Evidence-Based Recommendations for the Use of Desidustat in Chronic Kidney Disease

Sourabh Sharma[1], Bianca Davidson[2], Dina A Abdellatif[3], Sanjay Kalra[4]

Abstract

Anaemia is a common and clinically significant complication of chronic kidney disease (CKD), contributing to reduced quality of life, cardiovascular morbidity, and increased mortality. Conventional management has relied predominantly on injectable erythropoiesis-stimulating agents (ESAs) and iron supplementation; however, these approaches are associated with limitations including hyporesponsiveness, injection burden, and safety concerns. Hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) have emerged as a novel therapeutic class that stimulates endogenous erythropoietin production while improving iron metabolism. Recent Kidney Disease: Improving Global Outcomes (KDIGO) anaemia guidelines acknowledge HIF-PHIs as therapeutic alternatives in selected patients. This review synthesizes available evidence and provides practical, evidence-based recommendations for the use of desidustat across different stages of CKD.

Keywords: Chronic kidney disease, Anemia, Desidustat, HIF-PHI, Erythropoiesis, KDIGO.

DOI: https://doi.org/10.47391/JPMA.26-38

Introduction

Anaemia is a common and clinically significant complication of CKD, affecting patients across all stages of kidney dysfunction and contributing to fatigue, reduced quality of life, cardiovascular complications, and increased mortality.[1] The pathophysiology of CKD-associated anaemia is multifactorial, including reduced renal erythropoietin production, impaired iron utilization, chronic inflammation, and decreased red blood cell lifespan.[2] For decades, ESAs combined with iron supplementation have been the mainstay of anaemia management in CKD.[1,2] While ESAs effectively raise haemoglobin levels and reduce the need for transfusions, their use is limited by the requirement for parenteral administration, variable patient responsiveness, and safety concerns related to hypertension, thromboembolic events, and adverse cardiovascular outcomes when targetting higher haemoglobin levels.[3] These limitations prompted the development of alternative therapies that more closely mimic physiological erythropoiesis.

HIF-PHIs are a novel class of orally administered agents that stabilize hypoxia-inducible factor (HIF), stimulating endogenous erythropoietin production and improving iron metabolism through hepcidin suppression.[4,5] Desidustat is a selective HIF-PHI developed for the treatment of CKD-associated anaemia, with preclinical and translational studies demonstrating favourable effects on erythropoiesis, iron mobilization, and hepcidin regulation without excessive off-target angiogenic stimulation.[4,5] The KDIGO 2026 Clinical Practice Guideline for the Management of Anaemia in CKD recognizes HIF-PHIs, including desidustat, as evidence-based therapeutic options. The guideline highlights individualized treatment decisions, careful monitoring of haemoglobin, and the importance of iron optimization, all of which align closely with the clinical trial evidence.[6,7] In this review, we synthesize current evidence on desidustat, focussing on its mechanism of action, efficacy across CKD stages, safety and tolerability, practical clinical considerations, and alignment with contemporary guideline recommendations.

Mechanism of Action of Desidustat

Desidustat is an orally active HIF-PHI that mimics the cellular response to physiological hypoxia by selectively inhibiting prolyl hydroxylase domain (PHD) enzymes responsible for degradation of hypoxia-inducible factor-α (HIF-α) under normoxic conditions.[4] In patients with CKD, impaired renal erythropoietin (EPO) production and disordered iron metabolism contribute to anaemia. Desidustat addresses both these pathogenic pathways simultaneously.[4,5] By inhibiting PHD enzymes, desidustat stabilizes HIF-α subunits, allowing their translocation to the nucleus where they heterodimerize with HIF-β and bind to hypoxia-responsive elements on target genes. This results in transcriptional activation of genes involved in erythropoiesis, iron absorption, transport, and utilization. Unlike exogenous ESAs, desidustat induces endogenous EPO production at physiologic levels, predominantly in the kidney and liver, thereby avoiding supraphysiologic EPO

[1]Department of Nephrology, Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi; [2]Division of Hypertension and Nephrology, Department of Medicine, Groote Schuur Hospital, University of Cape Town, Anzio Road, Observatory, Cape Town, South Africa; [3]Renal Division, Cairo University Hospital, Cairo, Egypt; [4]Department of Endocrinology, Bharti Hospital, Karnal, India; University Centre for Research & Development, Chandigarh University, Mohali, India.

Correspondence: Sanjay Kalra. e-mail: brideknl@gmail.com
ORCID ID: 0000-0003-1308-121X

peaks associated with injectable ESA therapy.[4] Secondly, HIF activation leads to suppression of hepcidin synthesis and upregulation of key iron transport proteins, including divalent metal transporter-1 and duodenal cytochrome b, enhancing intestinal iron absorption and mobilization of stored iron. These effects are particularly relevant in CKD, where inflammation-driven functional iron deficiency frequently limits the response to ESAs.[4,5,8-10]

Table-1: Advantages and Key Differences Between Desidustat and Epoetin.

