Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors for Treatment of Anemia in Chronic Kidney Disease: Guidelines for South Asia

South Asia HIF-PHI for Anemia in CKD Guideline Development Group*

Abstract

This guideline addresses the use of hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) in patients >18 years with chronic kidney disease (CKD) and anemia in South Asia (Bangladesh, Bhutan, Nepal, India, Pakistan, Sri Lanka). It also summarizes recommendations for anemia treatment for individual HIF-PHI molecules under two categories: dialysis-dependent and non-dialysis-dependent CKD patients. The recommendations do not apply to pediatric (≤12 years) and adolescent (12 to 18) patients or those with primary anemia or anemia secondary to other causes such as blood loss, cancer (any type), polycystic kidney disease and infectious diseases.

Keywords: *Chronic kidney disease, Anemia, Dialysis, HIF-PHIs, Guidelines*

Introduction

Chronic kidney disease (CKD) is a significant public health issue worldwide. The Global Burden of Disease Study 2019 estimates CKD as the 12th leading cause of death, affecting 843.6 million people.[1] In South Asia, the pooled prevalence of CKD is 14%, most being from India (115·1 million), Bangladesh and Pakistan each having >10 million cases. In South Asia, 2.39% of total deaths and 1.61% of total disability-adjusted life years (DALYs) reported were attributed to CKD.[2–4] People with CKD are often affected by multiple comorbidities and complications, making its management complex.[5]

Anemia is a common complication of CKD and is associated with several negative outcomes, including an increased risk of cardiovascular disease (CVD), decreased quality of life (QoL), worsening of kidney function and increased morbidity and mortality:

1. *Cardiovascular disease*: The increased risk of CVD, including heart failure and cardiovascular death secondary to anemia in CKD, is thought to be due to the increased workload on the heart caused by anemia and the increased production of pro-inflammatory cytokines and oxidative stress.
2. *Decreased quality of life*: Anemia is associated with decreased physical function, fatigue, and decreased QoL in those with CKD. This can affect a patient's ability to perform activities of daily living and can lead to social isolation.
3. *Preserving kidney function*: Treating anemia can help preserve kidney function by reducing the metabolic demand on the kidneys.
4. *Increased morbidity and mortality*: Anemia in CKD is associated with increased morbidity and mortality. This is thought to be due to the increased risk of CVD infection, sepsis, and other complications.

Worsening kidney function, increasing age, female sex, presence of comorbidities, and nonavailability of iron therapy are known risk factors for anemia in CKD.[6]

Therefore, treating it is essential for improving patient outcomes. Box 1 shows the characteristics of the ideal agent for the treatment of anemia of CKD.

Characteristics of an ideal agent for the treatment of anemia in CKD

Targeting the underlying cause of anemia: Ideally, the agent should work by targeting the underlying causes of anemia, such as decreased erythropoietin (EPO) production and iron deficiency rather than simply increasing erythropoiesis.
Efficacy: The agent should be effective at increasing hemoglobin levels and improving anemia-related symptoms in patients with CKD.
Safety: The agent should be safe and have a favorable benefit-risk profile with minimal risk of serious side effects such as cardiovascular events and cancers.
Convenience of use: The agent should be easy to administer with minimal monitoring requirements and few or no dietary restrictions.
Cost-effective: The agent should be cost-effective and affordable for patients and not require prolonged treatment.
Preservation of kidney function: The agent should not negatively impact on the kidney function, and if possible, should improve it.

The current treatment options target multiple mechanisms of renal anemia and include oral and parenteral iron therapy, injectable erythropoietin-stimulating agents (ESAs), and blood transfusion.[7] ESAs [e.g., recombinant human erythropoietin (EPO), darbepoetin, and continuous EPO receptor activator] have been the cornerstone of anemia correction for >30 years. However, several

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concerns have been raised post the clinical trials of ESAs, such as the increased risk of cardiovascular events (heart attack, stroke), cancers, and mortality, especially in those with severe kidney disease. There is an ongoing debate about the appropriate target of hemoglobin level for ESA therapy. Some studies suggested that targeting higher hemoglobin levels increases the risk of cardiovascular events and death. In contrast, others found that targeting lower hemoglobin levels is associated with the worsening kidney function and QoL. Finally, these agents have defined storage requirements and must be administered by the parenteral route (intravenous or subcutaneously), making the administration problematic in domiciliary settings.

The hypoxia-inducible factor (HIF) transcriptional complex was discovered in 1995. Pharmacological inhibitors of this transcription factor (TF) recapitulate hypoxia events and upregulate the EPO gene expression causing a salutary effect on other genes involved in erythropoiesis. Hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) are attractive options for the treatment of anemia in CKD, and several have been tested in phase III clinical trials. They are now approved for treatment by drug regulators in many countries, including India, Bangladesh, the Republic of China, Japan, Chile, South Korea, UK, USA and the European Union Economic Area countries.[8] While both HIF-PHIs and ESAs eventually increase EPO levels, HIF-PHIs stimulate EPO production at physiological levels, providing a theoretical advantage of lower risk of major adverse cardiovascular events (MACE).[8] Their salutary effect on the iron regulatory proteins may allow for more efficient iron utilization and lower iron overload. Finally, availability as an oral agent and liberal storage conditions (no refrigeration requirement) present additional logistic advantages. However, considerable uncertainty exists around the use of HIF-PHIs in South Asia.

Objectives

The primary objective of the guideline is to provide an evidence-informed recommendation for nephrologists, general physicians, and internal medicine specialists in South Asia (Bangladesh, Bhutan, India, Nepal, Pakistan, and Sri Lanka) regarding the use of HIF-PHIs for anemia in CKD patients. A secondary objective is identifying knowledge gaps for future research that can help improve clinical care.

The guidelines aim to formulate consensus around the use of these novel agents. The guideline was developed using a structured process in accordance with the existing global standards. The guideline has been endorsed by the Bangladesh Renal Association and Indian Society of Nephrology.

Methods

The overall guideline development process, panel formation, management of conflicts of interest, peer review, and methodological support was convened by The George Institute for Global Health, India (TGI). Broadly, the process followed the Grading of Recommendations Assessment, Development, and Evaluations (GRADE) approach.[9,10] The guideline is reported to be using the Reporting Items for practice Guidelines in HealThcare (RIGHT) tool by the International RIGHT Working Group.[11] The RIGHT checklist is presented in Supplementary Appendix 1.

Organization, panel composition, planning, and coordination

The Guideline Steering Committee included a nominated chair, nephrologists, internal medicine specialists, nonphysician healthcare workers, and patient representative. The Methodology Committee included methodologists and kidney health specialists without any conflict of interests. The Methodology Committee advised the Steering Committee, developed terms of reference, acted as a secretariat for managing conflicts of interest, and provided oversight to the guideline development process. The chair of the Methodology Committee attended all Steering Committee meetings in an advisory role.

A larger Guideline Development Group (GDG) was appointed by the Steering Committee aiming for gender and professional diversity and comprised of nephrologists, general practitioners, nurses, dialysis technicians, and patients with anemia in CKD/caregivers.

Scope of the guideline

Target populations

The guideline addresses the use of HIF-PHIs in patients >18 years with CKD and anemia. It summarizes recommendations for the treatment of anemia in two subgroups: dialysis-dependent (DD) and non-dialysis-dependent (NDD) CKD patients. The recommendations do not apply to pediatric (≤ 12 years of age), adolescent (12–18 years of age) or anemic patients [primary or secondary to other causes such as blood loss, cancer (any type), polycystic kidney disease, and infectious diseases].

End users and settings

The guideline is intended to inform healthcare providers, clinical or institutional leaders, administrators, policy-makers, trialists, and research funders. The recommendation in the guideline is primarily for South Asian countries but can be used worldwide.

Patients or caregivers should only use the guideline to discuss treatment choices with the consultation of a registered medical practitioner. The guideline does not deal with the efficiency of care provision in anemia in CKD, including the organization of services to integrate care.

Selection of questions and outcomes of interest

An initial meeting was held among members of the GDG. Based on the discussion, the methodology committee

outlined the scope and purpose of the guidelines and identified and prioritized the key questions for the guidelines. The health question(s) covered by the guideline for the development of recommendations were:

1. Should HIF-PHIs be used as alternatives to ESAs in DD-CKD patients with anemia?

2. Should HIF-PHIs be used as alternatives to ESAs in NDD-CKD patients with anemia?

Separate recommendations were made for DD- and NDD-CKD patients and separately for each HIF-PHI molecule (instead of HIF-PHI as a group) to bring nuance into practice, and in recognition that although from the same molecular group, different molecules have different safety and efficacy profiles and are not marketed uniformly.

Selection of outcomes of interest

Guideline panel members were asked a priori to independently rate the importance of a long list of outcomes, which the methodology group developed based on an initial scoping of literature and review of core outcome sets for CKD. The outcomes were rated using a Likert Scale of 1–9 (GRADE approach), with the highest ranking on each domain chosen for evidence review. Details are available in Supplementary Appendix 2.

Evidence review

Two systematic reviews were conducted about the two questions.[12] The reviews were conducted by the methodology group in alignment with principles and standards outlined in the Cochrane Handbook for Systematic Reviews of Interventions (handbook.cochrane.org) for systematic reviews of intervention effects. The risk of bias was assessed at the health outcome level using the Cochrane Collaboration's Risk Of Bias version 1 tool (ROB-1) for randomized trials.[13] We used the GRADE approach to assess the certainty of evidence.[10] It assesses certainty based on risk of bias, precision, consistency and magnitude of the effects estimates, directness of the evidence, risk of publication bias, presence of significant effects, and dose-effect relationship. The certainty was categorized into four levels ranging from very low to high.[10,14,15]

Evidence to recommendation

For each recommendation, GRADE Evidence to Decision (EtD) framework was used as per the GRADEPro Guideline Development Tool (GRADEPro GDT) (https://www.gradepro.org/). The EtD table summarized the results of the evidence review together with practical aspects of the review. Initially, the methodological committee prepared the EtD tables, acquired feedback from the Steering Committee,[16] and presented the results to the GDG. The EtD table on the clinical recommendation of intervention looks at multiple criteria: certainty of evidence, patient experiences or values and preferences regarding treatment decisions, absolute benefits and harm for all patient-important outcomes, and population perspective in terms of equity, cost, acceptability, and feasibility of the intervention.

The methodology group circulated a survey with the GDG to understand values, preferences, resource implication, equity, acceptability, and feasibility of implementation of intervention, and the real-world variations in practice. The reflections and inputs from members were collated to inform the use of EtD frameworks in drafting recommendations. Interactions with individual patients, caregivers, and panel members helped ascertain each criterion and facilitated in the collaborative preparation and management of EtD tables.[16,17] Panel members were asked to suggest any studies that fulfilled the inclusion criteria but may have been missed for the individual questions.

The panel reviewed draft EtD tables before and during the guideline panel meeting and made modifications. Based on the feedback from the GDG, the Steering Committee redrafted the recommendations. A meeting was convened where the participants were asked to vote "agree," "agree with modification," or "disagree" for each recommendation on paper and using chatbox function (for those attending the meeting virtually). This was followed by a mediated group discussion to facilitate consensus. The participants reflected on and discussed comments and ratings. A recommendation was deemed to reach consensus if majority of the panel agreed.

Recommendations on the use of HIF-PHI in CKD patients for the guideline

The guideline includes two sets of six recommendations each. Each recommendation is supported by the following:

- Evidence profile: The overall effect estimates and makes references to the studies.

Certainty of the evidence:

- High: We are very sure that the true effect is close to the estimated effect.
- Moderate: We are moderately sure of the estimated effect. The true effect is probably close to this one, but there is a possibility that it is significantly different.
- Low: We have limited confidence in the estimated effect. The true effect may be significantly different from the estimated effect.
- Very low: We have very little confidence in the estimated effect. The true effect is likely to be significantly different from that estimated effect.
- Evidence to decision: Brief description of beneficial and harmful effects, the certainty of evidence, and considerations of patient preferences.

The recommendations labels and their interpretation are:

Strong recommendation

- For patients: Most individuals in this situation would want the recommended course of action, and only a small proportion would not.
- For clinicians: Most individuals should receive the intervention or test. Formal decision aids are not likely needed to help individual patients make decisions consistent with their values and preferences.
- For policy-makers: The recommendation can be adopted as policy in most situations. According to the guideline, adherence to this recommendation could be used as a quality criterion or performance indicator.

Weak recommendation

- For patients: Most individuals in this situation would want the suggested course of action, but many would not.
- For clinicians: Recognizing that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with their values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
- For policy-makers: Policy-making will require substantial debate and the involvement of various stakeholders. Performance measures about the suggested course of action should focus on the documentation of appropriate decision-making processes.

Recommendation for use in research setting

- For patients: There is insufficient evidence to support a decision for or against an intervention (usually new) for clinical practice. More research is needed, and the drug should be used only during research as per existing ethics and local regulations.
- For clinicians: There is insufficient evidence to support a decision for or against an intervention (usually new) for clinical practice. More research is needed, and the drug should be used only during research as per existing ethics and local governance regulations.
- For policy-makers: The recommendation is of use only in research with proper ethics committee permissions. It should not be used in a clinical practice setting.

Consensus statement

- There is not enough evidence to give an evidence-informed recommendation, but the panel still regarded it as essential to provide a statement to support practice decisions.

The live and online version of the guideline is available at https://app.magicapp.org/#/guideline/jXXBBj

1. Recommendations for HIF-PHIs for the treatment of anemia in patients with NDD-CKD

Results are presented in Tables 1-36.[18-49]

1.1 Desidustat as alternative to ESAs

Table 1: Recommendation for desidustat as an alternative to ESA for anemia in NDD-CKD patients

Consensus statement	This is a consensus statement, which implies that there is not enough evidence to give an evidence-informed recommendation, but the panel still regarded it as important to provide a statement to support practice decisions.
The panel consensus was that desidustat might be offered as an alternative to ESAs in NDD patients with CKD stages 3–5 who do not prefer ESAs. When offering desidustat, it should be thoroughly explained to the patients about the potential benefits and harm, including the low certainty of evidence on its effectiveness and safety. Patients should be iron replete before the initiation of therapy.	
Recommendation for future research	This recommendation is evidence informed.
The panel strongly recommends the conduct of large multicentric, head-to-head, randomized controlled trials in the South Asian region on NDD-CKD patients and measuring critically important outcomes (as elucidated in this guideline) such that the evidence base for desidustat is improved. Considering feasibility, acceptability, and equity considerations and that the drug is already approved in India, non-industry research funders should prioritize such trials. Robust Phase IV studies in other approved markets are also required to establish long-term safety and risk-benefit ratio. Cost-benefit analysis should be done to understand the relative cost of desidustat with ESAs.	

ESA: Eythropoiesis-stimulating agents, NDD: Nondialysis dependent, CKD: Chronic kidney disease

Table 2: Evidence profile for desidustat as an alternative to ESA for anemia in NDD-CKD patients

Population: Anemia in non-dialysis-dependent chronic kidney disease
Intervention: Desidustat (any dose)
Comparator: Darbepoetin alpha

Outcome Time frame	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		Darbepoetin alpha	Desidustat (any dose)		
Any adverse events up to 26 weeks in ESA-naïve patients	Odds ratio: 0.91 (CI 95% 0.66–1.26) Based on data from 588 participants in one study	503 per 1000	479 per 1000	Low Due to serious risk of bias, due to serious imprecision[1]	We are uncertain whether desidustat (any dose) decreases adverse events up to 26 weeks in ESA-naïve patients.
		Difference: 24 fewer per 1000 (CI 95% 103 fewer–301 fewer)			
All-cause mortality up to 26 weeks in ESA-naïve patients	Odds ratio: 1.0 (CI 95% 0.32–3.14) Based on data from 588 participants in one study	20 per 1000	20 per 1000	Low Due to serious risk of bias, due to serious imprecision[2]	We are uncertain whether compared to conventional ESA, desidustat has no difference in all-cause mortality up to 26 weeks in ESA-naïve patients.
		Difference: 0 fewer per 1000 (CI 95% 14 fewer–40 more)			
Incidences of MACE and MACE plus					No studies were found that viewed incidences of MACE and MACE plus.
Progression to end-stage kidney disease					No studies were found that viewed progression to end-stage kidney disease.
Need for iron supplement					No studies were found that viewed the need for iron supplementation.
Patient requiring blood transfusion					No studies were found that viewed a patient requiring blood transfusion.
Change in hemoglobin levels from baseline up to 24 weeks in ESA-naïve patients	Measured by: Scale: High better Based on data from 529 participants in one study	Mean	Mean	Low Due to serious risk of bias, due to serious imprecision[3]	Desidustat (any dose) probably has little or no difference on change in hemoglobin levels from baseline compared to ESA up to 24 weeks in ESA-naïve patients.
		Difference: MD 0.09 lower (CI 95% 0.15 lower–0.33 lower)			
QoL (SF 36 score) at 24 weeks in ESA-naïve patients	Measured by: Scale: High better Based on data from 480 participants in one study	Mean	Mean	Low Due to serious risk of bias, due to serious imprecision[4]	Desidustat may have little or no difference on QoL (SF 36 score) at 24 weeks in ESA-naïve patients.
		Difference: MD 0.00 lower (CI 95% 98.20 lower–98.20 lower)			
Fatigue					No studies were found that viewed fatigue.
Need for ESA up to 24 weeks in ESA-naïve patients	Based on data from 588 participants in one study			Low Due to serious risk of bias, due to serious imprecision[5]	There were too few ESA-naïve patients who experienced the need for ESA up to 24 weeks to determine whether desidustat (any dose) made a difference.

Risk of Bias: serious. Missing intention-to-treat analysis, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: serious.** Wide confidence intervals, only data from one study, inadequate optimal information size (OIS); The 95% CI of the included study overlaps line of no effect (i.e., CI includes 1.0) rate. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, missing intention-to-treat analysis; **Imprecision: serious.** Wide confidence intervals, only data from one study, inadequate optimal information size (OIS); **Publication bias: not serious.** Study is commercially funded. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, missing intention-to-treat analysis; **Imprecision: serious.** Only data from one study, inadequate optimal information size (OIS); **Publication bias: not serious.** Study is commercially funded. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, missing intention-to-treat analysis; **Imprecision: serious.** Only data from one study, inadequate optimal information size (OIS); **Publication bias: not serious.** Study is commercially funded. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and

personnel, resulting in potential for performance bias, missing intention-to-treat analysis; **Imprecision: serious.** Low number of patients, only data from one study, inadequate optimal information size (OIS); **Publication bias: not serious.** Study is commercially funded. ESA: Eythropoiesis-stimulating agents, NDD: Nondialysis dependent, CKD: Chronic kidney disease, MACE: Major adverse cardiovascular events, CI: Confidence interval, SF 36: Short Form 36, MD: Mean difference, QoL: Quality of life.

Table 3: Evidence to decision for desidustat as an alternative to ESA for anemia in NDD-CKD patients

Benefits and harms	Small net benefit or little difference between alternatives
Desidustat decreased adverse events up to 26 weeks in ESA-naïve patients by 24/1000 as compared to darbepoetin alpha. Almost 100% of GDG members (not including patients) find such a cut-off acceptable for using HIF-PHIs. However, evidence on this was uncertain. Compared to ESAs, Desidustat had little or no difference on hemoglobin levels from baseline up to 24 weeks. However, evidence on this was uncertain. All GDG find such a scenario acceptable to switch to HIF-PHIs. Compared to ESA, the desidustat group had little or no difference on QoL measured by SF-36 score at 24 weeks in ESA-naïve patients, but evidence on this was uncertain. About 59% GDG members (not including patients) are comfortable using HIF-PHIs over ESAs in a scenario where there is evidence of no difference in QoL. Similarly, desidustat had no difference on all-cause mortality up to 26 weeks as compared to darbepoetin alpha. However, evidence on this was uncertain. About 74% GDG members (not including patients) find such a cut-off acceptable for using HIF-PHIs. There were too few ESA-naïve patients who experienced the need for ESA up to 24 weeks, to determine whether desidustat (any dose) made a difference when compared with darbepoetin alpha. Evidence on this was uncertain. There was no data available in the included studies that examined fatigue, incidence of MACE and MACE plus, progression to end-stage kidney disease (defined by stage 5 CKD), need for oral or intravenous iron supplementation or patients requiring blood transfusion. Overall, the panel judged that there were comparable anticipated effects and trivial harms for using desidustat (over ESAs), noting there was very low certainty on the evidence base. There is concern regarding the lack of robust evidence on cardiovascular safety in NDD-CKD patients with anemia.	
Certainty of the evidence	Low [Table 2]
Values and preferences	No substantial variability expected
Empirical examinations of patients' values and preferences from South Asia are not available. This section is based on unstructured interactions with individual patients and caregivers and discussions with panel members. The consensus statement places a relatively high value on the belief that patients, clinicians, and caregivers prefer oral drugs over subcutaneous injections for those who are NDD and may not have access to refrigeration facilities. However, the GDG also inferred that some healthcare workers and patients might be reluctant to use desidustat due to the low certainty of evidence and lack of evidence on cardiovascular risk.	
Resources	No important issues with the recommended alternative
Desidustat is administered orally and does not require cold chain maintenance, thereby minimizing the resources required as compared to ESAs which require refrigeration prior to administration. This is especially relevant to rural areas where these resources are scarce.	
Equity	No important issues with the recommended alternative
Desidustat does not need refrigeration (cold chain) as compared to ESAs. It is thus more useful in remote areas with irregular supply of electricity and in equity groups who might not have refrigeration in their homes. Furthermore, as ESAs require injection, a certain level of training will be needed to learn how to self-administer the treatment.	
Acceptability	No important issues with the recommended alternative
Desidustat has a preferable route of administration for patients; patients either must self-administer ESA injections or make a hospital visit for the injection. However, ESAs have weekly/fortnightly dose requirements, whereas desidustat should be taken daily or on alternate days. Both these factors can impact compliance and treatment adherence. ESAs may also be easier to supervise than desidustat due to the differences in dose frequency requirements. Overall, for NDD patients, the oral nature of desidustat was thought to be more acceptable by the GDG.	
Feasibility	No important issues with the recommended alternative
Desidustat can be orally administered and does not require cold chain, unlike ESAs, which is relatively easy to administer and store. In addition, desidustat may increase accessibility, particularly for non-dialysis patients, as it does not require hospital visit or self-injection. As desidustat is approved in India, the treatment seems to be feasible at the current time.	

ESA: Eythropoiesis-stimulating agents, NDD: Nondialysis dependent, CKD: Chronic kidney disease, MACE: Major adverse cardiovascular events, QoL: Quality of life, GDG: Guideline development group, HIF PHI: Hypoxia-inducible factor prolyl hydroxylase inhibitor

1.2 Daprodustat as an alternative to ESAs

Table 4: Recommendation for daprodustat as an alternative to ESA for anemia in NDD-CKD patients

Recommendation for use in research setting only	This recommendation is evidence informed
Daprodustat should not be used for NDD-CKD patients, except in the context of an approved randomized controlled trial. The panel recommends conduct of large multicentric head-to-head randomized trials in the South Asian region on NDD-CKD patients and measuring critically important outcomes (as elucidated in this guideline) such that evidence base for daprodustat is improved.	

ESA: Eythropoiesis-stimulating agents, NDD: Nondialysis dependent, CKD: Chronic kidney disease

Table 5: Evidence profile for daprodustat as an alternative to ESA for anemia in NDD-CKD patients

Population: Anemia in non-dialysis-dependent chronic kidney disease
Intervention: Daprodustat (any dose)
Comparator: rhEPO (epoetins or their biosimilars or darbepoetin)

Outcome **Time frame**	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence**	**Plain language summary**
		rhEPO (epoetins or their biosimilars or darbepoetin)	**Daprodustat (any dose)**		
Adverse events up to 52 weeks	Odds ratio: 1.18 (CI 95% 1.02–1.37) Based on data from 4419 participants in three studies	774 per 1000	801 per 1000	Low Due to very serious risk of bias[1]	Daprodustat (any dose) probably increases adverse events up to 52 weeks.
		Difference: 28 more per 1000 (CI 95% 3 more–50 more)			
All-cause mortality up to 52 weeks	Odds ratio: 1.90 (CI 95% 0.21–17.31) Based on data from 250 participants in one study	13 per 1000	24 per 1000	Low Due to serious risk of bias, due to very serious imprecision[2]	We are uncertain whether daprodustat (any dose) increases all-cause mortality up to 52 weeks.
		Difference: 11 more per 1000 (CI 95% 10 fewer–173 more)			
All-cause mortality up to 60 weeks	Odds ratio: 1.01 (CI 95% 0.85–1.20) Based on data from 3872 participants in one study	154 per 1000	155 per 1000	Very low Due to very serious risk of bias, due to serious imprecision[3]	We are uncertain whether daprodustat (any dose) has little or no difference on all-cause mortality up to 60 weeks.
		Difference: 1 more per 1000 (CI 95% 20 fewer–25 more)			
Incidences of MACE plus up to 32 weeks	Odds ratio: 0.82 (CI 95% 0.23–2.87) Based on data from 250 participants in one study	50 per 1000	41 per 1000	Very low Due to serious risk of bias, due to very serious imprecision[4]	We are uncertain whether daprodustat (any dose) decreases incidences of MACE plus up to 32 weeks in ESA-naïve/ESA-conditioned patients.
		Difference: 9 fewer per 1000 (CI 95% 38 fewer–81 more)			
Need for iron supplementation					No studies were found that viewed the need for iron supplementation
Need for ESA					No studies were found that viewed the need for ESA.
Incidences of MACE up to 60 weeks	Odds ratio: 1.07 (CI 95% 0.92–1.24) Based on data from 3872 participants in one study	228 per 1000	240 per 1000	Very low Due to very serious risk of bias, due to very serious imprecision[5]	We are uncertain whether daprodustat (any dose) increases incidences of MACE up to 60 weeks.
		Difference: 12 more per 1000 (CI 95% 14 fewer–40 more)			
Progression to end-stage kidney disease up to 60 weeks	Odds ratio: 0.99 (CI 95% 0.83–1.18) Based on data from 2485 participants in one study	284 per 1000	281 per 1000	Very low Due to very serious risk of bias, due to very serious imprecision[6]	We are uncertain whether daprodustat (any dose) has little or no difference on progression to end-stage kidney disease up to 60 weeks.
		Difference: 2 fewer per 1000 (CI 95% 36 fewer–35 more)			
Patients requiring blood transfusion up to 52 weeks	Odds ratio: 0.94 (CI 95% 0.78–1.13) Based on data from 3870 participants in one study	135 per 1000	127 per 1000	Very low Due to very serious risk of bias, due to very serious imprecision[7]	Daprodustat (any dose) may decrease blood transfusion requirement up to 52 weeks.
		Difference: 7 fewer per 1000 (CI 95% 26 fewer–15 more)			

Contd...

Table 5: (Continued)

Health-related QoL					No studies were found that viewed health-related QoL.
Fatigue					No studies were found that viewed fatigue.
Change in hemoglobin levels from baseline up to 52 weeks	Measured by: Scale: High better Based on data from 4089 participants in two studies	Mean	Mean	Low Due to very serious risk of bias[8]	Daprodustat (any dose) probably has little or no difference on hemoglobin levels compared to conventional ESA from baseline up to 52 weeks in ESA-naïve/ESA-conditioned patients.
		Difference: MD 0.08 lower (CI 95% 0.08 lower–0.08 lower)			
Change in hemoglobin levels from baseline up to 52 weeks in ESA-conditioned patients	Measured by: Scale: High better Based on data from 117 participants in one study	Mean	Mean	Very low Due to serious risk of bias, due to very serious indirectness, due to very serious imprecision[9]	Daprodustat (any dose) may have little or no difference on hemoglobin level from baseline up to 52 weeks compared to those on ESAs in ESA-conditioned patients.
		Difference: MD 0.00 lower (CI 95% 0.28 lower–0.28 lower)			

Risk of Bias: very serious. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: very serious.** Low number of patients, only data from one study, wide confidence intervals; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate concealment of allocation during randomization process, resulting in potential for selection bias, incomplete data and/or large loss to follow-up; **Imprecision: serious.** Wide confidence intervals, only data from one study; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: very serious.** Wide confidence intervals, low number of patients, only data from one study; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: very serious.** Only data from one study, wide confidence intervals. **Risk of Bias: very serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: very serious.** Wide confidence intervals, only data from one study; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: very serious.** Only data from one study, wide confidence intervals; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate concealment of allocation during randomization process, resulting in potential for selection bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Indirectness: very serious.** The included study was from only one country and was downgraded for lack of directness by two levels; **Imprecision: very serious.** Only data from one study, low number of patients; **Publication bias: not serious.** Mostly commercially funded studies. ESA: Eythropoiesis-stimulating agents, NDD: Nondialysis dependent, CKD: Chronic kidney disease, rhEPO: Epoetins or their biosimilars or darbepoetin, MD: Mean difference, CI: Confidence interval, MACE: Major adverse cardiovascular events.

