The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

Olutasidenib (REZLIDHIA™)
Mini-Monograph
August 2023

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

FDA APPROVAL	**Description/MOA**	Isocitrate dehydrogenase-1 (*IDH1*) inhibitor
	Indication(s) Under Review	Treatment of relapsed or refractory AML with susceptible *IDH1* mutation
	Dosage Form(s)	Oral capsules

CLINICAL EVIDENCE	**Study/Design**	Open-label, single-arm, multicenter phase 1/2 trial; Phase 2 contains multiple patient cohorts with AML and MDS
	Population	Cohort of adults aged ≥ 18 yrs with relapsed or refractory AML with an IDH1 mutation (m*IDH1*); ECOG PS 0-2; QT-interval ≤ 450 ms; Excluded: patients with symptomatic CNS leukemia, uncontrolled infection or metabolic disorders; prior IDH inhibitor therapy
	Demographics	N=147; mAge 71 yrs (25% < 65 yo; 44% 65-75 yo; 31% ≥ 75 yo); male 50%; Race: White 46%; Black 3%; Asian 3%; not stated 48%; ECOG PS 1 (52%) 2 (16%); Prior HSCT 12%; transfusion-dependent 59%; median # prior therapies 2: 1L 33%; 2L 31%; > 3L 37%
	Intervention	Olutasidenib 150 mg orally twice daily until disease progression, toxicity or HSCT; Cycle = 28-days
	Results	At median f/u 10.2 mos, median treatment duration was 4.7 mos Primary endpoints: CR+CRh, duration of CR+CRh and rate of transfusion independence CR+CRh 35% (95% CI 27-43); median duration 25.9 mos (95% CI 13.5 – NR); ORR 48%; mDoR 11.7 mos; mOS 11.6 mos N=86 transfusion dependent -> 34% became independent during 56-day period N=61 transfusion independent -> 64% remained independent during 56-day period

ECOG Eastern Cooperative Oncology Group PS performance status. HSCT hematopoietic stem cell transplant. CR Complete Remission CRh CR with partial hematologic recovery. ORR Overall Response Rate. mDoR median duration of response. mOS median overall survival. AML acute myeloid leukemia. MDS myelodysplastic syndrome

SAFETY	**Boxed warnings**	Differentiation syndrome. Noted in 16% (gr 3-4 in 8%); If suspected, hold olutasidenib, initiate corticosteroids and hemodynamic monitoring until symptom resolution.
	Contraindications	None
	Warnings/Precautions	Hepatotoxicity. Noted in 23% (gr 3-4 in 13%); Monitor LFTs at baseline, at least once weekly x 2 months; every other week for 3rd month; once in 4th month, and every other month for remainder of therapy. May need to interrupt, hold or discontinue therapy.
	Adverse reactions	≥ 20%: ↑AST, ↑ALT, ↓potassium, ↓sodium, ↑alk phos, nausea, ↑SCr, fatigue, arthralgia, constipation, ↑lymphocytes, ↑T bili, leukocytosis, ↑uric acid, dyspnea, pyrexia, rash, ↑lipase, mucositis, diarrhea, transaminitis
	Drug Interactions	Avoid strong or moderate CYP3A4 inducers. Avoid sensitive CYP3A substrates; if unavoidable, monitor for loss of substrate effect.
	Pregnancy/ Breastfeeding	Avoid in pregnancy, may cause fetal harm. Avoid breastfeeding during therapy and for 2 weeks after last dose.

Projected Place in Therapy/Conclusions

- Olutasidenib is the second FDA-approved *IDH1* inhibitor for the treatment of *IDH1*-mutated relapsed/refractory AML, which is present in up to 15% of cases.
- Presence of the *IDH1* mutation from blood or marrow sample should be confirmed prior to therapy
- Of note, olutasidenib is not FDA-approved in combination with a hypomethylating agent (i.e. azacitidine, decitabine) but has been recently studied in combination with azacitidine in a phase 1-2 trial among patients with AML and MDS. Reports of the phase 1 portion indicate a tolerable safety profile and clinical activity, supporting continued investigation.

Indirect Comparison of Marketed IDH1 inhibitors, as monotherapy in R/R AML setting

Drug/ VANF status/ Guidance	Dosing	Risk of DS?	Select AE differences	Other FDA approval(s)	Endpoint(s) in R/R AML indication	NCCN v4.2023 per indication
Olutasidenib TBD	Twice daily	16% (gr 3/4 8%)	Hepatotoxicity 23% (gr 3-4 in 13%); Nausea 38% QT prolongation < 10% Edema 18% (gr 3/4 3%)	• R/R AML w/m*IDH1*	CR 32%, CR+CRh 35%	Cat 2A
Ivosidenib PA-F CFU	Once daily	19% (gr 3/4 13%)	QT prolongation 10-26% Guillain-Barre < 1% Edema 32% (gr 3/4 1%) Chest pain 16% (gr 3/4 3%)	• R/R AML w/m*IDH1* • m*IDH1*, ND AML in adults > 75 yo as monotherapy • m*IDH1*, ND AML in adults > 75 yo + azacitidine • locally advanced or metastatic CCA	CR 25%, CR+CRh 33%	Cat 2A Cat 2A Cat 1, Preferred*

* Preferred in patients who meet at least one criterion: age > 75 yrs, baseline ECOG PS 2, severe cardiac or pulmonary disease, hepatic impairment with bilirubin > 1.5 x ULN, CrCl < 45 ml/min or other comorbidity; ND. Newly diagnosed, R/R. Relapsed and/or Refractory. Cat. Category. CCA cholangiocarcinoma

References

- De Botton S, Fenaux P, Yee K, et al. Olutasidenib induces durable complete remissions in patients with relapsed or refractory IDH1-mutated AML. Blood Advances 2023; 7: 3117-3127
- Olutasidenib (REZLIDHIA) prescribing information. Metrics Contract Services, Forma Therapeutics, Inc. Greenville, NC. December 2022
- Watts JM, Baer MR, Yang J, et al. Olutasidenib alone or with azacitidine in IDH1-mutated acute myeloid leukemia and myelodysplastic syndrome: phase 1 results of a phase 1-2 trial. Lancet Haematol 2023; 10: e46-e58. Doi: 10.1016/S2352-3026(22)00202-7
- Montesinos P, et al. Ivosidenib and azacitidine in IDH1-mutated acute myeloid leukemia. N Engl J Med 2022; 386: 1519-1531
- National Comprehensive Cancer Network Guidelines Version 4.2023. Acute Myeloid Leukemia (Age ≥18 years). Accessed July 11, 2023. https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf