

Vadadustat (VAFSEO) FOR Anemia in Dialysis-Dependent Chronic Kidney Disease National Drug Mini-monograph August 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	Vadadustat is a hypoxia-inducible factor prolyl hydroxylase (HIF PH) inhibitor
	Indication Under Review¹	Anemia in Chronic Kidney Disease (CKD) in patients receiving dialysis for at least 3 months with Limitations of Use: *Has not been shown to improve quality of life, fatigue, or patient well-being *Not indicated for use as a substitute for transfusion in patients requiring immediate correction of anemia *In patients with anemia due to CKD not on dialysis
	Dosage Regimen	Initial dose 300mg once daily with dose adjusted in 150mg increments with dose increases occurring no sooner than at 4 week intervals. Decreases in dose can occur more frequently. Recommended doses range 150mg to 600mg/day with dose adjusted to reduce need for RBC transfusions while maintaining Hgb 10-11g/dL
	Dosage Forms Under Review	Vadadustat 150mg, 300mg, and 450mg tablets

EFFICACY CONSIDERATIONS	Trial Design	INNO2VATE² Open label randomized (1), active controlled (darbepoetin) study of 2 separate trials reported in a pooled analysis (total n=3923). Individual trials were similar in design with exception that one cohort was ESA-naïve, and enrollment was at time of initiation of dialysis (e.g. dialysis incident) and second cohort was chronically receiving dialysis and currently receiving ESA treatment prior to enrollment (e.g. dialysis prevalent)	PRO2TECT³ Open label randomized (1:1), active controlled (darbepoetin) study of 2 separate trials reported in a pooled analysis (total n= 3471 patients). Individual trials were similar in design with exception that one cohort was ESA naïve and other cohort was currently receiving ESA treatment prior to enrollment
	Population	Adults with dialysis-dependent CKD (DD-CKD) and anemia not due to other causes (Hgb 8-11g/dL in both dialysis incident and dialysis prevalent studies)	Adults with non-dialysis dependence CKD (NDD-CKD) and anemia not due to other causes (Hgb<10g/dL ESA-untreated, Hgb 8-11 g/dL ESA-treated)
	Intervention	Vadadustat 300mg/day (range 150-600) or darbepoetin titrated to a target Hgb of 10-11 g/dL and treated for a total of 52 weeks.	Vadadustat 300mg/day (range 150-600) or darbepoetin titrated to a target Hgb of 10-11 g/dL and treated for a total of 52 weeks.
	Comparator	As above	As above
	Results	There were co-primary endpoints of a primary safety (Major Adverse Cardiovascular Events -- MACE) and efficacy (change in Hgb from baseline) outcome. Vadadustat was non-inferior to darbepoetin for both the safety and efficacy, co-primary, endpoints. MACE occurred in 18.2% of vadadustat treated patients vs. 19.3% of darbepoetin treated patients (95% CI 0.83 to 1.11) in the pooled analysis. Results were qualitatively similar in the individual incident dialysis and prevalent dialysis cohorts. Hemoglobin levels increased from baseline similarly in all cohorts at both the primary (24 to 26 weeks) and secondary (40 to 52 weeks) specified endpoint times. Adverse events due to any cause were common (e.g. 85%) and similar in both arms. Serious drug related events were uncommon (1-2%) and similar in both arms. Transfusion was more common in the vadadustat	There were co-primary endpoints of a primary safety (Major Adverse Cardiovascular Events -- MACE) and efficacy (change in Hgb from baseline) outcome. Vadadustat was non-inferior to darbepoetin at increasing Hgb levels from baseline (approximate increase of 1.5 g/dL ESA-naïve, 0.4 g/dL ESA-treated with no significant difference between vadadustat or darbepoetin). The pre-specified margin for non-inferiority for the primary safety endpoint was NOT met with MACE occurring in 22% (vadadustat) vs. 19.9% (darbepoetin) patients (95% CI 1.01 to 1.36). Adverse events due to any cause were common (e.g. 90%) and similar in both arms. Serious drug related events were uncommon (1-2%) and similar in both arms.

arms, but no significance was reported and absolute differences were small

SAFETY CONSIDERATIONS	Boxed Warnings¹	Increased risk of thrombotic vascular events including MACE; Targeting a Hgb level > 11g/dL is expected to further increase risk of death and thrombotic events; No trial has identified a Hgb target level, dose of vadadustat, or dosing strategy that does not increase these risks; Use lowest dose of vadadustat sufficient to reduce the need for RBC transfusions
	Contraindications	Uncontrolled hypertension; Known hypersensitivity to vadadustat or its components
	Other Warnings	<ul style="list-style-type: none"> • Increased risk of MACE, and venous or arterial thrombus including thrombus of vascular access; • Increased risk of hepatotoxicity and use not recommended in patients with active liver disease • Vadadustat may cause a worsening of hypertension • Seizures, gastrointestinal erosions, and malignancies have all been reported in patients using both vadadustat • Due to increased risk of adverse events compared to darbepoetin alfa, use of vadadustat for anemia due to CKD in patients not on dialysis is not recommended
	Top 5 AEs	Hypertension, diarrhea, headache, nausea, fatigue
	Drug Interactions	<ul style="list-style-type: none"> • Iron products and phosphate binders decrease absorption of vadadustat • OAT1/OAT3 inhibitors may increase vadadustat exposure • Vadadustat may increase exposure of BCRP substrates • Vadadustat increases the exposure of some statins (specific dose adjustment for rosuvastatin and simvastatin) • Vadadustat may increase the exposure of OAT3 substrates

VHA PLACE IN THERAPY	Potential Use in VHA	<ol style="list-style-type: none"> 1. ESA's should remain the standard for treatment of anemia due to CKD due to greater clinical experience and known long-term safety profile 2. Use of vadadustat should be restricted to patients with anemia due to CKD receiving maintenance dialysis AND who have failed to respond to treatment with a formulary ESA 3. Vadadustat is non-inferior to ESA's from a safety (MACE) and efficacy (Hgb increased) standpoint but has not been shown to improve QoL, fatigue or patient well-being. 4. Per FDA review,⁴ <i>“There are two risks of vadadustat that are not risks of ESAs – hepatotoxicity and gastrointestinal erosions – that need to be factored into vadadustat’s benefit-risk assessment”</i> 5. The first agent in class, (Daprodustat DUVROQ), was withdrawn from the market in December 2024 for business reasons and PADR requests for this agent were exceedingly low. Vadadustat could be expected to fill a similar niche role for patients who are non-responsive or unable to utilize ESAs
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References

- 1 VAFSEO (vadadustat) tablets [prescribing information online]. Cambridge, MA: Akebia Therapeutics: Available at: [VAFSEO prescribing information.pdf](#) Accessed Jan 2025
- 2 Eckardt KU, et al., Safety and Efficacy of Vadadustat for Anemia in Patients Undergoing Dialysis. N Engl J Med. 2021 Apr 29;384(17):1601-1612. doi: 10.1056/NEJMoa2025956. PMID: 33913638
- 3 Chertow GM, et. al, and PROTECT Study Group. Vadadustat in Patients with Anemia and Non-Dialysis-Dependent CKD. N Engl J Med. 2021 Apr 29;384(17):1589-1600. doi: 10.1056/NEJMoa2035938. PMID: 33913637.
4. FDA integrated review of VAFSEO (vadadustat) Accessed May 2025 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2024/215192Orig1s000IntegratedR.pdf