EPO exposure	Desidustat	ESAs	Clinical Implication
EPO exposure	Produces physiologic, regulated EPO levels	Often causes supraphysiologic EPO peaks	Lower peak exposure may translate into improved cardiovascular safety signals
Effect on iron metabolism	Suppresses hepcidin, enhances intestinal absorption, and mobilizes stored iron	Limited direct effect on iron handling	May reduce functional iron deficiency and IV iron requirements
Route of administration	Oral	Injectable (IV or SC)	Greater convenience, improved adherence, and reduced injection burden
Patient preference	Non-invasive therapy	Requires repeated injections	Particularly advantageous in pre-dialysis patients and those with needle aversion
ESA hypo-responsiveness	Effective even in inflammatory states due to improved iron availability	Response may be blunted in inflammation	Useful in patients with ESA resistance
Haemoglobin stability	Demonstrated non-inferiority in maintaining target Hb	Established efficacy	Comparable effectiveness with a different mechanism
Healthcare resource utilization	Potentially fewer clinic visits for injections; no need for cold chain maintenance	Requires trained personnel or self-injection along with cold chain maintenance	May improve feasibility in resource-limited settings
Iron supplementation needs	Reduced reliance on parenteral iron reported in trials	Often requires IV iron support	Simplifies anaemia management strategy
Overall therapeutic approach	Addresses both EPO deficiency and disordered iron homeostasis	Primarily corrects EPO deficiency	Represents more integrated pathophysiologic treatment strategy

Clinical Evidence for Desidustat Across CKD Stages

A randomized, double-blind, placebo-controlled phase II trial conducted by Parmar DV et al[8] demonstrated a dose-dependent and statistically significant increase in haemoglobin levels in patients with CKD-related anaemia, along with acceptable short-term safety and tolerability. Subsequently, the efficacy and safety of desidustat in non–dialysis-dependent CKD were confirmed in the phase III DREAM-ND trial,[9] a multicentre randomized controlled study that demonstrated non-inferiority of desidustat compared with darbepoetin alfa in achieving and maintaining target haemoglobin levels. Patients receiving desidustat showed stable haemoglobin correction, reduced need for parenteral iron supplementation, and a safety profile comparable to ESA therapy, supporting its role in CKD stages 3-5 not on dialysis.[9] In patients with dialysis-dependent CKD, the DREAM-D trial[10] provided robust evidence that desidustat was non-inferior to epoetin alfa for haemoglobin maintenance. The trial also demonstrated consistent efficacy across predefined subgroups, including varying dialysis vintage and baseline iron status, with no excess risk of major adverse cardiovascular events observed during the trial duration.[10] A recent systematic review of 47 studies encompassing 55 randomised controlled trials demonstrated that HIF-PHIs, as a class, are effective in improving haemoglobin levels in patients with CKD.[11] KDIGO 2026 Clinical Practice Guideline for the Management of Anaemia in CKD recognizes HIF-PHIs as an evidence-based therapeutic option for anaemia management in appropriately selected CKD patients, emphasizing individualized treatment decisions based on CKD stage, iron status, cardiovascular risk, and patient preference.[6,7]

Another systematic review by Li J et al[12] suggested that HIF-PHIs increased iron utilization in patients with non-dialysis-dependent CKD. They reiterated that HIF-PHIs are associated with increased transferrin levels, along with TIBC, and cause fall in TSAT. The associated reduction of TSAT after HIF-PHI initiation is anticipated and should not be labelled iron deficiency.[12]

Safety and Tolerability

The safety and tolerability profile of desidustat has been systematically evaluated across phase II and phase III clinical trials involving both dialysis and non–dialysis dependent CKD populations.[8-12] No excess risk of major adverse cardiovascular events, including myocardial infarction or stroke, was observed with desidustat during the DREAM-ND trial.[9] Desidustat did not demonstrate an increased risk of vascular access thrombosis or dialysis-related adverse outcomes in dialysis dependent CKD in DREAM-D trial.[10] The existing evidence supports desidustat as a well-tolerated oral therapy for anaemia in CKD, with a safety profile comparable to injectable ESAs when used in appropriately selected patients and monitored according to guideline-based recommendations.[8-10]

Advantages and Key Differences from ESA

Desidustat offers a physiologically aligned alternative to conventional ESAs. Its oral administration enhances treatment convenience while avoiding supraphysiologic EPO peaks associated with injectable therapies. Collectively, these properties position desidustat as a patient-friendly option for anaemia management in CKD.[4,5] Table 1 showcases key advantages and differences between desidustat and ESAs.

