Vafseo® (vadadustat) Tablets

For adults with anemia due to chronic kidney disease (CKD) on dialysis for at least 3 months[1]

Guide to dosing and titrating Vafseo

Once-daily oral Vafseo offers convenient dosing with dose titration to **help patients achieve and sustain target hemoglobin (Hb) levels** of 10 to 11 g/dL.[1]

Not actual size.

INDICATION

VAFSEO is indicated for the treatment of anemia due to chronic kidney disease (CKD) in adults who have been receiving dialysis for at least three months.

Limitations of Use

- VAFSEO has not been shown to improve quality of life, fatigue, or patient well-being.
- VAFSEO is not indicated for use:
  - As a substitute for red blood cell transfusions in patients who require immediate correction of anemia.
  - In patients with anemia due to CKD not on dialysis.

IMPORTANT SAFETY INFORMATION about VAFSEO (vadadustat) tablets

WARNING: INCREASED RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, and THROMBOSIS OF VASCULAR ACCESS.

VAFSEO increases the risk of thrombotic vascular events, including major adverse cardiovascular events (MACE).

Targeting a hemoglobin level greater than 11 g/dL is expected to further increase the risk of death and arterial and venous thrombotic events, as occurs with erythropoietin stimulating agents (ESAs), which also increase erythropoietin levels.

No trial has identified a hemoglobin target level, dose of VAFSEO, or dosing strategy that does not increase these risks.

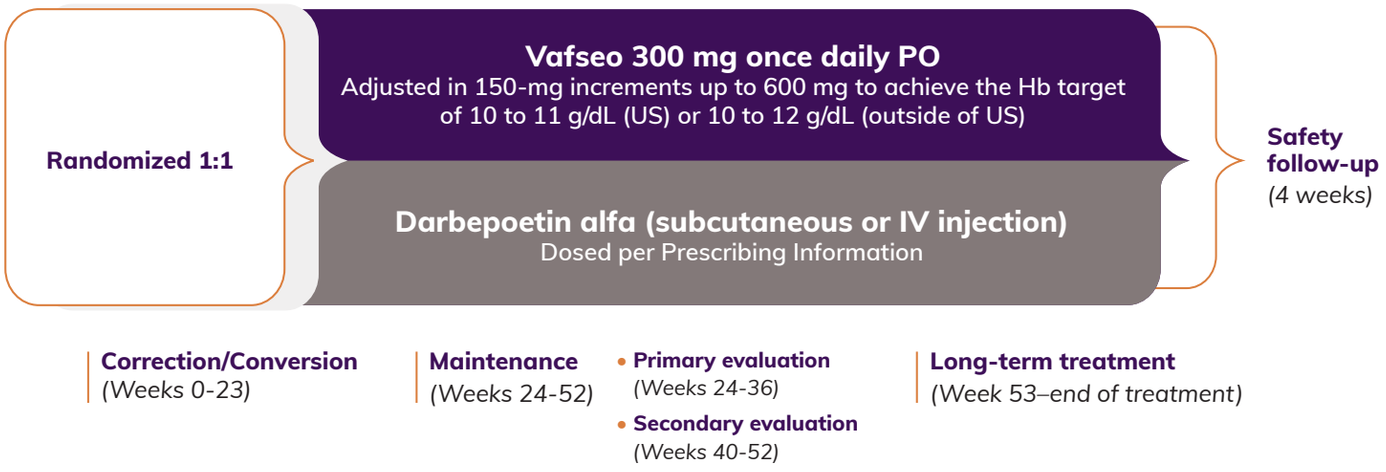
Use the lowest dose of VAFSEO sufficient to reduce the need for red blood cell transfusions.

Please see Important Safety Information throughout and click here for Full Prescribing Information, including BOXED WARNING and Medication Guide.

