

RESEARCH MONOGRAPH . COMPOUND PROFILE

Vadadustat

An oral 2-oxoglutarate-competitive inhibitor of prolyl-4-hydroxylase domain enzymes developed by Akebia Therapeutics for the treatment of anemia due to chronic kidney disease, distinguished from erythropoiesis-stimulating agents by its mechanism of stabilizing hypoxia-inducible factor to coordinate endogenous erythropoietin production, iron mobilization, and erythroid progenitor maturation.

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ABSTRACT

Vadadustat (AKB-6548; marketed as Vafseo) is an orally bioavailable small molecule inhibitor of the three human prolyl-4-hydroxylase domain (PHD) isoforms (PHD1, PHD2, PHD3) that regulate the oxygen-sensing hypoxia-inducible factor (HIF) pathway. By competitively displacing the endogenous cofactor 2-oxoglutarate from the PHD active site, vadadustat prevents the hydroxylation and subsequent proteasomal degradation of HIF- α subunits, thereby stabilizing HIF-1 α and HIF-2 α and activating transcription of erythropoietin, transferrin, transferrin receptor, ferroportin, and other genes that coordinate erythropoiesis and iron homeostasis. The compound was developed by Akebia Therapeutics (Cambridge, Massachusetts) as an alternative to injectable erythropoiesis-stimulating agents (ESAs) for the management of anemia associated with chronic kidney disease (CKD). Vadadustat inhibits all three PHD isoforms with similar low-nanomolar inhibitory constants, and PHD inhibition is competitive with 2-oxoglutarate and insensitive to ambient iron concentration. In preclinical models, a single oral dose in rats potently increased circulating erythropoietin, and daily dosing for 14 days increased red blood cell indices in both healthy rats and the 5/6 nephrectomy model of CKD. In mice and dogs, once-daily repeat oral dosing increased hemoglobin and hematocrit without detectable stimulation of vascular endothelial growth factor.

The clinical development program comprised the global Phase 3 INNO2VATE trials in dialysis-dependent CKD and the PRO2TECT trials in non-dialysis-dependent CKD, both comparing vadadustat

to darbepoetin alfa. In the INNO2VATE program, vadadustat met the prespecified noninferiority criteria for both hematologic efficacy and cardiovascular safety. In the PRO2TECT program, vadadustat met the noninferiority criterion for hematologic efficacy but did not meet the noninferiority criterion for cardiovascular safety, with signals of increased major adverse cardiovascular events (MACE), stroke, and hepatic injury relative to darbepoetin alfa. The United States Food and Drug Administration issued a complete response letter in March 2022 citing cardiovascular and hepatotoxicity concerns. Following review of additional post-marketing safety data from Japan (where Vafseo was approved in 2020) and the clinical trial database, the FDA approved vadadustat in March 2024 for the treatment of anemia due to CKD in adults who have been receiving dialysis for at least three months. The approved labeling carries a boxed warning for increased risk of death, myocardial infarction, stroke, venous thromboembolism, and thrombosis of vascular access, and the compound is explicitly not indicated for non-dialysis CKD patients.

Pharmacokinetics are characterized by rapid oral absorption (time to peak concentration approximately 3 to 4 hours in healthy volunteers, 5 to 6 hours in CKD patients), high plasma protein binding (greater than 99 percent), dose-proportional exposure over a wide dose range, and hepatic glucuronidation as the principal metabolic pathway. The elimination half-life is approximately 4.5 hours in healthy volunteers and extends to 7 to 9 hours in patients with advanced CKD. The compound is a potent inhibitor of the breast cancer resistance protein (BCRP) transporter and a moderate inhibitor of organic anion transporting polypeptide 1B1/1B3 (OATP1B1/1B3), with clinically relevant drug-drug interaction potential for substrates of these

transporters. This monograph reviews the chemistry, synthesis, and structural class of vadadustat; the molecular pharmacology of PHD inhibition and HIF stabilization; the comprehensive pharmacokinetic profile; preclinical pharmacology in rodent and canine models; the clinical evidence base from Phase 2 and Phase 3 programs; sourcing and quality verification; reconstitution and handling; stack interactions and combinations; adverse events and safety signals; and a comparative assessment of five alternative HIF-PHI compounds (roxadustat, daprodustat, molidustat, desidustat, enarodustat) against vadadustat on five standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Vadadustat.

Marketed name: Vafseo (Akebia Therapeutics / CSL Vifor; United States, Japan).

Development codes: AKB-6548 (Akebia Therapeutics), PG-1016548. The development code AKB-6548 is the canonical identifier in the early preclinical and Phase 1/2 clinical literature [1, 2].

Chemical Abstracts Service registry number: 1000025-07-9.

International Union of Pure and Applied Chemistry name: 2-[[5-(3-chlorophenyl)-3-hydroxypyridine-2-carbonyl]amino]acetic acid. The compound is the glycine amide of 5-(3-chlorophenyl)-3-hydroxypicolinic acid, placing it within the carbonylglycine class of 2-oxoglutarate mimetics that constitute the majority of clinically developed HIF prolyl hydroxylase inhibitors.

1.2 Structural class and chemistry

Vadadustat belongs to the carbonylglycine structural class of HIF prolyl hydroxylase inhibitors, which also includes roxadustat and daprodustat. These compounds share a glycine-derived side chain that mimics the 2-oxoglutarate cofactor at the PHD active site. The core scaffold of vadadustat is a 3-hydroxypyridine-2-carboxamide bearing a 3-chlorophenyl substituent at the 5-position, which occupies a hydrophobic pocket in the PHD catalytic domain and contributes to binding affinity and selectivity over other 2-oxoglutarate-dependent dioxygenases [1].

Molecular formula: C₁₄H₁₁ClN₂O₄.

Molecular weight: 306.70 g/mol.

Exact mass: 306.0407 g/mol (monoisotopic).

Physical properties: White to off-white crystalline powder. Melting point approximately 172 degrees Celsius. Soluble in dimethyl sulfoxide, sparingly soluble in methanol and ethanol, and poorly soluble in water at neutral pH. The glycine car-

boxylic acid moiety confers pH-dependent aqueous solubility, with increased solubility under mildly alkaline conditions.

Stereochemistry: Vadadustat contains no stereocenters. The compound is a chiral and is supplied as a single molecular entity without enantiomeric considerations.

