgery including biopsy, sub-total resection, or gross total resection. The major efficacy outcome was progression-free survival, and Voranigo® was significantly more effective than placebo for this primary outcome (HR 0.39, p<0.0001).

Summary

It is recommended that Voranigo® should be non-recommended in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Recommended**
☒ **Non-Recommended with Conditions**

References

[1] Voranigo [package insert]. Boston, MA: Servier Pharmaceuticals LLC; 2024.