Trial design (Incident & Prevalent Dialysis Trials)

Efficacy and safety of Vafseo were demonstrated in 2 pivotal Phase 3 trials[1,2]

The efficacy and safety of Vafseo were evaluated in 2 global, Phase 3, multi-center, randomized, active-controlled, noninferiority, open-label trials (N=3923), the Incident Dialysis Trial ($INNO_2VATE$-1) and the Prevalent Dialysis Trial ($INNO_2VATE$-2)[1,2]



Limitations: Residual kidney function was not measured, but results were uniform across both trials and various dialysis durations in the Prevalent Dialysis Trial.[2]

Key clinical trial endpoints[1]

- **Efficacy:** Difference in mean change of Hb levels from baseline to primary (Weeks 24 to 36) and secondary (Weeks 40 to 52) evaluation periods, using the prespecified, noninferiority margin of -0.75 g/dL
- **Cardiovascular outcomes:** After 52 weeks, patients continued on study medication to assess long-term safety until the event-driven MACE* endpoints were reached. Time to first occurrence of MACE was assessed in a pooled analysis of both trials, using the prespecified, noninferiority margin of 1.25

*MACE was defined as all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke.[2]
Hb=hemoglobin; IV=intravenous; MACE=major adverse cardiovascular event; PO=by mouth.

IMPORTANT SAFETY INFORMATION (cont'd)

CONTRAINDICATIONS

- Known hypersensitivity to VAFSEO or any of its components
- Uncontrolled hypertension

WARNINGS AND PRECAUTIONS

- **Increased Risk of Death, Myocardial Infarction (MI), Stroke, Venous Thromboembolism, and Thrombosis of Vascular Access**
  A rise in hemoglobin (Hb) levels greater than 1 g/dL over 2 weeks can increase these risks. Avoid in patients with a history of MI, cerebrovascular event, or acute coronary syndrome within the 3 months prior to starting VAFSEO. Targeting a Hb level of greater than 11 g/dL is expected to further increase the risk of death and arterial and venous thrombotic events. Use the lowest effective dose to reduce the need for red blood cell (RBC) transfusions. Adhere to dosing and Hb monitoring recommendations to avoid excessive erythropoiesis.

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Prior ESA use was permitted in the Incident Dialysis Trial (INNO$_2$VATE-1) and required in the Prevalent Dialysis Trial (INNO$_2$VATE-2)[1,2]

Patient population[1,2]	Incident Dialysis Trial (INNO$_2$VATE-1)		Prevalent Dialysis Trial (INNO$_2$VATE-2)	
	Vafseo (n=181)	**Darbepoetin alfa** (n=188)	**Vafseo** (n=1777)	**Darbepoetin alfa** (n=1777)
Dialysis Status	Incident dialysis patient for ≤16 weeks		Chronic maintenance dialysis patient for ≥12 weeks	
ESA Status	ESA-naïve, limited prior ESA use, or maintained on ESAs		Maintained on ESAs	
Hb Values	8 to 11 g/dL (US and outside the US)		8 to 11 g/dL (US) 9 to 12 g/dL (outside the US)	
Iron Status	Serum ferritin ≥100 ng/mL Transferrin saturation ≥20%		Serum ferritin ≥100 ng/mL Transferrin saturation ≥20%	

- Baseline mean±SD Hb levels were 9.4 ± 1.1 g/dL with Vafseo and 9.2 ± 1.1 g/dL with darbepoetin alfa in the Incident Dialysis Trial (INNO$_2$VATE-1), and 10.3 ± 0.9 g/dL with Vafseo and 10.2 ± 0.8 g/dL with darbepoetin alfa in the Prevalent Dialysis Trial (INNO$_2$VATE-2)[1]
- **Key exclusion criteria:** Patients with anemia due to non-CKD causes, uncontrolled hypertension, or a recent cardiovascular event were excluded from the trials[2]

Results

- In both trials, Vafseo demonstrated noninferiority in efficacy compared to darbepoetin alfa[1,2,†]
- In a pooled analysis of both trials, Vafseo was noninferior to darbepoetin alfa on the time to first occurrence of MACE[1,‡]

†Vafseo is approved for adults with anemia due to CKD who have been on dialysis for at least 3 months.[1]
‡MACE was defined as all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke.[2]
CKD=chronic kidney disease; ESA=erythropoiesis-stimulating agent; Hb=hemoglobin; MACE=major adverse cardiovascular event; SD=standard deviation.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Hepatotoxicity**
  Hepatocellular injury attributed to VAFSEO was reported in less than 1% of patients, including one severe case with jaundice. Elevated serum ALT, AST, and bilirubin levels were observed in 1.8%, 1.8%, and 0.3% of CKD patients treated with VAFSEO, respectively. Measure ALT, AST, and bilirubin before treatment and monthly for the first 6 months, then as clinically indicated. Discontinue VAFSEO if ALT or AST is persistently elevated or accompanied by elevated bilirubin. Not recommended in patients with cirrhosis or active, acute liver disease.