1.3 Synthesis

The synthesis of vadadustat proceeds through the construction of the 3-hydroxypyridine-2-carboxylic acid core followed by amide coupling to glycine. The key synthetic steps involve: (a) preparation of 5-(3-chlorophenyl)-3-hydroxypyridine-2-carboxylic acid through Suzuki cross-coupling of a 5-halogenated 3-hydroxypyridinyl precursor with 3-chlorophenylboronic acid under palladium catalysis, or through direct functionalization of the pyridine ring; (b) activation of the carboxylic acid (using standard coupling reagents such as HATU, EDCI/HOBt, or mixed anhydride methods) and condensation with glycine or a glycine ester; and (c) if a glycine ester is used, final deprotection under mild acidic or basic hydrolysis conditions. The product is purified by recrystallization or preparative chromatography and characterized by nuclear magnetic resonance spectroscopy, mass spectrometry, and high-performance liquid chromatography. Industrial manufacturing processes optimize the palladium-catalyzed cross-coupling step for yield, purity, and removal of residual palladium to levels below ICH Q3D elemental impurity limits [1].

2. Abstract

Vadadustat (AKB-6548; Vafseo) is an oral, once-daily inhibitor of the three human prolyl-4-hydroxylase domain (PHD) enzymes that regulate the oxygen-dependent degradation of hypoxia-inducible factor (HIF) alpha subunits. By competitively blocking the 2-oxoglutarate binding site of PHD1, PHD2, and PHD3 with similar low-nanomolar inhibitory potency, vadadustat stabilizes HIF-1alpha and HIF-2alpha, activating transcription of erythropoietin, transferrin, transferrin receptor, ferroportin, and other target genes that coordinate the physiologic erythropoietic response to hypoxia [1, 3]. The compound was developed by Akebia Therapeutics as an oral alternative to injectable erythropoiesis-stimulating agents (ESAs) for the treatment of anemia due to chronic kidney disease (CKD).

The clinical development program was anchored by two global Phase 3 programs. The INNO2VATE trials enrolled approximately 3,900 dialysis-dependent CKD patients and compared vadadustat to darbepoetin alfa, demonstrating noninferiority for both hemoglobin maintenance and cardiovascular safety [4]. The PRO2TECT trials enrolled approximately 3,500 non-dialysis-dependent CKD patients; vadadustat met the noninferiority criterion for hemoglobin correction but did not meet the noninferiority criterion for cardiovascular safety, with a hazard ratio for the first occurrence of MACE (composite of all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke) of 1.17 (95% confidence interval, 1.01 to 1.36) relative to darbepoetin alfa [5]. The FDA issued a complete response letter in March 2022 on the basis of cardiovascular and hepatotoxicity concerns across the combined program. Following review of post-marketing safety data from Japan (where vadadustat was approved and launched as Vafseo in August 2020) and additional analysis of the clinical trial database, the FDA approved vadadustat in March 2024 for the treatment of anemia due to CKD in adults who have been receiving dialysis for at least three months [6]. The approved labeling carries a boxed warning for increased risk of death, myocardial infarction, stroke, venous thromboembolism, and thrombosis of vascular access. The compound is not indicated for non-dialysis CKD patients.

Pharmacokinetics are linear, with dose-proportional exposure, rapid absorption, high plasma protein binding (greater than 99 percent), and hepatic glucuronidation as the dominant metabolic pathway. The elimination half-life is approximately 4.5 hours in healthy volunteers and 7 to 9 hours in advanced CKD. Vadadustat is a po-

tent inhibitor of the BCRP transporter and a moderate inhibitor of OATP1B1/1B3, with clinically relevant interaction potential for substrates of these transporters [7]. The recommended starting dose is 300 mg orally once daily in dialysis-dependent adults.

3. Discovery and Development History

3.1 Origin

Vadadustat was discovered at Akebia Therapeutics, a biopharmaceutical company founded in 2007 in Cambridge, Massachusetts, with the specific goal of developing oral HIF prolyl hydroxylase inhibitors for the treatment of renal anemia. The compound emerged from a medicinal chemistry program targeting 2-oxoglutarate-competitive inhibitors of the PHD family. The carbonylglycine scaffold was selected for its structural mimicry of the 2-oxoglutarate cofactor, its favorable oral bioavailability, and its selectivity for the PHD catalytic domain over other 2-oxoglutarate-dependent dioxygenases [1]. The 3-chlorophenyl substituent at the 5-position of the hydroxypyridine ring was optimized for potency and metabolic stability. The compound received the development code AKB-6548 and advanced into preclinical safety assessment in the early 2010s.

3.2 Preclinical development

The preclinical characterization of vadadustat was published by Akebia investigators in the *Journal of Pharmacology and Experimental Therapeutics* in 2022 [1]. The study demonstrated that vadadustat inhibits all three human PHD isoforms with low-nanomolar inhibitory constants (K_i values in the range of 1 to 20 nM), with the inhibition being competitive with 2-oxoglutarate and insensitive to free iron concentration. In cell-based assays, vadadustat stabilized HIF-1 α and HIF-2 α protein, induced erythropoietin gene transcription, and did not stimulate vascular endothelial growth factor (VEGF) at concentrations relevant to erythropoiesis. In vivo, a single oral dose in rats produced dose-dependent increases in circulating erythropoietin within 4 to 8 hours. Repeat daily oral dosing for 14 days increased hemoglobin, hematocrit, and reticulocyte count in healthy rats and in the 5/6 nephrectomy model of CKD. Repeat dosing in mice and dogs confirmed erythropoietic activity across species.

3.3 Phase 1 and Phase 2 clinical development

Phase 1 studies in healthy volunteers established the pharmacokinetic profile, dose proportionality, and erythropoietin pharmacodynamic response. Ascending single doses of 80 to 1200 mg demonstrated dose-proportional plasma exposure, rapid absorption (time to peak concentration approximately 3 to 4 hours), and transient, dose-dependent increases in plasma erythropoietin [2, 8].

Phase 2a studies in CKD patients not on dialysis (Pergola et al. 2016) demonstrated that vadadustat at doses of 240 to 500 mg daily for 20 to 28 days increased hemoglobin by 0.5 to 1.5 g/dL and modestly increased erythropoietin levels, without supraphysiologic erythropoietin peaks [9]. These Phase 2 results supported advancement to the global Phase 3 program.