Table 6: Evidence profile for daprodustat as an alternative to ESA for anemia in NDD-CKD patients

Benefits and harm	Small net benefit or little difference between alternatives
Daprodustat reduced the incidences of MACE plus up to 32 weeks by 9/1000 compared to rhEPO. Evidence on this was uncertain. About 19% of GDG members (not including patients) would find such a scenario acceptable. In the group that received daprodustat, there was 7/1000 less patients requiring blood transfusion up to 52 weeks as compared to rhEPO. Evidence on this was uncertain. Only 6% of GDG members (not including patients) would find such a scenario acceptable. The daprodust group made little or no difference in hemoglobin levels from baseline up to 52 weeks for ESA-naïve and ESA-conditioned patients. All GDG members (not including patients) find such a scenario acceptable to switch to HIF-PHIs. Similarly, in ESA-conditioned patients only, the daprodustat group had little or no difference in hemoglobin levels from baseline up to 52 weeks as compared to rhEPO. However, evidence on this was uncertain. All GDG members (not including patients) find such a scenario acceptable to switch to HIF-PHI. Daprodustat may have little or no difference on all-cause mortality up to 60 weeks as compared to rhEPO. About 14% of GDG members (not including patients) find such a scenario acceptable to switch to HIF-PHI. Similarly, patients receiving daprodustat had little or no difference in progression to end-stage kidney disease up to 60 weeks. Evidence on this was uncertain. Daprodustat increased adverse events up to 52 weeks by 28/1000 as compared to rhEPO. All the GDG members (not including patients) find such a cut-off unacceptable for using HIF-PHIs. In the group that received daprodustat, there was 11/1000 more incidences all-cause mortality up to 52 weeks. All the GDG members (not including patients) find such a cut-off unacceptable for using HIF-PHIs. However, the evidence was uncertain. Daprodustat increased the incidences of MACE by 12/1000 up to 60 weeks as compared to rhEPO. Evidence on this was uncertain. All (100%) GDG members (not including patients) find such a cut-off unacceptable for using HIF-PHIs. None of the included studies measured health-related QoL, fatigue, need for iron supplementation, or need for ESA as outcomes. Overall, the panel judged that the desirable anticipated effects of daprodustat compared to rhEPO were small but that there were moderate harms, noting that there was very low certainty in the evidence base.	
Certainty of the evidence	Very low [Table 5]
Values and preferences	No substantial variability expected
Empirical examinations of patients' values and preferences from South Asia are unavailable. This section is based on unstructured interactions with individual patients and caregivers and discussions with panel members. Our recommendation reflects a belief that patients and caregivers prefer oral drugs over subcutaneous injections for those who are not DD. However, the GDG also inferred that some well-informed healthcare workers and patients might be reluctant to use daprodustat due to the very low certainty of evidence.	
Resources	No important issues with the recommended alternative
Daprodustat is currently not available in South Asia, so it is not possible to compare the cost. It is administered orally, requiring minimal resources compared to rhEPO which is injectable and requires refrigeration before administration. The ease of administration and easy storage for daprodustat can reduce the additional resource requirements.	
Equity	No important issues with the recommended alternative
Daprodustat does not need refrigeration (cold chain) as compared to rhEPO. It is thus more useful in remote areas with an irregular supply of electricity and in equity groups who might not have refrigeration in their homes. Furthermore, as rhEPO requires injection, a certain level of health literacy may be needed on how to self-administer the treatment.	
Acceptability	No important issues with the recommended alternative
Daprodustat has a preferable route of administration for patients; patients either must self-administer ESA injections or make a hospital visit for the injection. However, ESAs have weekly/fortnightly dose requirements, whereas daprodustat should be taken daily or on alternate days. Both these factors can impact compliance and treatment adherence. ESAs may also be easier to supervise than daprodustat due to the differences in dose frequency requirements. Overall, for NDD patients, the oral nature of daprodustat was thought to be more acceptable by the GDG.	
Feasibility	Intervention is likely difficult to implement
Daprodustat can be orally administered and does not require a cold chain, unlike rhEPO, which is relatively easy to administer and store. In addition, daprodustat may increase accessibility, particularly for non-dialysis patients, as it does not require hospital visitation or self-injection. As daprodustat is not yet approved in India or any other South Asian country, the treatment is currently not feasible.	

ESA: Eythropoiesis-stimulating agents, NDD: Nondialysis dependent, CKD: Chronic kidney disease, rhEPO: Epoetins or their biosimilars or darbepoetin, MACE: Major adverse cardiovascular events, GDG: Guideline development group, HIF PHI: Hypoxia-inducible factor prolyl hydroxylase inhibitor

1.3 Enarodustat as an alternative to ESAs

Table 7: Recommendation for enarodustat as an alternative to ESA for anemia in NDD-CKD patients

Recommendation for use in research setting only	This recommendation is evidence informed.
Enarodustat should not be used for NDD-CKD patients, except in the context of an approved randomized controlled trial. The panel recommends conduct of large head-to-head multicentric randomized controlled trials in the South Asian region on NDD-CKD patients and measuring critically important outcomes (as elucidated in this guideline) such that the evidence base for enarodustat is improved.	

ESA: Eythropoiesis-stimulating agents, NDD: Nondialysis dependent, CKD: Chronic kidney disease

Table 8: Evidence profile for enarodustat as an alternative to ESA for anemia in NDD-CKD patients

Population: Anemia in non-dialysis-dependent chronic kidney disease Intervention: Enarodustat (any dose) Comparator: Darbepoetin alpha					
Outcome **Time frame**	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence**	**Plain language summary**
		Darbepoetin alpha	**Enarodustat (any dose)**		
All-cause mortality up to 26 weeks in ESA-naïve and ESA-conditioned patients	Odds ratio: 0.34 (CI 95% 0.01–8.35) Based on data from 216 participants in one study	9 per 1000	3 per 1000	Very low Due to very serious risk of bias, due to very serious indirectness, due to very serious imprecision[1]	We are uncertain whether enarodustat (any dose) decreases all-cause mortality up to 26 weeks in ESA-naïve and ESA-conditioned patients.
		Difference: 6 fewer per 1000 (CI 95% 9 fewer–61 more)			
Adverse events up to 26 weeks in ESA-naïve and ESA-conditioned patients	Odds ratio: 0.40 (CI 95% 0.21–0.75) Based on data from 216 participants in one study	826 per 1000	655 per 1000	Very low Due to very serious risk of bias, due to very serious indirectness[2]	We are uncertain whether enarodustat (any dose) decreases adverse events up to 26 weeks in ESA-naïve and ESA-conditioned patients.
		Difference: 171 fewer per 1000 (CI 95% 327 fewer–45 fewer)			
Adverse events up to 26 weeks in ESA-naïve patients	Odds ratio: 0.40 (CI 95% 0.15–1.10) Based on data from 102 participants in one study	865 per 1000	719 per 1000	Very low Due to very serious risk of bias, due to very serious indirectness, due to very serious imprecision[3]	We are uncertain whether enarodustat (any dose) decreases adverse events up to 26 weeks in ESA-naïve patients.
		Difference: 146 fewer per 1000 (CI 95% 375 fewer–11 more)			
Adverse events up to 26 weeks in ESA-conditioned patients	Odds ratio: 0.39 (CI 95% 0.17–0.90) Based on data from 114 participants in one study	789 per 1000	593 per 1000	Very low Due to very serious risk of bias, due to very serious indirectness, due to serious imprecision[4]	We are uncertain whether enarodustat (any dose) decreases adverse events up to 26 weeks in ESA-conditioned patients.
		Difference: 196 fewer per 1000 (CI 95% 400 fewer–18 fewer)			
Incidences of MACE and MACE plus					No studies were found that viewed incidences of MACE and MACE plus.
Need for iron supplementation					No studies were found that viewed the need for iron supplementation.
Need for ESA					No studies were found that viewed the need for ESA.
Progression to end-stage kidney disease					No studies were found that viewed the progression to end-stage kidney disease.
Patients requiring blood transfusio					No studies were found that viewed patients requiring blood transfusion.
Health-related QoL					No studies were found that viewed health-related QoL.
Fatigue					No studies were found that viewed fatigue.
Change in hemoglobin levels from baseline up to 24 weeks	Measured by: Scale: High better Based on data from 193 participants in one study	Mean	Mean	Very low Due to very serious risk of bias, due to very serious indirectness, due to serious imprecision[5]	We are uncertain whether enarodustat (any dose) has little or no difference on change in hemoglobin levels from baseline up to 24 weeks.
		Difference: MD 0.09 lower (CI 95% 0.08 lower–0.26 lower)			