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Pre-treatment and on-treatment evaluations

Before starting and during treatment, it is important to conduct the following evaluations[1]

Anemia and iron store evaluations

- Correct and exclude other causes of anemia before initiating Vafseo*
- Measure Hb at baseline and during treatment
- Evaluate iron status in all patients before and during treatment
- Administer supplemental iron therapy when serum ferritin is <100 mcg/L or when serum transfusion saturation is <20%
- Most patients with CKD will require supplemental iron during the course of therapy

Liver tests

- Assess serum ALT, AST, and bilirubin prior to initiating Vafseo and monthly after initiation for the first 6 months, and then monitor as clinically indicated
- Discontinue Vafseo if there are persistent ALT or AST elevations >3 times ULN or if ALT or AST elevations >3 times ULN are accompanied by a bilirubin increase >2 times ULN

» Offer adult patients with anemia due to CKD on hemodialysis or peritoneal dialysis for at least 3 months the **convenience of oral, once-daily Vafseo**[1,3]

*Other causes of anemia include vitamin deficiencies, metabolic or chronic inflammatory conditions, and/or bleeding.[1]
ALT=alanine aminotransferase; AST=aspartate aminotransferase; CKD=chronic kidney disease; Hb=hemoglobin; ULN=upper limit of normal.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Hypertension**
  Worsening of hypertension was reported in 14% of VAFSEO and 17% of darbepoetin alfa patients. Serious worsening of hypertension was reported in 2.7% of VAFSEO and 3% of darbepoetin alfa patients. Cases of hypertensive crisis, including hypertensive encephalopathy and seizures, have also been reported in patients receiving VAFSEO. Monitor blood pressure. Adjust anti-hypertensive therapy as needed.
- **Seizures**
  Seizures occurred in 1.6% of VAFSEO and 1.6% of darbepoetin alfa patients. Monitor for new-onset seizures, premonitory symptoms, or change in seizure frequency.

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Starting your patients on once-daily oral Vafseo[1]

Dosing and administration information[1]

General guidance

- Individualize dosing and use the lowest dose of Vafseo sufficient to reduce the need for RBC transfusions
- Do not target an Hb level higher than 11 g/dL—the target Hb range is 10 to 11 g/dL

Guidance for administration

- Vafseo is an oral medication, self-administered with needle-free dosing
  - Each dose can be taken with or without food
  - Tablets should be swallowed whole and not cut, crushed, or chewed
  - Each dose can be taken without regard to the timing or type of dialysis
- **If a patient misses a dose and it is still the same day,** they should take the missed dose as soon as possible
- **If the missed dose is not identified until the following day,** the patient should skip the missed dose and resume the regular dosing schedule
- **Double doses should not be taken** to make up for a missed dose

Regardless of the patient's prior ESA dose, the **recommended starting dose of Vafseo is 300 mg, once daily**[1]

ESA=erythropoiesis-stimulating agent; Hb=hemoglobin; RBC=red blood cell.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Gastrointestinal (GI) Erosion**
  Gastric or esophageal erosions occurred in 6.4% of VAFSEO and 5.3% of darbepoetin alfa patients. Serious GI erosions, including GI bleeding and the need for RBC transfusions, were reported in 3.4% of VAFSEO and 3.3% of darbepoetin alfa patients. Consider this risk in patients at increased risk of GI erosion. Advise patients about signs of erosions and GI bleeding and urge them to seek prompt medical care if present.