3.4 Phase 3 clinical development

Akebia designed two parallel global Phase 3 programs:

The INNO2VATE program comprised two randomized, open-label, active-controlled trials (INNO2VATE-1 and INNO2VATE-2) enrolling approximately 3,900 patients with anemia due to CKD who were receiving dialysis. Patients were randomized to vadadustat (starting dose 300 mg once daily, with dose adjustments based on hemoglobin response) or darbepoetin alfa (dose-adjusted per label). The co-primary endpoints were mean change in hemoglobin from baseline and a cardiovascular safety composite (first occurrence of MACE: all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke). Results, published in the New England Journal of Medicine in 2021, demonstrated noninferiority of vadadustat to darbepoetin alfa for both hemoglobin maintenance and cardiovascular safety [4].

The PRO2TECT program comprised two randomized, open-label, active-controlled trials (PRO2TECT-Correction and PRO2TECT-Conversion) enrolling approximately 3,500 patients with anemia due to non-dialysis-dependent CKD. Results, also published in the New England Journal of Medicine in 2021, demonstrated noninferiority for hemoglobin correction and conversion but did not meet the noninferiority criterion for cardiovascular safety [5].

3.5 Regulatory history

The FDA issued a complete response letter for the vadadustat New Drug Application on March 29, 2022, citing concerns about increased risks of thromboembolic events and drug-induced liver injury identified in the PRO2TECT program [10]. Akebia appealed the decision; the FDA denied the appeal but outlined a resubmission pathway that did not require additional clinical trials. In Japan, the Ministry of Health, Labour and Welfare approved vadadustat (Vafseo) in June 2020 for the treatment of anemia due to CKD in both dialysis-dependent and non-dialysis-dependent adults. Post-marketing surveillance in Japan provided additional safety data.

On March 27, 2024, the FDA approved Vafseo (vadadustat) tablets for the treatment of anemia due to CKD in adults who have been receiving dialysis for at least three months [6]. The approval was supported by the INNO2VATE efficacy and safety data plus the post-marketing safety experience from Japan (where Vafseo had been commercially available since August 2020). The FDA explicitly limited the indication to dialysis-dependent patients and included a boxed warning regarding cardiovascular and thromboembolic risks.

4. Mechanism of Action

Vadadustat is a selective inhibitor of the prolyl-4-hydroxylase domain (PHD) family of 2-oxoglutarate-dependent, iron-containing dioxygenases. The PHD enzymes are the primary oxygen sensors in the HIF pathway, which controls the transcriptional response to changes in tissue oxygenation. The mechanism operates through several interconnected molecular events.

4.1 PHD enzyme inhibition

The three human PHD isoforms (PHD1/EGLN2, PHD2/EGLN1, PHD3/EGLN3) catalyze the oxygen-dependent hydroxylation of two conserved proline residues (Pro402 and Pro564 in human HIF-1alpha) within the oxygen-dependent degradation domain of HIF-alpha subunits. This hydroxylation requires molecular oxygen, 2-oxoglutarate, iron(II), and ascorbate as cofactors. The hydroxylated prolines are recognized by the von Hippel-Lindau (VHL) E3 ubiquitin ligase complex, which targets HIF-alpha for proteasomal degradation.

Vadadustat binds the PHD active site by chelating the catalytic iron(II) through its hydroxypyridine nitrogen and hydroxyl group and by occupying the 2-oxoglutarate binding pocket through its carbonylglycine moiety [1]. The inhibition is competitive with 2-oxoglutarate and insensitive to the ambient iron concentration, a property that distinguishes vadadustat from earlier iron-chelating HIF stabilizers such as desferrioxamine. Vadadustat inhibits all three PHD isoforms with similar low-nanomolar potency, in contrast to some HIF-PHI compounds that show preferential inhibition of one isoform.

4.2 HIF stabilization and transcriptional activation

By preventing PHD-mediated hydroxylation of HIF-alpha, vadadustat stabilizes both HIF-1alpha and HIF-2alpha subunits. The stabilized alpha subunits translocate to the nucleus, heterodimerize with the constitutively expressed HIF-1beta (ARNT) subunit, and bind to hypoxia response elements (HREs) in the promoter and enhancer regions of target genes. The transcriptional program activated by HIF in-

cludes genes encoding erythropoietin (EPO), transferrin, transferrin receptor 1 (TfR1), divalent metal transporter 1 (DMT1), ferroportin, ceruloplasmin, and hepcidin-suppressing factors [3, 11].

The net physiologic effect is a coordinated erythropoietic response that parallels the body's adaptation to altitude or moderate hypoxia: increased erythropoietin production (primarily from renal interstitial fibroblasts and hepatocytes), enhanced iron absorption from the gut, improved iron mobilization from reticuloendothelial stores (through hepcidin suppression), and stimulation of erythroid progenitor proliferation and differentiation in the bone marrow.

4.3 Selectivity considerations

A critical pharmacological distinction among HIF-PHI compounds is their selectivity for PHD enzymes over other members of the 2-oxoglutarate-dependent dioxygenase superfamily, which includes collagen prolyl hydroxylases, the HIF asparaginyl hydroxylase factor inhibiting HIF (FIH), histone demethylases, and the TET family of DNA demethylases. Vadadustat exhibits selectivity for the PHD family over collagen prolyl hydroxylases, consistent with the absence of clinical collagen metabolism abnormalities in the Phase 3 programs. The compound does not produce detectable stimulation of VEGF in preclinical models at erythropoietically active doses, suggesting adequate selectivity within the HIF transcriptional program [1].

4.4 Differentiation from erythropoiesis-stimulating agents

The HIF-PHI mechanism differs fundamentally from recombinant ESAs (epoetin alfa, darbepoetin alfa) in several respects. ESAs provide supraphysiologic concentrations of exogenous erythropoietin through injection, producing high peak erythropoietin levels followed by trough decline. Vadadustat stimulates endogenous erythropoietin production through transcriptional activation, resulting in modest, physiologic-range erythropoietin elevations without supraphysiologic peaks [9]. Additionally, vadadustat simultaneously improves iron availability through hepcidin suppression and transferrin/ferroportin upregulation, potentially reducing the need for concomitant intravenous iron supplementation. The oral route of administration eliminates the need for injection, which is an operational advantage for patients, particularly those not receiving in-center dialysis.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Vadadustat is absorbed from the gastrointestinal tract after oral administration with dose-proportional pharmacokinetics over a dose range of 80 to 1200 mg. Time to peak plasma concentration (T_{max}) is approximately 3 to 4 hours in healthy volunteers and 5 to 6 hours in patients with CKD [2, 8]. The absolute oral bioavailability has not been publicly reported in a formal bioavailability study, but the dose-proportional kinetics and pharmacodynamic response at clinically relevant doses support substantial absorption. Food has modest effects on vadadustat pharmacokinetics; the FDA-approved labeling does not specify a food requirement.