Risk of Bias: very serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, incomplete data and/or large loss to follow-up, missing intention-to-treat analysis; **Indirectness: very serious.** The included study was from only one country and was downgraded for lack of directness by two levels; **Imprecision: very serious.** Low number of patients, only data from one study, wide confidence intervals; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Missing intention-to-treat analysis, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, incomplete data and/or large loss to follow-up; **Indirectness: very serious.** The included study was from only one country and was downgraded for lack of directness by two levels; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, incomplete data and/or large loss to follow-up, missing intention-

to-treat analysis; **Indirectness: very serious.** The included study was from only one country and was downgraded for lack of directness by two levels; **Imprecision: very serious.** Low number of patients, only data from one study, wide confidence intervals; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, incomplete data and/or large loss to follow-up, missing intention-to-treat analysis; **Indirectness: very serious.** The included study was from only one country and was downgraded for lack of directness by two levels; **Imprecision: serious.** Low number of patients, only data from one study; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, incomplete data and/or large loss to follow-up, missing intention-to-treat analysis; **Indirectness: very serious.** The included study was from only one country and was downgraded for lack of directness by two levels; **Imprecision: serious.** Low number of patients, only data from one study; **Publication bias: not serious.** Mostly commercially funded studies. ESA: Eythropoiesis-stimulating agents, NDD: Nondialysis dependent, CKD: Chronic kidney disease, CI: Confidence interval, MACE: Major adverse cardiovascular events, QoL: Quality of life.

Table 9: Evidence to decision table for earodustat as an alternative to ESA for anemia in NDD-CKD patients

Benefits and harms	Small net benefit or little difference between alternatives
Enarodustat decreased all-cause mortality up to 26 weeks by 6/1000 as compared to darbepoetin alpha. Evidence on this was uncertain. About 14% of GDG members (not including patients) would find such a scenario acceptable. In the group that received enarodustat, there was 171/1000 fewer adverse events up to 26 weeks compared to the darbepoetin alpha group. Evidence on this was uncertain. All GDG members (not including patients) would find such a scenario acceptable. In ESA-naïve patients receiving enarodustat, there were 146/1000 fewer adverse events up to 26 weeks as compared to darbepoetin alpha group. However, evidence on this was uncertain. All GDG members (not including patients) would find such a scenario acceptable. Similarly, in ESA-conditioned patients receiving enarodustat, there were 196/1000 fewer adverse events up to 26 weeks compared to darbepoetin alpha group. However, evidence on this was uncertain. Almost all GDG members (not including patients) would find such a scenario acceptable. Enarodustat had little or no difference on hemoglobin levels from baseline up to 24 weeks. However, evidence on this was uncertain. All GDG members (not including patients) find such a scenario acceptable to switch to HIF-PHI. There were no included studies that examined the impact on the QoL, fatigue, incidence of MACE/MACE plus, need for iron supplementation, need for blood transfusion, progression to end-stage kidney disease, or need for ESA as outcomes. Overall, the panel judged that the desirable anticipated effects of enarodustat (compared to darbepoetin alpha) were moderate, as it was trivial/no harm. They noted that there was very low certainty in the evidence base. There is also concern regarding the lack of robust evidence on cardiovascular safety in NDD-CKD patients with anemia.	
Certainty of the evidence	Very low [Table 8]
Values and preferences	No substantial variability expected
Empirical examinations of patients' values and preferences from South Asia are unavailable. The section is based on unstructured interactions with individual patients and caregivers and discussions with panel members. Our recommendation reflects a belief that patients and caregivers prefer oral drugs over subcutaneous injections for those who are not DD. However, the GDG also inferred that some well-informed healthcare workers and patients might be reluctant to use enarodustat due to the very low certainty of evidence, and the lack of evidence on QoL and fatigue, which are outcomes of importance for patients.	
Resources	Important issues or potential issues not investigated
Enarodustat is currently not available in India, so it is not possible to compare the cost at this time. It is administered orally, thereby requiring minimal resources as compared to darbepoetin alpha which is injectable and requires refrigeration prior to administration. The ease of administration and easy storage for enarodustat can reduce the additional resource requirements.	
Equity	Important issues or potential issues not investigated
Enarodustat does not need refrigeration (cold chain) as compared to darbepoetin alpha. It is thus more useful in remote areas with irregular supply of electricity and in equity groups, who might not have refrigeration in their homes. Furthermore, as darbepoetin alpha requires injection, a certain level of health literacy may be needed on how to self-administer the treatment.	
Acceptability	No important issues with the recommended alternative
Enarodustat has a preferable route of administration for patients; patients either must self-administer ESA injections or make a hospital visit for the injection. However, ESAs have weekly/fortnightly dose requirements, whereas enarodustat should be taken daily or on alternate days. Both these factors can impact compliance and treatment adherence. ESAs may also be easier to supervise than enarodustat due to the differences in dose frequency requirements. Overall, for NDD patients, the oral nature of enarodustat was thought to be more acceptable by the GDG.	
Feasibility	Intervention is likely difficult to implement
Enarodustat can be orally administered and does not require cold chain, unlike darbepoetin alpha, which is relatively easy to administer and store. In addition, Enarodustat may increase accessibility, particularly for non-dialysis patients, as it does not require hospital visitation or self-injection. As enarodustat is not yet approved in India or any other South Asian country, the treatment is not feasible at the current time.	

ESA: Eythropoiesis-stimulating agents, NDD: Nondialysis dependent, CKD: Chronic kidney disease, GDG: Guideline development group, MACE: Major adverse cardiovascular events

1.4 Molidustat as alternative to ESAs

Table 10: Recommendation for molidustat as an alternative to ESA for anemia in NDD-CKD patients

Recommendation for use in research setting only	This recommendation is evidence informed.
Molidustat should not be used for NDD-CKD patients, except in the context of an approved randomized controlled trial. The panel recommends conducting large head-to-head multicentric randomized controlled trials in the South Asian region on NDD-CKD patients and measuring critically important outcomes (as elucidated in this guideline) such that evidence base for molidustat is improved.	

ESA: Eythropoiesis-stimulating agents, NDD: Nondialysis dependent, CKD: Chronic kidney disease

Table 11: Evidence profile for molidustat as an alternative to ESA for anemia in NDD-CKD patients

Population: Anemia in non-dialysis-dependent chronic kidney disease
Intervention: Molidustat (any dose)
Comparator: Darbepoetin alpha

