Vorasidenib (VORANIGO)
National Drug Monograph
March 2025

VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA National Formulary Committee drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA APPROVAL INFORMATION	
Description / MOA	A small molecule inhibitor that targets isocitrate dehydrogenase -1 and 2 (IDH1 and IDH2) enzymes.
Indication Under Review	An IDH1 and IDH2 inhibitor for Grade 2 astrocytoma or oligodendroglioma with a susceptible IDH1 or IDH2 mutation following surgery (including biopsy, sub-total resection, or total resection).
Dosage Regimen	40 mg orally daily with or without food
Dosage Forms Under Review	10mg and 40mg tablets

EFFICACY CONSIDERATIONS	
Trial	**INDIGO**[1]
Design	International, DB, PC, Phase 3
Population	Residual or recurrent **Grade 2 oligodendroglioma or astrocytoma with centrally confirmed IDH1 or IDH2 mutation**, Karnofsky PS ≥80, at least 1 prior surgery (biopsy, sub-total resection, gross-total resection), no use of corticosteroids for glioma, measurable (non-enhancing) disease. **Excluded** uncontrolled seizures, brain-stem involvement, clinically relevant functional neurocognitive deficits, baseline QTc ≥450 msec, pregnancy, lactation, concomitant CYP3A4 or CYP2C9 substrates with narrow therapeutic index
Demographics	Med Age: 40.5; Male 60.1%; KPS 100: 53.6%; Oligo 52.4%; IDH1+: 97%; IDH2+: 3%; 1p/19q co-deleted 52.4%
Intervention	Vorasidenib 40mg orally daily
Comparator	Matching placebo orally daily
Results	• Med follow-up: 14 months • mPFS by BIRC 27.2 vs 11.2 months (image-based) HR 0.39 (95%CI 0.27-0.56) • Time to next intervention: HR 0.26 (95%CI 0.15-0.43); alive/no second intervention (24 m): 84.4 v 27% • 32% crossover to vorasidenib in placebo group (study unblinded after 2nd interim analysis) • OS: immature
Notes	**NCCN: good KPS oligo or astro Grade 2** No residual disease: observation Residual or recurrent and RT plus chemo not preferred: IDH inhibitor or observation **NCCN: poor KPS oligo or astro** RT + concurrent or adjuvant temozolomide or IDH inhibitor or palliative care or temozolomide (2B) **VA Oncology Clinical Pathway: <u>Grade 2 IDH-mutant Astrocytoma or Oligodendroglioma without high-risk features</u> (age, neurologic symptoms, contrast-enhancing tumor, etc) with minimal residual non-enhancing disease** Currently, surveillance; imminent change to vorasidenib **Alternative:** Temozolomide

SAFETY CONSIDERATIONS	
Boxed Warnings	None
Contraindications	None
Other Warnings	Hepatoxicity (monitor q 2weeks for first 2 months, then monthly); EF toxicity (non-hormonal contraception due to drug interaction);
Top 5 AEs	Fatigue, headache, musculoskeletal pain, diarrhea, nausea
Drug Interactions	potential drug-drug interactions: CYP1A2 inhibitors/Inducers; Certain CYP3A4 substrates

VHA PLACE IN THERAPY	**Potential Use in VHA** 1. Low-grade gliomas (WHO grade 2 and 3) are slow growing but remain incurable with most patients experiencing recurrence and progression. 2. A large percentage of low-grade gliomas have a mutation in the isocitrate dehydrogenase 1 & 2 enzymes (IDH1 and IDH2), IDH mutation with co-deletion of chromosome 1p and 19q defines oligodendroglioma and IDH mutation without a codeletion defines astrocytoma. 3. Existing treatments for Grade 2 glioma include surgery, radiation, and chemotherapy. Most patients receive surgery (biopsy, sub-total resection or gross total resection) with radiation or chemotherapy given as adjuvant therapy. Surveillance is an option for patients at low risk of early progression. Radiation therapy prolongs progression, does not affect overall survival, and may produce cognitive dysfunction. Chemotherapy with temozolomide is generally followed by recurrence and progression. 4. Vorasidenib inhibits IDH1 and IDH2 and penetrates the blood brain barrier. In the INDIGO trial it increased progression-free survival versus placebo and delays the need for a 2nd intervention compared to placebo; overall survival results are still immature. Toxicity is relatively low, but patients must be evaluated for potential hepatoxicity. 5. Ivosidenib is being studied in combination with immunotherapy or temozolomide. 6. In the VA Clinical Pathway for Brain Cancers for Grade 2 IDH mutant tumors in patients without high-risk features (e.g. age >40 with residual tumor, neurologic symptoms, atypical neuroimaging) vorasidenib will be added for patients with residual non-enhancing disease on MRI or for patients without a gross total resection as was studied in INDIGO.

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References

[1] Mellinghoff IK, et al. Vorasidenib in IDH1- or IDH2-mutant low-grade glioma. New Eng J Med 2023; 389: 589-601.