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Treatment response and dose titration

1 Monitor Hb levels[1]

Following initiation of therapy and after each dose adjustment, monitor Hb levels every 2 weeks until stable, then monitor at least monthly

Clinical trial observations:

In the Prevalent Dialysis Trial ($INNO_2VATE$-2), an initial, transient decrease in mean Hb levels was observed in patients who transitioned from an ESA* to Vafseo compared to those maintained on an ESA. All patients were started on a standardized Vafseo dose of 300 mg once daily, regardless of the prior ESA dose. In the trial, investigators could only titrate once every 4 weeks and in increments of 150 mg.[1,2,4,†]

2 Titrate the dose of Vafseo[1]

Adjust the dose in increments of 150 mg within the dose range of 150 mg to 600 mg to help achieve or sustain an Hb level of 10 to 11 g/dL

- Increase the dose no more frequently than once every 4 weeks—dose decreases can occur more frequently
- When adjusting the dose, consider the patient's Hb variability, Hb rate of rise and decline, and Vafseo responsiveness—a single Hb excursion may not require dosing change
- If the Hb rises rapidly (eg, more than 1 g/dL in any 2-week period or more than 2 g/dL in 4 weeks), interrupt or reduce the dose
- If Hb level exceeds 11 g/dL, interrupt the dose until Hb is ≤11 g/dL, then resume with a dose that is 150 mg less than the dose prior to interruption
- Treatment with Vafseo should not be continued beyond 24 weeks of therapy if a clinically meaningful increase in Hb level is not achieved, and alternative explanations for an inadequate response should be sought and treated before restarting therapy

*Darbepoetin alfa.

†The data described are from the Prevalent Dialysis Trial ($INNO_2VATE$-2), a Phase 3, multi-center, randomized, active-controlled, noninferiority, open-label trial of patients on chronic maintenance dialysis for more than 12 weeks who converted to Vafseo from a prior ESA.[1,2]

Hb=hemoglobin.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Serious Adverse Reactions in Patients with Anemia Due to CKD and Not on Dialysis**
  The safety of VAFSEO has not been established for the treatment of anemia due to CKD in adults not on dialysis and its use is not recommended in this setting. In large clinical trials in adults with anemia of CKD who were not on dialysis, an increased risk of mortality, stroke, MI, serious acute kidney injury, serious hepatic injury, and serious GI erosions was observed in patients treated with VAFSEO compared to darbepoetin alfa.

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Select drug interactions

Interactions with iron phosphate binders[1]

Administer Vafseo at least 1 hour before or 2 hours after:

- Non-iron-containing phosphate binders

Administer Vafseo at least 1 hour before:

- Oral iron supplements
- Products containing iron
- Iron-containing phosphate binders

Interactions with statins[1]

- Vafseo increases the C_{max} and the AUC of some statins when co-administered
- This means that when taken together, Vafseo increases the blood levels of certain statins, including simvastatin and rosuvastatin, and should be managed as follows:
  - The starting dose of simvastatin should be 5 mg/day, and the maximum daily dose of simvastatin should not exceed 20 mg
  - The maximum daily dose of rosuvastatin not to exceed 5 mg

» Refer to the Full Prescribing Information for more **information on drug interactions**

AUC=area under the concentration curve; C_{max}=maximal concentration.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Malignancy**
  VAFSEO has not been studied and is not recommended in patients with active malignancies. Malignancies were observed in 2.2% of VAFSEO and 3.0% of darbepoetin alfa patients. No evidence of increased carcinogenicity was observed in animal studies.

ADVERSE REACTIONS

- The most common adverse reactions (occurring at ≥ 10%) were hypertension and diarrhea.