Outcome Time frame	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Plain language summary
		Darbepoetin alpha	Molidustat (any dose)		
Treatment emergent adverse events up to 52 weeks	Odds ratio: 1.18 (CI 95% 0.52–2.67) Based on data from 449 participants in three studies	881 per 1000	897 per 1000	Very low Due to very serious risk of bias, due to serious imprecision[1]	We are uncertain whether molidustat (any dose) increases treatment emergent adverse events up to 52 weeks in ESA-naïve and ESA-conditioned patients.
		Difference: 16 more per 1000 (CI 95% 87 fewer–71 more)			
Incidence of MACE and MACE plus up to 52 weeks	Odds ratio: 5.43 (CI 95% 0.90–32.61) Based on data from 325 participants in two studies	6 per 1000	31 per 1000	Very low Due to very serious risk of bias, due to very serious imprecision, due to serious indirectness[2]	We are uncertain whether molidustat (any dose) increases incidence of MACE and MACE plus up to 52 weeks in ESA-naïve and ESA-conditioned patients.
		Difference: 26 more per 1000 (CI 95% 1 fewer–158 more)			
All-cause mortality up to 52 weeks	Odds ratio: 1.78 (CI 95% 0.38–8.28) Based on data from 449 participants in three studies	10 per 1000	17 per 1000	Very low Due to very serious risk of bias, due to serious imprecision[3]	We are uncertain whether molidustat (any dose) increases all-cause mortality up to 52 weeks in ESA-naïve and ESA-conditioned patients.
		Difference: 8 more per 1000 (CI 95% 6 fewer–67 more)			
Need for iron supplementation (IV) up to 52 weeks	Odds ratio: 0.97 (CI 95% 0.31–3.09) Based on data from 325 participants in two studies	37 per 1000	35 per 1000	Very low Due to very serious risk of bias, due to very serious indirectness, due to serious imprecision[4]	We are uncertain whether molidustat (any dose) has little or no difference on the need for iron supplementation (iv) up to 52 weeks in ESA-naïve and ESA-conditioned patients.
		Difference: 1 fewer per 1000 (CI 95% 25 fewer–69 more)			
Need for iron supplementation (oral) up to 52 weeks	Odds ratio: 1.71 (CI 95% 1.10–2.66) Based on data from 325 participants in two studies	398 per 1000	530 per 1000	Very low Due to very serious risk of bias, due to serious indirectness, due to serious imprecision[5]	We are uncertain whether molidustat (any dose) increases the need for iron supplementation (oral) up to 52 weeks in ESA-naïve and ESA-conditioned patients.
		Difference: 133 more per 1000 (CI 95% 23 more–239 more)			
Need for ESA up to 36 weeks	Odds ratio: 0.39 (CI 95% 0.11–1.42) Based on data from 449 participants in three studies	36 per 1000	14 per 1000	Very low Due to very serious risk of bias, due to serious imprecision[6]	We are uncertain whether molidustat (any dose) decreases need for ESA up to 36 weeks in ESA-naïve/ESA-conditioned patients.
		Difference: 22 fewer per 1000 (CI 95% 32 fewer–14 more)			
Progression to end-stage kidney disease (defined by stage 5 CKD) up to 52 weeks	Odds ratio: 1.97 (CI 95% 1.04–3.73) Based on data from 325 participants in two studies	106 per 1000	189 per 1000	Very low Due to serious indirectness, due to very serious risk of bias, due to serious imprecision[7]	We are uncertain whether molidustat (any dose) increases progression to end-stage kidney disease (defined by stage 5 CKD) up to 52 weeks in ESA-naïve/ESA-conditioned patients.
		Difference: 83 more per 1000 (CI 95% 4 more–201 more)			
Patients requiring blood transfusion for 16–52 weeks	Odds ratio: 0.69 (CI 95% 0.14–3.47) Based on data from 449 participants in three studies	16 per 1000	11 per 1000	Very low Due to very serious risk of bias, due to serious imprecision[8]	Molidustat (any dose) may decrease patients requiring blood transfusion for 16–52 weeks.
		Difference: 5 fewer per 1000 (CI 95% 14 fewer–37 more)			

Contd...

Table 11: (Continued)

Health-related QoL					No studies were found that viewed health-related QoL.
Fatigue					No studies were found that viewed fatigue.
Change in hemoglobin levels from baseline up to 36 weeks	Measured by: Scale: High better Based on data from 434 participants in three studies	Mean	Mean	Very low Due to serious inconsistency, due to very serious risk of bias[9]	We are uncertain whether molidustat (any dose) decreases hemoglobin levels from baseline up to 36 weeks in ESA-naïve/ESA-conditioned patients.
		Difference: MD 0.11 lower (CI 95% 0.52 lower–0.30 lower)			

Risk of Bias: very serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Imprecision: serious.** Wide confidence intervals; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis, **Indirectness: serious.** The included study was from only one non-South Asian country and was downgraded for lack of directness by one level; **Imprecision: very serious.** Wide confidence intervals, low number of patients; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Imprecision: serious.** Wide confidence intervals; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Indirectness: serious.** The included study was from only one non-South Asian country and was downgraded for lack of directness by one level; **Imprecision: very serious.** Low number of patients, wide confidence intervals. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Indirectness: serious.** The included study was from only one non-South Asian country and was downgraded for lack of directness by one level; **Imprecision: serious.** Low number of patients; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Imprecision: serious.** Wide confidence intervals; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Indirectness: serious.** The included study was from only one non-South Asian country and was downgraded for lack of directness by one level; **Imprecision: serious.** Low number of patients. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Imprecision: serious.** Wide confidence intervals; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2:73%; **Publication bias: not serious.** Mostly commercially funded studies. ESA: Eythropoiesis-stimulating agents, NDD: Nondialysis dependent, CKD: Chronic kidney disease, GDG: Guideline development group, MACE: Major adverse cardiovascular events, CI: Confidence interval, QoL: Quality of life

Table 12: Evidence to decision table for molidustat as an alternative to ESA for anemia in NDD-CKD patients

Benefits and harms	Small net benefit or little difference between alternatives
Molidustat reduced patients requiring blood transfusion from 16 to 52 weeks by 5/1000 as compared to darbepoetin alpha. However, evidence on this was uncertain. Only 6% of GDG members (not including patients) find such a cut-off acceptable for using HIF-PHIs. Molidustat further reduced need for ESA up to 36 weeks by 22/1000 as compared to darbepoetin alpha. However, evidence on this was uncertain. The molidustat group had little or no difference in hemoglobin levels from baseline up to 36 weeks as compared to darbepoetin alpha. However, evidence on this was uncertain. All GDG members (not including patients) find such a scenario acceptable to switch to HIF-PHIs. Molidustat had little or no difference on need for intravenous iron supplementation up to 52 weeks as compared to darbepoetin alpha. About 27% of GDG members (not including patients) find such a cut-off acceptable for using HIF-PHIs. However, evidence on this was uncertain. Molidustat increased the treatment emergent adverse events up to 52 weeks for 16/1000 participants as compared to darbepoetin alpha. However, evidence on this was uncertain. Almost 97% of GDG members (not including patients) find this unacceptable for using HIF-PHIs. In the group that received molidustat, there were 26/1000 more incidences of MACE and MACE plus as compared to darbepoetin alpha. This evidence was uncertain. Nonetheless, all GDG members (not including patients) find this unacceptable to switch to HIF-PHIs. In addition, molidustat increased all-cause mortality up to 52 weeks by 8/1000 compared to darbepoetin alpha. Almost 86% of GDG members (not including patients) find this unacceptable for preferring HIF-PHI over ESAs. However, this evidence was uncertain. Molidustat increased need for oral iron supplementation up to 52 weeks by 133/1000 compared to darbepoetin alpha, which was unacceptable to 100% of GDG members (excluding patients). However, this evidence was also uncertain. The molidustat group further has 83/1000 more incidences of progression to end-stage kidney disease (defined by stage 5 CKD) up to 52 weeks when compared to darbepoetin alpha. However, this evidence was uncertain. None of the included studies examined health-related QoL or fatigue as outcomes. Overall, the panel judged that the desirable anticipated effects of molidustat were trivial and that there were moderate harms, noting that there was very low certainty on the evidence base.	
Certainty of the evidence	Very low [Table 11]
Values and preferences	No substantial variability expected
Empirical examinations of patients' values and preferences from South Asia are not available. The section is based on unstructured interactions with individual patients and caregivers and discussions with panel members. Our recommendation reflects a belief that patients and caregivers prefer oral drugs over subcutaneous injections for those who are not DD. However, the GDG also inferred that informed patient might be reluctant to use molidustat due to the very low certainty of evidence and the lack of evidence on QoL and fatigue which are of importance to patients.	
Resources	Important issues or potential issues not investigated
Molidustat is currently not available in India, so it is not possible to compare the cost. It is administered orally, thereby requiring minimal resources as compared to darbepoetin alpha, which is injectable and requires refrigeration prior to administration. The ease of administration and easy storage for molidustat can reduce the additional resource requirements.	
Equity	No important issues with the recommended alternative
Molidustat does not need refrigeration (cold chain) as compared to darbepoetin alpha. It is thus more useful in remote areas with irregular supply of electricity and in equity groups who might not have refrigeration in their homes. Furthermore, as darbepoetin alpha requires injection, a certain level of health literacy may be needed on how to self-administer the treatment.	
Acceptability	No important issues with the recommended alternative
Molidustat has a preferable route of administration for patients; patients either must self-administer ESA injections or make a hospital visit for the injection. However, ESAs have weekly/fortnightly dose requirements, whereas molidustat should be taken daily or on alternate days. Both these factors can impact compliance and treatment adherence. ESAs may also be easier to supervise than molidustat due to the differences in dose frequency requirements. Overall, for NDD patients, the oral nature of molidustat was thought to be more acceptable by the GDG.	
Feasibility	Intervention is likely difficult to implement
Molidustat can be orally administered and does not require cold chain, unlike darbepoetin alpha, which is relatively easy to administer and store. In addition, molidustat may increase accessibility, particularly for non-dialysis patients, as it does not require hospital visitation or self-injection. However, the availability and accessibility, including in the government sector, under the essential medicine list is still a challenge. As molidustat is not yet approved in India or any other South Asian country, the treatment is not feasible at the current time.	