5.2 Distribution

Vadadustat is highly bound to plasma proteins (greater than 99 percent), primarily to albumin. The compound does not distribute significantly into red blood cells. The high plasma protein binding limits the free fraction available for tissue distribution and may contribute to the relatively short elimination half-life. Volume of distribution data from formal radiolabeled mass balance studies have not been published; the high protein binding and moderate molecular weight (306.70 g/mol) suggest limited extravascular distribution [7, 8].

5.3 Metabolism

The principal metabolic pathway of vadadustat is hepatic glucuronidation, producing vadadustat-O-glucuronide, which is pharmacologically inactive. The glucuronidation is catalyzed by uridine diphosphate glucuronosyltransferase (UGT) enzymes. Cytochrome P450-mediated oxidative metabolism is a minor pathway. The dominance of glucuronidation over CYP-mediated metabolism reduces the potential for drug-drug interactions through the CYP system, although the compound does interact with drug transporters (see Section 10) [7].

5.4 Elimination

Elimination proceeds primarily through renal excretion of the glucuronide conjugate, with a smaller fraction eliminated through feces. The terminal elimination half-life varies with renal function: approximately 4.5 hours in healthy volunteers, 7.2 hours in Stage 3 CKD, 8.5 hours in Stage 4 CKD, and 9.2 hours in patients receiving chronic hemodialysis [2, 8]. The progressive prolongation of half-life with declining estimated glomerular filtration rate (eGFR) reflects a renal component to vadadustat or metabolite elimination and results in modestly increased drug exposure in patients with advanced CKD, the target treatment population.

Vadadustat is not significantly removed by hemodialysis, consistent with its high plasma protein binding. Dose adjustment based on dialysis schedule is not required [7].

5.5 Routes of administration

Vadadustat is administered exclusively by the oral route. The approved formulation is a film-coated tablet available in 150 mg and 300 mg strengths. The recommended starting dose is 300 mg orally once daily, with dose adjustments (150 mg increments, dose range 150 to 600 mg) based on hemoglobin response. The dosing interval is once daily for standard administration; a thrice-weekly dosing schedule coordinated with dialysis sessions has been evaluated in clinical studies and shown to maintain hemoglobin within the target range [12].

5.6 Special populations

Renal impairment: Exposure increases modestly with declining eGFR. No dose adjustment is required on the basis of renal function, as the starting dose and subsequent titration are guided by hemoglobin response [7].

Hepatic impairment: Vadadustat is not recommended in patients with cirrhosis or active, acute liver disease. The glucuronidation-dependent metabolism may be impaired in severe hepatic dysfunction, potentially increasing drug exposure.

Geriatric patients: No clinically meaningful differences in pharmacokinetics have been observed based on age alone. The elderly CKD population constitutes a substantial fraction of the target treatment population and was well represented in Phase 3 trials.

Pediatric patients: Vadadustat has not been studied in pediatric populations. The FDA-approved labeling does not include a pediatric indication.

6. Preclinical Pharmacology

6.1 In vitro pharmacology

Vadadustat inhibits all three human PHD isoforms with inhibitory constant (K_i) values in the low-nanomolar range. The inhibition is competitive with 2-oxoglutarate and noncompetitive with the HIF- α peptide substrate. In cell-based reporter assays, vadadustat activates HIF-dependent transcription at concentrations consistent with the cell-free enzyme inhibition potency. The compound stabilizes both HIF-1 α and HIF-2 α protein in multiple cell types, including Hep3B hepatoma cells (a standard erythropoietin-producing cell line), renal interstitial fibroblast lines, and primary human renal cells [1].

Erythropoietin mRNA and protein are induced in Hep3B cells treated with vadadustat at low-micromolar concentrations. VEGF mRNA is not significantly induced at the same concentrations, supporting selectivity within the HIF transcriptional program for the erythropoietic target gene set [1].

In comparative cellular assays, vadadustat was reported to be less potent at inhibiting PHD2 compared with roxadustat, daprodustat, and molidustat [11]. The clinical significance of this relative potency difference is unclear, as all four compounds achieve adequate PHD inhibition at their respective clinical doses.

6.2 In vivo pharmacology

In Sprague-Dawley rats, a single oral dose of vadadustat (3 to 100 mg/kg) produced dose-dependent increases in plasma erythropoietin, with peak levels observed at 4 to 8 hours post-dose and return to baseline within 24 hours. The transient erythropoietin elevation pattern mimics the physiologic diurnal erythropoietin profile observed under hypoxic conditions, in contrast to the sustained supraphysiologic erythropoietin levels produced by ESA injection [1].

Repeat oral dosing of vadadustat for 14 days in healthy rats (10 to 30 mg/kg/day) produced significant increases in hemoglobin, hematocrit, and reticulocyte count. In the 5/6 nephrectomy rat model of CKD, the same dosing regimen produced com-

parable erythropoietic effects, demonstrating efficacy in the setting of reduced renal mass and impaired endogenous erythropoietin production [1].

In mice, daily oral dosing of vadadustat for 14 to 28 days increased hemoglobin and hematocrit. In beagle dogs, daily oral dosing for 28 days produced dose-dependent increases in hemoglobin, reticulocytes, and red blood cell count, confirming cross-species erythropoietic activity and supporting the translation to human dosing [1].

6.3 Chronic toxicology

Chronic toxicology studies in rats and dogs supported the safety profile for long-term clinical dosing. The principal findings at high multiples of the clinical dose included exaggerated pharmacology (polycythemia, increased bone marrow erythroid cellularity) and, at the highest tested doses, non-specific findings consistent with hematologic overproduction. Genotoxicity and carcinogenicity data from the regulatory submission have not been fully published; the FDA approval in 2024 indicates that the nonclinical safety package was considered acceptable for the approved indication [6].

7. Clinical Evidence Base

7.1 Phase 2 studies

Pergola et al. (2016) reported the results of a Phase 2a randomized, dose-ranging, placebo-controlled study of vadadustat in patients with anemia and Stage 3 to 4 non-dialysis-dependent CKD [9]. Patients received vadadustat at doses of 240, 370, or 500 mg once daily or placebo for 20 to 28 days. All vadadustat doses produced significant, dose-dependent increases in hemoglobin, with mean increases of 0.5 to 1.5 g/dL from baseline. Erythropoietin levels increased modestly and remained within the physiologic range, without the supraphysiologic peaks observed with ESA therapy. The compound was well tolerated; no clinically significant hepatic enzyme elevations or thromboembolic events were observed in this short-duration study. However, one case of severe drug-induced liver injury was identified in Phase 2 data, which became a component of the subsequent FDA safety review [10].