Indications and Contraindications

Patient selection is critical for the appropriate use of desidustat. Evidence-based indications and

Table-2: Indications, Contraindications, and Cautions for the Use of Desidustat in CKD-Associated Anaemia.

Category	Clinical Scenario	Evidence Base
Indications	Anaemia in non–dialysis-dependent CKD (Stages 3-5ND)	Phase III DREAM-ND trial demonstrated non-inferiority of desidustat to darbepoetin alfa for haemoglobin correction and maintenance, with comparable safety and reduced need for injectable therapy Oral administration offers a patient-friendly alternative, particularly in predialysis CKD.
	Anaemia in dialysis-dependent CKD (HD or PD)	DREAM-D trial showed desidustat to be non-inferior to epoetin alfa for haemoglobin maintenance, with similar cardiovascular and thrombotic event rates, supporting its use as an alternative to injectable ESAs in dialysis patients.
	ESA hyporesponsiveness or intolerance	Desidustat stimulates endogenous EPO production and improves iron utilization via hepcidin suppression, offering advantage in patients with inflammation-driven ESA resistance
	Functional iron deficiency	HIF-PHI improves iron absorption and mobilization, potentially reducing reliance on intravenous iron therapy.
Relative Indications	Poor adherence or aversion to injectable therapies	Oral administration improves treatment convenience and may enhance adherence in long-term anaemia management.
	Limited access to parenteral ESA administration	Particularly relevant in resource-limited or outpatient settings where frequent injections are impractical.
Contraindications	Uncontrolled hypertension	Similar to ESA therapy, excessive erythropoietic stimulation may exacerbate hypertension Patients with poorly controlled blood pressure were excluded from pivotal trials.
	Active malignancy receiving curative treatment	HIF pathway activation theoretically may influence tumour biology; KDIGO 2026 guidelines recommend caution or avoidance pending long-term safety data.
	Severe hepatic impairment	Desidustat undergoes hepatic metabolism Safety data in advanced liver disease are limited.
	Known hypersensitivity to desidustat	Standard contraindication applicable to all pharmacologic agents.
Special Populations	High cardiovascular risk (recent MI, stroke)	Individualized risk-benefit assessment is recommended.
	History of thromboembolic events	Maintain haemoglobin within guideline-recommended targets to minimize thrombotic risk.
	Rapid haemoglobin rise	Overcorrection may increase cardiovascular risk Dose titration and close monitoring are required.
	Pregnancy and lactation	Insufficient human data Use only if potential benefit justifies potential risk

contraindications are summarized in Table 2. Desidustat should not be used in patients with uncontrolled hypertension, known hypersensitivity to the drug, or severe hepatic impairment due to limited safety data. Caution is advised in individuals with active malignancy or high thromboembolic risk, where potential benefits must be carefully weighed against theoretical and clinical safety concerns.[4]

Practical Considerations in Clinical Use

The successful integration of desidustat into routine practice requires adherence to structured initiation, monitoring, and dose adjustment strategies. Practical recommendations are outlined in Table 3.

Table-3: Practical Points for Using Desidustat in CKD-Associated Anemia.

Domain	Practical Consideration	Clinical Rationale and Evidence-Based Guidance
Patient selection	Confirm CKD-related anaemia	Exclude reversible causes of anaemia such as iron deficiency, vitamin B12 or folate deficiency, active bleeding, and haemolysis prior to initiation.
Baseline assessment	Haemoglobin level	Initiate when haemoglobin falls below 10.0 g/dL, after correction of reversible causes of anaemia and following individualized clinical assessment.
	Iron status (TSAT, ferritin)	Desidustat may reduce hepcidin levels and improve iron utilization, but absolute iron deficiency still requires supplementation.
	Blood pressure	Ensure adequate blood pressure control prior to initiation
Dosing and administration	Route of administration	Desidustat is administered orally, offering a practical alternative to injectable ESAs.
	Dose titration	Gradual dose titration is recommended to avoid rapid haemoglobin rise (>1 g/dL over 2–4 weeks).
	Switching from ESA	An appropriate washout period with close haemoglobin monitoring is recommended to avoid rapid haemoglobin rise and overshooting of target levels.
Monitoring during therapy	Haemoglobin monitoring	Haemoglobin monitoring.
	Iron parameters	Periodic monitoring of ferritin and TSAT is recommended TSAT reduction after HIF-PHI initiation is anticipated and should not be labelled iron deficiency.
	Adverse events	Monitor for hypertension, headache, gastrointestinal symptoms, and signs of thromboembolic events.
Special situations	Dialysis patients	Desidustat can be administered irrespective of dialysis timing. No dose adjustment based solely on dialysis modality is required.
	High cardiovascular risk	Use with caution and maintain haemoglobin within recommended targets.
	Inflammatory states	Patients with chronic inflammation or ESA. hyporesponsiveness may particularly benefit due to hepcidin suppression and improved iron handling.
Treatment goals	Target haemoglobin	Desidustat therapy should be titrated to achieve an individualized target haemoglobin of 10–11.5 g/dL, with haemoglobin levels not to exceed 11.5 g/dL.
	Long-term strategy	Comprehensive anemia management strategy that includes periodic reassessment of hemoglobin targets, iron status, cardiovascular risk, and ongoing need for therapy Continued pharmacovigilance and long-term outcome data are essential to refine patient selection and optimize the durability and safety of desidustat therapy in CKD.