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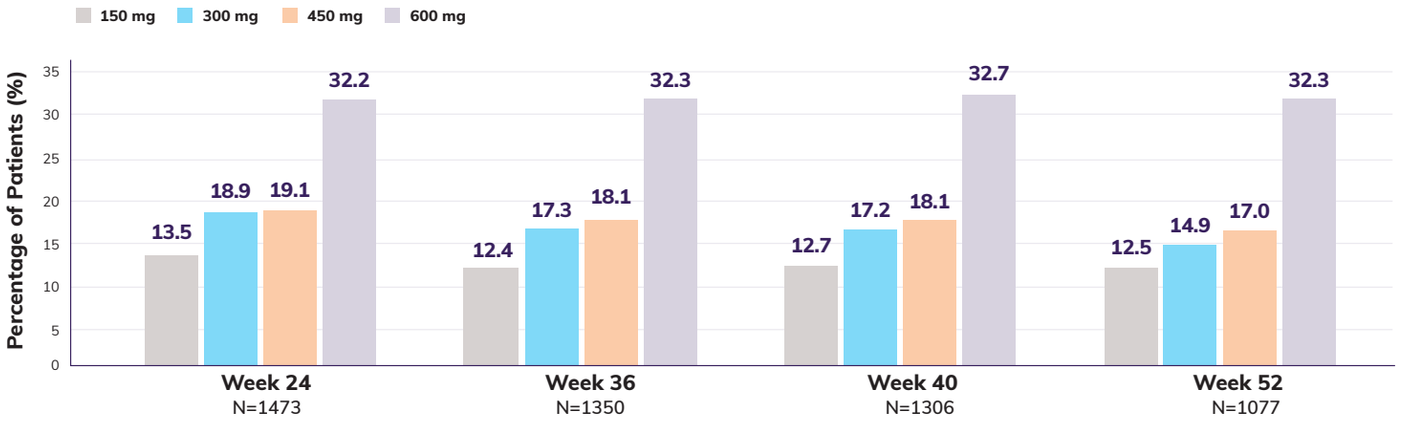
Vafseo dose levels in clinical trials

Percent of subjects by Vafseo dose level: Prevalent Dialysis Trial (INNO$_2$VATE-2)[2,5,*]



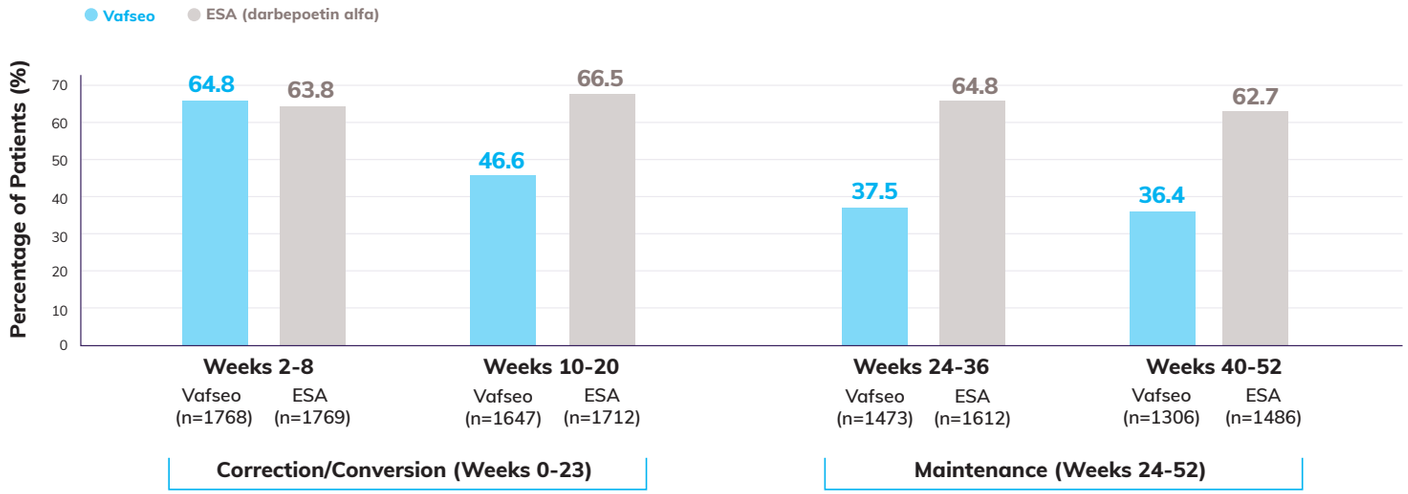
Data presented are the most common administered dose received during that study week. Data are observational, and doses may have been increased or decreased per protocol.[2,5]

- The distribution of doses from 150 mg to 600 mg was similar in the Incident Dialysis Trial (INNO$_2$VATE-1) compared with the Prevalent Dialysis Trial (INNO$_2$VATE-2)[2,5]

*Omits percentage of patients with 0 mg.[2,5]

Vafseo dose adjustments in clinical trials†

The proportion of patients receiving dose adjustments based on Hb assessments during the Prevalent Dialysis Trial (INNO$_2$VATE-2)[2,5,†,‡,§]



Presented data are a descriptive summary using observed data. Data were not corrected for multiplicity. All analyses should be interpreted with caution.[5]

†Dose adjustments defined as a dose increase or a dose decrease.