Additional Phase 2 studies evaluated vadadustat in dialysis-dependent populations and confirmed dose-response relationships for hemoglobin correction and maintenance [13].

7.2 INNO2VATE Phase 3 program (dialysis-dependent CKD)

The INNO2VATE program comprised two identically designed, randomized, open-label, active-controlled, event-driven noninferiority trials (INNO2VATE-1 and INNO2VATE-2) conducted at sites in the United States, Europe, and Asia-Pacific [4].

Population: Approximately 3,900 adults with anemia due to CKD receiving maintenance hemodialysis or peritoneal dialysis. Patients were enrolled in an ESA-treated (conversion) or ESA-naïve/untreated (correction) stratum.

Interventions: Vadadustat (starting dose 300 mg once daily, titrated by 150 mg increments based on hemoglobin response, dose range 150 to 600 mg) versus darbepoetin alfa (dose-adjusted per standard of care).

Efficacy outcomes: In the pooled INNO2VATE analysis, vadadustat was noninferior to darbepoetin alfa for the primary hematologic efficacy endpoint (mean change in hemoglobin from baseline over weeks 24 to 36). The mean hemoglobin levels achieved in the vadadustat group were comparable to those in the darbepoetin alfa group across both studies.

Cardiovascular safety: The primary cardiovascular safety endpoint was the time to first occurrence of MACE (composite of all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke). In the pooled INNO2VATE analysis, MACE occurred in 420 of 1947 patients (21.6 percent) randomized to vadadustat and in 449 of 1955 patients (23.0 percent) randomized to darbepoetin alfa. The hazard ratio met the prespecified noninferiority margin, establishing cardiovascular safety noninferiority in the dialysis population [4].

7.3 PRO2TECT Phase 3 program (non-dialysis-dependent CKD)

The PRO2TECT program comprised two identically designed trials (PRO2TECT-Correction for ESA-naïve patients and PRO2TECT-Conversion for patients converting from ESA therapy) enrolling approximately 3,500 adults with anemia due to non-dialysis-dependent CKD [5].

Efficacy outcomes: Vadadustat met the prespecified noninferiority criterion for hemoglobin correction and conversion relative to darbepoetin alfa.

Cardiovascular safety: The first occurrence of MACE was higher in the vadadustat group compared to the darbepoetin alfa group, with a hazard ratio of 1.17 (95% confidence interval, 1.01 to 1.36). This hazard ratio exceeded the prespecified noninferiority margin of 1.25 in the upper bound of the confidence interval, and the noninferiority criterion for cardiovascular safety was not met. The excess risk was driven primarily by increased rates of stroke and myocardial infarction in the vadadustat group [5].

Additional safety signals in the PRO2TECT program included increased rates of serious acute kidney injury, serious hepatic injury (including drug-induced liver injury), and serious gastrointestinal erosions in the vadadustat group compared to darbepoetin alfa [5, 10].

7.4 Japanese approval and post-marketing experience

Vadadustat received marketing authorization in Japan from the Ministry of Health, Labour and Welfare in June 2020 for the treatment of anemia due to CKD in both dialysis-dependent and non-dialysis-dependent adults. The compound was launched commercially in Japan in August 2020 under the brand name Vafseo. Post-marketing surveillance data from Japan, covering several years of clinical use, provided additional safety information that supported the subsequent FDA approval in 2024. The Japanese post-marketing data did not reveal unexpected safety signals beyond those characterized in the global Phase 3 program [6].

7.5 FDA approval and indication

The FDA approved Vafseo (vadadustat) tablets on March 27, 2024, for the treatment of anemia due to CKD in adults who have been receiving dialysis for at least three months [6]. The limitation to dialysis-dependent patients (with at least three months of dialysis exposure) reflects the unfavorable cardiovascular safety profile observed in the non-dialysis PRO2TECT program and the positive noninferiority data from the dialysis INNO2VATE program. The approved labeling includes a boxed warning, a REMS requirement, and specific monitoring recommendations for hepatic function.

8. Sourcing and Quality Verification

Pharmaceutical-grade vadadustat is available as the marketed product Vafseo, supplied as 150 mg and 300 mg film-coated tablets for oral administration. Pharmaceutical sourcing is available through standard prescription channels in the United States (for dialysis-dependent CKD patients meeting the indication criteria) and in Japan.

Research-grade vadadustat is supplied by multiple chemical and pharmaceutical research suppliers (MedChemExpress, Selleckchem, Cayman Chemical, Sigma-Aldrich/MilliporeSigma, BocSci, Tocris, others) at greater than 98 percent purity by HPLC. Supply is in milligram to gram quantities as the free acid form. Pricing is moderate, in the range of \$40 to \$150 per 100 milligrams of research-grade material at the time of monograph preparation.

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity (target: greater than 98 percent)
- Mass spectrometry confirmation of molecular weight (306.04 +/- 0.01 for the protonated molecule [M+H]⁺ at m/z 307.05)
- Proton and carbon-13 nuclear magnetic resonance spectroscopy for structural confirmation
- Karl Fischer titration or thermogravimetric analysis for residual water content
- Residual solvent analysis (gas chromatography) for common synthesis solvents (dimethyl sulfoxide, methanol, dichloromethane, ethyl acetate)
- Elemental analysis for residual palladium if the synthesis involved palladium-catalyzed cross-coupling steps (target: less than 10 ppm)

Third-party analytical laboratories provide independent confirmation of vendor certificates of analysis. The research-grade vadadustat market is well established given the compound's clinical development history, and lot-to-lot variability is typically modest. On-receipt analytical confirmation is appropriate for any investigation where dose-response or target engagement precision is important.

9. Reconstitution and Handling

Vadadustat free acid is a crystalline powder with limited aqueous solubility at neutral pH. For in vitro research applications, stock solutions are typically prepared at 10 to 50 mM in dimethyl sulfoxide (DMSO), with the resulting solution stable for at least six months at minus 20 degrees Celsius and for at least one month at minus 80 degrees Celsius. Aliquoting of DMSO stock solutions is recommended to avoid repeated freeze-thaw cycles. For cell-based assays, the DMSO stock is diluted into culture medium such that the final DMSO concentration does not exceed 0.1 to 0.5 percent (v/v).