Conclusion

Management of anaemia in CKD requires a patient-centred approach that extends beyond uniform haemoglobin targets or single-agent strategies. Desidustat offers a physiologically grounded, oral therapeutic option that aligns with contemporary principles of individualized care, particularly in patients with functional iron deficiency, variable responsiveness to conventional therapies, or preference for non-injectable treatment modalities. Its dual action on erythropoiesis and iron metabolism allows clinicians to tailor therapy according to disease stage, comorbidity burden, cardiovascular risk, and patient lifestyle considerations. Optimal use of desidustat depends on careful patient selection, judicious dose titration, and regular reassessment of haemoglobin trends, iron parameters, and overall clinical status. Incorporated thoughtfully into a comprehensive anaemia management

framework, desidustat has the potential to support more flexible, patient-focussed care pathways in CKD, emphasizing shared decision-making, treatment convenience, and sustained clinical benefit over time.

References

1. Portolés J, Martín L, Broseta JJ, Cases A. Anemia in Chronic Kidney Disease: From Pathophysiology and Current Treatments, to Future Agents. Front Med (Lausanne). 2021;8:642296.
2. Zadrazil J, Horak P. Pathophysiology of anemia in chronic kidney diseases: A review. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2015;159:197-202.
3. Chung EY, Palmer SC, Saglimbene VM, Craig JC, Tonelli M, Strippoli GF. Erythropoiesis-stimulating agents for anaemia in adults with chronic kidney disease: a network meta-analysis. Cochrane Database Syst Rev. 2023;2:CD010590.
4. Joharapurkar A, Pandya V, Patel H, Jain M, Desai R. Desidustat: a novel PHD inhibitor for the treatment of CKD-induced anemia. Front Nephrol. 2024;4:1459425.
5. Patel VJ, Joharapurkar A, Kshirsagar SG, Patel MS, Savsani HH, Dodiya HS, Rakhasiya MH, Kajavadara C, Valani D, Jain MR. HIF-PHD inhibitor desidustat ameliorates iron deficiency anemia. Toxicol Appl Pharmacol. 2024;483:116832.
6. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO 2026 clinical practice guideline for the management of anemia in chronic kidney disease. Kidney Int. 2026;109(1 Suppl):S1-S99.
7. Babitt JL, Berns JS, Bozkurt B, Cheung Khedairy RS, Cuevas Y, Effa EE, et al. Executive Summary of the KDIGO 2026 Clinical Practice Guideline for the Management of Anemia in Chronic Kidney Disease (CKD). Kidney Int. 2026;109:44-56.
8. Parmar DV, Kansagra KA, Patel JC, Joshi SN, Sharma NS, Shelat AD, et al; on behalf of the ZYAN1 Trial Investigators. Outcomes of Desidustat Treatment in People with Anemia and Chronic Kidney Disease: A Phase 2 Study. Am J Nephrol. 2019;49:470-478.
9. Agrawal D, Varade D, Shah H, Nazar A, Krishnan J, Shukla V, et al; Study Investigator Group. Desidustat in Anemia due to Non-Dialysis-Dependent Chronic Kidney Disease: A Phase 3 Study (DREAM-ND). Am J Nephrol. 2022;53:352-360.
10. Gang S, Khetan P, Varade D, Chinta VR, Mavani S, Gupta U, et al; Study Investigator Group. Desidustat in Anemia due to Dialysis-Dependent Chronic Kidney Disease: A Phase 3 Study (DREAM-D). Am J Nephrol. 2022;53:343-351.
11. Ren S, Zhao Y, Wu J, Ren S, Feng Y. Hypoxia-inducible factor-prolyl hydroxylase inhibitors for treatment of anemia in chronic kidney disease: a systematic review and network meta-analysis. Front Pharmacol. 2024;15:1406588.
12. Li J, Xie QH, You L, Xu NX, Hao CM. Effects of hypoxia-inducible factor prolyl hydroxylase inhibitors on iron regulation in non-dialysis-dependent chronic kidney disease patients with anemia: A systematic review and meta-analysis. Pharmacol Res. 2021;163:105256.