‡The starting dose of Vafseo was 300 mg orally, once daily. Darbepoetin alfa dosing was based on prior use or product label. Both drugs were adjusted per protocol-specified dose-adjustment algorithms to achieve target Hb levels (10 to 11 g/dL in the US; 10 to 12 g/dL EX-US).[2]

§Vafseo and darbepoetin alfa dose increases, decreases, or interruptions to maintain Hb within geography-specific target range were determined by HemoCue, local laboratory, or central laboratory. From weeks 0-12, Hb was monitored every 2 weeks. From weeks 12 to 52, Hb was monitored every 4 weeks unless more frequent monitoring was clinically indicated or warranted based on dosing changes.[5,6]

ESA=erythropoiesis-stimulating agent; Hb=hemoglobin.

For adults with anemia due to CKD on dialysis for at least 3 months[1]

Vafseo® (vadadustat) Tablets

Vafseo offers convenient once-daily oral dosing[1]

The recommended starting dose is 300 mg regardless of prior ESA dose[1]

- Evaluate anemia, iron stores, and liver testing before and during treatment
- Regardless of the patient's prior ESA dose, the recommended starting dose of Vafseo is 300 mg, once daily. The dose may range from 150 mg up to 600 mg
- Individualize dosing and use the lowest dose of Vafseo sufficient to reduce the need for RBC transfusions. Do not target a Hb level higher than 11 g/dL
- Can be taken with or without food

Please click here to see Full Prescribing Information for more details, including dose titration, interruption, discontinuation, and drug-drug interactions.

CKD=chronic kidney disease; ESA=erythropoiesis-stimulating agent; Hb=hemoglobin; RBC=red blood cell.

IMPORTANT SAFETY INFORMATION (cont'd)

DRUG INTERACTIONS

- **Iron supplements and iron-containing phosphate binders:** Administer VAFSEO at least 1 hour before products containing iron.
- **Non-iron-containing phosphate binders:** Administer VAFSEO at least 1 hour before or 2 hours after non-iron-containing phosphate binders.
- **BCRP substrates:** Monitor for signs of substrate adverse reactions and consider dose reduction.
- **Statins:** Monitor for statin-related adverse reactions. Limit the daily dose of simvastatin to 20 mg and rosuvastatin to 5 mg.

USE IN SPECIFIC POPULATIONS

- Pregnancy: May cause fetal harm.
- Lactation: Breastfeeding not recommended until two days after the final dose.
- Hepatic Impairment: Not recommended in patients with cirrhosis or active, acute liver disease.

Please note that this information is not comprehensive. Please click here to see additional Important Safety Information throughout and accompanying Full Prescribing Information, including BOXED WARNING and Medication Guide.

Visit VafseoHCP.com to explore clinical data and more

References: 1. Vafseo. Prescribing information. Akebia Therapeutics, Inc. **2.** Eckardt KU, Agarwal R, Aswad A, et al. Safety and efficacy of vadadustat for anemia in patients undergoing dialysis. *N Engl J Med*. 2021;384(17):1601-1612. doi:10.1056/NEJMoa2025956 **3.** Sarnak MJ, Agarwal R, Boudville N, et al. Vadadustat for treatment of anemia in patients with dialysis-dependent chronic kidney disease receiving peritoneal dialysis. *Nephrol Dial Transplant*. 2023;38(10):2358-2367. doi:10.1093/ndt/gfad074 **4.** Chertow GM, Jardine A, Burke S, et al. Safety and efficacy of vadadustat versus darbepoetin alfa in patients with CKD-related anemia on maintenance dialysis by prespecified subgroups of baseline ESA dose. Poster presented at: European Renal Association (ERA) Congress; May 23-26, 2024. **5.** Data on file. Akebia Therapeutics, Inc. **6.** Eckardt KU, Agarwal R, Farag YM, et al. Global Phase 3 programme of vadadustat for treatment of anaemia of chronic kidney disease: rationale, study design and baseline characteristics of dialysis-dependent patients in the INNO$_2$VATE trials. *Nephrol Dial Transplant*. 2021;36(11):2039-2048. doi:10.1093/ndt/gfaa204

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