For in vivo research applications in rodents, vadadustat is typically formulated as a suspension in 0.5 percent methylcellulose, 0.5 percent carboxymethylcellulose, or similar aqueous vehicle systems. The pH of the vehicle can be adjusted to mildly alkaline (pH 8 to 9) to improve dissolution of the carboxylic acid moiety. Oral gavage is the standard route for rodent pharmacology studies; the compound has adequate oral bioavailability in rats, mice, and dogs to support this route [1].

Storage of the solid compound is at room temperature (15 to 25 degrees Celsius) in a dry, light-protected environment. The compound is chemically stable under standard laboratory storage conditions for at least two years from the date of manufacture, based on accelerated stability data from research-grade suppliers. Aqueous solutions at physiologic pH are less stable than DMSO solutions and should be prepared fresh or used within 24 hours of preparation.

For clinical-research formulations, the approved Vafseo tablets are film-coated for oral administration and are stored at controlled room temperature (20 to 25 degrees Celsius, with excursions permitted to 15 to 30 degrees Celsius) [7].

10. Stack Interactions and Combinations

Vadadustat interacts with several drug classes through its transporter inhibition activity and through its pharmacologic effects on erythropoiesis and iron metabolism. Investigators conducting research with vadadustat, especially in chronic dosing regimens or in combination with other compounds, should consider the following interactions.

BCRP substrates: Vadadustat is a potent inhibitor of the breast cancer resistance protein (BCRP/ABCG2) efflux transporter. In a clinical drug-drug interaction study, vadadustat increased the area under the curve (AUC) of the BCRP substrate sulfasalazine by approximately 4.6-fold [7]. Substrates of BCRP that may be affected include rosuvastatin, sulfasalazine, methotrexate, and topotecan. Monitoring for adverse effects of co-administered BCRP substrates and dose adjustments per their approved labeling are recommended.

OATP1B1/1B3 substrates: Vadadustat inhibits organic anion transporting polypeptide 1B1 and 1B3 (OATP1B1/1B3). In a clinical study, vadadustat increased atorvastatin AUC by approximately 1.4-fold [7]. The interaction is modest but may be clinically relevant for OATP1B1/1B3 substrates with narrow therapeutic indices.

Iron supplementation: Oral iron supplements and iron-containing antacids may reduce vadadustat absorption through chelation of the compound in the gastrointestinal tract. The approved labeling recommends that vadadustat be taken at least one hour before or two hours after oral iron supplements [7]. Intravenous iron supplementation does not interact pharmacokinetically and may be used concurrently.

Phosphate binders: Calcium-based and aluminum-based phosphate binders may reduce vadadustat absorption through adsorption or pH effects. Separation of dosing is recommended.

Erythropoiesis-stimulating agents: Concurrent use of vadadustat with injectable ESAs (epoetin alfa, darbepoetin alfa) is not recommended due to the risk of excessive erythropoiesis and polycythemia. The HIF-PHI mechanism produces endoge-

nous erythropoietin; adding exogenous erythropoietin would bypass the physiologic feedback regulation.

Anticoagulants and antiplatelet agents: Given the increased thromboembolic risk associated with vadadustat, concurrent use with agents that increase thrombotic risk (estrogens, selective estrogen receptor modulators) should be approached with caution. Conversely, the concurrent use of anticoagulants (warfarin, direct oral anticoagulants) and antiplatelet agents may be appropriate for thrombotic risk management in the target population.

Statins: The OATP1B1/1B3 and BCRP inhibition may increase exposure to statins that are substrates of these transporters (rosuvastatin, atorvastatin, simvastatin acid). Monitoring for statin-related adverse effects (myalgia, hepatic enzyme elevation, rhabdomyolysis at extreme exposures) is appropriate [7].

CYP enzymes: Vadadustat does not appear to be a significant inhibitor or inducer of major CYP enzymes at clinical concentrations. The dominant glucuronidation metabolic pathway reduces the potential for CYP-mediated drug-drug interactions.

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events observed in the Phase 3 INNO2VATE program at the approved 300 mg starting dose include:

- Diarrhea (10 to 12 percent)
- Hypertension or worsening of pre-existing hypertension (14 percent vadadustat versus 17 percent darbepoetin alfa; serious worsening in 2.7 percent)
- Nausea (5 to 8 percent)
- Peripheral edema (4 to 6 percent)
- Fatigue (3 to 5 percent)
- Abdominal pain (3 to 4 percent)
- Headache (2 to 4 percent)

These adverse-event rates were generally similar to or modestly lower than rates observed in the darbepoetin alfa control arms. The gastrointestinal adverse events (diarrhea, nausea, abdominal pain) are modestly more frequent with vadadustat and may reflect the oral route of administration or HIF-mediated effects on gastrointestinal mucosal biology [4, 14].

11.2 Cardiovascular and thromboembolic events

The FDA-approved labeling carries a boxed warning for increased risk of death, myocardial infarction, stroke, venous thromboembolism, and thrombosis of vascular access [7]. The thromboembolic risk is a class effect observed across the HIF-PHI class and is hypothesized to result from HIF-mediated upregulation of prothrombotic factors (including plasminogen activator inhibitor-1 and tissue factor) and from the erythropoietic effect itself (increased red blood cell mass and blood viscosity).

In the dialysis-dependent INNO2VATE program, the MACE rate was numerically similar between vadadustat and darbepoetin alfa (21.6 percent versus 23.0 percent). In the non-dialysis PRO2TECT program, the MACE rate was higher with vadadustat

(hazard ratio 1.17; 95% CI, 1.01 to 1.36), driven by excess stroke and myocardial infarction [4, 5].

The difference in cardiovascular safety between the dialysis and non-dialysis populations may reflect the higher baseline cardiovascular risk and greater hemodynamic instability of the dialysis population (which dilutes the incremental risk signal), differences in the hemoglobin targets achieved, or population-specific pharmacodynamic effects.

11.3 Hepatotoxicity

Hepatocellular injury attributed to vadadustat was reported in less than 1 percent of patients in the Phase 3 programs, including one severe case with jaundice in Phase 2 [10]. Elevated serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin were observed in 1.8 percent, 1.8 percent, and 0.3 percent of vadadustat-treated patients, respectively. The approved labeling requires liver function testing (ALT, AST, and bilirubin) before treatment initiation and monthly for the first six months of therapy, with vadadustat discontinuation if ALT or AST is persistently elevated (greater than 3 times the upper limit of normal) or accompanied by elevated bilirubin [7].

11.4 Hyperkalemia

The CKD population is at baseline elevated risk for hyperkalemia. Vadadustat did not appear to increase hyperkalemia rates relative to darbepoetin alfa in the Phase 3 programs. Network meta-analyses across HIF-PHI compounds have suggested that molidustat may uniquely reduce hyperkalemia risk within the class [15].

11.5 Malignancy considerations

HIF activation has theoretical potential to promote tumor angiogenesis and growth through upregulation of VEGF and other angiogenic factors. Preclinical data with vadadustat showed no detectable VEGF stimulation at erythropoietically active doses [1]. The Phase 3 programs did not demonstrate increased malignancy rates with vadadustat compared to darbepoetin alfa over the study follow-up period. However, long-term post-marketing surveillance for malignancy signal is ongoing and is a class-wide concern for all HIF-PHI agents.

11.6 Pregnancy and lactation

Vadadustat is classified as having potential embryofetal risk based on its mechanism of action (HIF pathway activation is critical for placental development and embryonic angiogenesis). Animal reproductive toxicity data have not been fully published. The FDA-approved labeling advises avoiding use during pregnancy unless the potential benefit justifies the potential risk to the fetus. It is not known whether vadadustat is excreted in human breast milk [7].

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative HIF prolyl hydroxylase inhibitors against vadadustat, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five comparators were selected as the principal HIF-PHI compounds with substantive clinical development programs for the treatment of anemia due to CKD.

12.1 Roxadustat (FG-4592; Evrenzo)

Mechanism: Oral HIF-PHI with 2-oxoglutarate-competitive inhibition of PHD1, PHD2, and PHD3. Roxadustat shares the carbonylglycine structural class with vadadustat and daprodustat but has a distinct isoquinoline core scaffold [16].

Development trajectory: Developed by FibroGen in collaboration with AstraZeneca and Astellas Pharma. Roxadustat was the first HIF-PHI to receive regulatory approval, first in China (December 2018) for dialysis-dependent CKD and subsequently in Japan (November 2019) and the European Union (August 2021). The FDA issued a complete response letter in August 2021 citing cardiovascular safety concerns from the pooled Phase 3 program [17].

Novelty: Low. Roxadustat was the first-in-class clinical HIF-PHI and established the precedent for the mechanism. Its mechanism is substantially similar to vadadustat.

Effect size: In Phase 3 trials, roxadustat demonstrated noninferiority to ESAs for hemoglobin correction and maintenance. In network meta-analyses, roxadustat ranked highest among HIF-PHIs for hemoglobin response, particularly in dialysis populations [15]. The hemoglobin response is generally robust, achieving target ranges in the majority of patients.

Promising potential: Moderate to high. Roxadustat is approved in multiple jurisdictions (China, Japan, European Union, United Kingdom, South Korea) but not in the United States. The global commercial availability provides extensive real-world

safety and efficacy data. The FDA rejection limits the United States market presence.

Side-effect profile: Roxadustat has been associated with a significantly increased risk of vascular occlusion and stenosis (approximately 1.9-fold versus ESA in network meta-analyses) [15]. Hyperkalemia, nausea, and diarrhea have been reported. The thromboembolic risk is a class effect shared with vadadustat.

Overall validation: High. Roxadustat has the most extensive clinical and post-marketing database among HIF-PHIs, with regulatory approvals in multiple major jurisdictions and extensive published Phase 3 data.

Comparison to vadadustat: Roxadustat and vadadustat share the same mechanism and carbonylglycine structural class. In comparative cellular assays, roxadustat is more potent at PHD2 inhibition than vadadustat. Clinically, both compounds demonstrate noninferiority to ESAs in dialysis populations. Roxadustat has broader regulatory approval (EU, Japan, China) while vadadustat has FDA approval (limited to dialysis patients). The cardiovascular safety signals are qualitatively similar. Roxadustat requires thrice-weekly dosing, while vadadustat is administered once daily, an operational advantage for patient adherence.

12.2 Daprodustat (GSK1278863; Jesduvroq)

Mechanism: Oral HIF-PHI with 2-oxoglutarate-competitive inhibition of PHD enzymes. Daprodustat has a carbonylglycine moiety but a distinct pyrimidinetrione core scaffold [18].

Development trajectory: Developed by GlaxoSmithKline. The ASCEND Phase 3 program comprised multiple trials in dialysis-dependent and non-dialysis-dependent CKD. The FDA approved daprodustat (Jesduvroq) in February 2023 for the treatment of anemia due to CKD in adults on dialysis, making it the first HIF-PHI approved in the United States [18]. Japan also approved daprodustat for CKD anemia in both dialysis and non-dialysis populations.

Novelty: Low. The mechanism is shared with vadadustat and roxadustat. The structural scaffold is distinct but the pharmacologic principle is identical.

Effect size: In the ASCEND-D trial (dialysis-dependent), daprodustat was noninferior to ESA for hemoglobin maintenance and cardiovascular safety. In clinical comparisons, daprodustat achieved slightly higher hemoglobin levels than vadadustat

over equivalent treatment periods (12.1 g/dL versus 11.3 g/dL at six months in one head-to-head comparison of dosing protocols) [19]. Daprodustat has demonstrated advantages in iron metabolism parameters, including greater improvements in transferrin saturation, hepcidin, and ferritin [15].

Promising potential: High. Daprodustat is FDA-approved and commercially available in the United States. It was the first HIF-PHI to achieve FDA approval and has established the regulatory precedent for the class.

Side-effect profile: Daprodustat has been associated with increased rates of diarrhea and constipation compared to ESA. The cardiovascular safety profile was non-inferior to ESA in the dialysis population. The thromboembolic risk profile is qualitatively similar to vadadustat.

Overall validation: High. Daprodustat has the strongest regulatory and commercial position in the United States among HIF-PHIs, with FDA approval predating vadadustat by approximately one year.

Comparison to vadadustat: Daprodustat and vadadustat are direct competitors in the United States dialysis anemia market. Daprodustat has the first-mover advantage (FDA approval February 2023 versus March 2024 for vadadustat). Both are once-daily oral agents; daprodustat may have modestly greater hemoglobin-raising efficacy in some comparisons. Vadadustat's BCRP inhibition potential is a differentiating drug interaction concern. The iron mobilization advantages of daprodustat (greater hepcidin suppression) may reduce the need for intravenous iron supplementation.

12.3 Molidustat (BAY 85-3934; Masimo)

Mechanism: Oral HIF-PHI. Molidustat is structurally distinct from the carbonyl-glycine class; it contains a triazine core scaffold and does not have the glycine-derived side chain shared by vadadustat, roxadustat, and daprodustat [20]. The binding mode at the PHD active site differs, potentially contributing to differences in selectivity and off-target effects.

Development trajectory: Developed by Bayer. Phase 3 trials (MIYABI program) were conducted primarily in Japan. Molidustat was approved in Japan in 2021 for the treatment of anemia due to CKD. The compound has not been submitted for regulatory approval in the United States or European Union.

Novelty: Moderate. The triazine scaffold and non-carboxylglycine binding mode distinguish molidustat structurally from the other HIF-PHIs.

Effect size: Phase 3 data from the Japanese MIYABI program demonstrated non-inferiority to ESA for hemoglobin maintenance in both dialysis and non-dialysis populations. The hemoglobin effect size is comparable to the other HIF-PHIs [20].

Promising potential: Low to moderate outside Japan. The compound is approved only in Japan and is not in active development for United States or European regulatory submission.

Side-effect profile: Network meta-analyses suggest that molidustat is the only HIF-PHI that reduces the likelihood of hyperkalemia [15]. Gastrointestinal side effects are modest. The cardiovascular safety profile has been noninferior to ESA in the Japanese Phase 3 program.

Overall validation: Moderate. The clinical-pharmacology research literature is smaller than for roxadustat or daprodustat but adequate for regulatory approval in Japan.

Comparison to vadadustat: Molidustat is structurally distinct and may have a differentiated pharmacologic profile due to its non-carboxylglycine binding mode. The potential advantage in hyperkalemia risk is clinically relevant in the CKD population. Vadadustat has the advantage of FDA approval and broader global regulatory presence.

12.4 Desidustat (ZYAN1; Duvroq)

Mechanism: Oral HIF-PHI with 2-oxoglutarate-competitive PHD inhibition. Desidustat was developed by Zydus Lifesciences (formerly Cadila Healthcare) in India [21].

Development trajectory: Phase 3 trials (DREAM program) were conducted in India in both dialysis-dependent and non-dialysis-dependent CKD populations. Desidustat received marketing authorization in India in 2022 for the treatment of anemia due to CKD [21].

Novelty: Low. The mechanism is identical to the other carboxylglycine-class HIF-PHIs.

Effect size: Phase 3 data from Indian trials demonstrated noninferiority to ESA (epoetin alfa) for hemoglobin correction and maintenance. The hemoglobin effect size is comparable to the other HIF-PHIs.

Promising potential: Low outside India. The compound is approved only in India and is not in active development for United States, European, or Japanese regulatory submission. The limited global clinical program and the single-country regulatory approval constrain the evidence base.

Side-effect profile: Network meta-analyses suggest that desidustat and vadadustat offer the least gastrointestinal discomfort among the HIF-PHI class [15]. Cardiovascular safety data from the Indian Phase 3 program are limited by shorter follow-up and smaller sample size relative to the global programs of roxadustat, daprodustat, and vadadustat.

Overall validation: Low to moderate. The clinical evidence base is regionally limited and the peer-reviewed literature is smaller than for the other comparators.

Comparison to vadadustat: Vadadustat has a substantially larger global clinical evidence base, FDA approval, and more extensive safety characterization. Desidustat offers an alternative HIF-PHI option in the Indian market.

12.5 Enarodustat (JTZ-951; Enaroy)

Mechanism: Oral HIF-PHI with competitive PHD inhibition. Developed by Japan Tobacco and Torii Pharmaceutical [22].

Development trajectory: Phase 3 trials were conducted in Japan. Enarodustat received marketing authorization in Japan in 2020 for the treatment of anemia due to CKD.

Novelty: Low. The mechanism is shared with the other HIF-PHIs.

Effect size: Phase 3 data from Japanese trials demonstrated noninferiority to ESA for hemoglobin maintenance. Network meta-analyses have limited data for enarodustat due to the restricted clinical program [15].

Promising potential: Low outside Japan. The compound is approved only in Japan and is not in development for other regulatory jurisdictions.

Side-effect profile: Limited safety data from Japanese trials suggest a tolerability profile consistent with the HIF-PHI class. The small sample sizes limit the detection of rare adverse events.

Overall validation: Low. The clinical evidence base is restricted to Japanese Phase 3 data and the peer-reviewed literature is the smallest among the comparators.

Comparison to vadadustat: Vadadustat has a substantially larger clinical program, broader regulatory approval, and more extensive safety characterization. Enarodustat provides an additional HIF-PHI option in the Japanese market but does not constitute a competitive alternative in other regions.

12.6 Comparator summary

The five HIF-PHI comparators occupy distinct positions in the clinical landscape. **Roxadustat** has the broadest global regulatory approval (EU, Japan, China) and the largest post-marketing experience, but lacks FDA approval. **Daprodustat** was the first HIF-PHI to receive FDA approval and is the primary United States market competitor to vadadustat. **Molidustat** is structurally differentiated by its non-carbonyl-glycine scaffold and may have an advantageous hyperkalemia profile, but is approved only in Japan. **Desidustat** and **enarodustat** are regionally approved (India and Japan, respectively) with limited global evidence bases.

Vadadustat occupies a position as the second FDA-approved HIF-PHI, with the largest single Phase 3 cardiovascular safety database (the combined INNO2VATE and PRO2TECT programs enrolled over 7,000 patients). Its once-daily oral dosing, demonstrated noninferiority to ESA in dialysis populations, and the restriction to dialysis-dependent patients (which addresses the cardiovascular safety concern identified in the non-dialysis population) define its clinical niche. The principal differentiating considerations for vadadustat within the HIF-PHI class are: (a) the potent BCRP transporter inhibition, which creates a unique drug-drug interaction profile; (b) the once-daily dosing schedule (versus thrice-weekly for roxadustat); (c) the well-characterized non-dialysis safety concern that limits the indicated population; and (d) the extensive post-marketing safety data from Japan supporting long-term use.

The choice among HIF-PHIs in clinical practice and research is driven by regional availability, dosing schedule preference, concurrent medication profile (particularly BCRP and OATP substrates), iron metabolism considerations, and individual patient cardiovascular risk assessment.

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This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly. Vadadustat is approved by the United States Food and Drug Administration for the treatment of anemia due to chronic kidney disease in adults who have been receiving dialysis for at least three months. The compound carries a boxed warning for increased risk of death, myocardial infarction, stroke, venous thromboembolism, and thrombosis of vascular access. Investigators should consult the full prescribing information and their local regulatory authority before any research application.