ESA: Eythropoiesis-stimulating agents, NDD: Nondialysis dependent, CKD: Chronic kidney disease, GDG: Guideline development group, MACE: Major adverse cardiovascular events, HIF PHI: Hypoxia-inducible factor prolyl hydroxylase inhibitor

1.5 Roxadustat as an alternative to ESAs

Table 13: Evidence profile for roxadustat as an alternative to ESA for anemia in NDD-CKD patients

Recommendation for use in research setting only	This recommendation is evidence informed.
Roxadustat should not be used for NDD-CKD patients, except in the context of an approved randomized controlled trial. The panel recommends conduct of large head-to-head multicentric randomized controlled trials in the South Asian region on NDD-CKD patients and measuring critically important outcomes (as elucidated in this guideline) such that evidence base for roxadustat is improved.	

ESA: Eythropoiesis-stimulating agents, NDD: Nondialysis dependent, CKD: Chronic kidney disease

Table 14: Evidence profile for roxadustat as an alternative to ESA for anemia in NDD-CKD patients

Population: Anemia in non-dialysis-dependent chronic kidney disease
Intervention: Roxadustat (any dose)
Comparator: Darbepoetin alpha

Outcome Time frame	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Plain language summary
		Darbepoetin alpha	Roxadustat (any dose)		
Treatment emergent adverse events up to 52 weeks in ESA-conditioned patients	Odds ratio: 1.56 (CI 95% 0.89–2.73) Based on data from 262 participants in one study	702 per 1000	786 per 1000	Very low Due to very serious risk of bias, due to serious indirectness, due to very serious imprecision[1]	We are uncertain whether roxadustat (any dose) increases treatment emergent adverse events up to 52 weeks in ESA-conditioned patients.
		Difference: 84 more per 1000 (CI 95% 25 fewer–163 more)			
Treatment emergent adverse events up to 108 weeks in ESA-naïve patients	Odds ratio: 0.89 (CI 95% 0.50–1.6) Based on data from 616 participants in one study	925 per 1000	916 per 1000	Very low Due to very serious risk of bias, due to serious imprecision[2]	We are uncertain whether roxadustat (any dose) decreases treatment emergent adverse events up to 108 weeks in ESA-naïve patients.
		Difference: 8 fewer per 1000 (CI 95% 65 fewer–27 more)			
All-cause mortality up to 52 weeks in ESA-conditioned patients	Odds ratio: 0.33 (CI 95% 0.01–8.19) Based on data from 262 participants in one study	8 per 1000	2 per 1000	Very low Due to very serious imprecision, due to serious indirectness[3]	We are uncertain whether roxadustat (any dose) decreases all-cause mortality up to 52 weeks in ESA-conditioned patients.
		Difference: 5 fewer per 1000 (CI 95% 8 fewer–54 more)			
All-cause mortality up to 108 weeks in ESA-naïve patients	Odds ratio: 0.87 (CI 95% 0.51–1.47) Based on data from 616 participants in one study	106 per 1000	93 per 1000	Very low Due to very serious risk of bias, due to serious imprecision[4]	We are uncertain whether roxadustat (any dose) decreases all-cause mortality up to 108 weeks in ESA-naïve patients.
		Difference: 12 fewer per 1000 (CI 95% 49 fewer–42 more)			
Incidence of MACE up to 108 weeks in ESA-naïve patients	Odds ratio: 0.82 (CI 95% 0.51–1.31) Based on data from 616 participants in one study	140 per 1000	117 per 1000	Very low Due to very serious risk of bias, due to serious imprecision[5]	We are uncertain whether roxadustat (any dose) decreases incidence of MACE up to 108 weeks in ESA-naïve patients.
		Difference: 22 fewer per 1000 (CI 95% 63 fewer–36 more)			
Incidence of MACE plus up to 108 weeks in ESA-naïve patients	Odds ratio: 0.91 (CI 95% 0.6–1.38) Based on data from 616 participants in one study	181 per 1000	167 per 1000	Very low Due to very serious risk of bias, due to serious imprecision[6]	We are uncertain whether roxadustat (any dose) decreases incidence of MACE plus up to 108 weeks in ESA-naïve patients.
		Difference: 14 fewer per 1000 (CI 95% 64 fewer–53 more)			
Need for iron supplementation (bivalent oral) up to 36 weeks in ESA-naïve patients	Odds ratio: 0.78 (CI 95% 0.57–1.07) Based on data from 616 participants in one study[3]	498 per 1000	436 per 1000	Very low Due to very serious risk of bias, due to serious imprecision[7]	We are uncertain whether roxadustat (any dose) decreases need for iron supplementation (bivalent oral) up to 36 weeks in ESA-naïve patients.
		Difference: 62 fewer per 1000 (CI 95% 137 fewer–17 more)			
Need for iron supplementation (IV) up to 36 weeks in ESA-naïve patients	Odds ratio: 0.46 (CI 95% 0.26–0.81) Based on data from 616 participants in one study	126 per 1000	62 per 1000	**Very low** Due to very serious risk of bias, due to serious imprecision[8]	We are uncertain whether roxadustat (any dose) decreases need for iron supplementation (IV) up to 36 weeks in ESA-naïve patients.
		Difference: 64 fewer per 1000 (CI 95% 90 fewer–21 fewer)			

Contd...

Table 14: (Continued)

Need for iron supplementation (trivalent oral) up to 36 weeks in ESA-naïve patients	Odds ratio: 0.67 (CI 95% 0.49–0.93) Based on data from 616 participants in one study[7]	447 per 1000	351 per 1000	Very low Due to very serious risk of bias, due to serious imprecision[9]	We are uncertain whether roxadustat (any dose) decreases the need for iron supplementation (trivalent oral) up to 36 weeks in ESA-naïve patients.
		Difference: 96 fewer per 1000 (CI 95% 163 fewer–18 fewer)			
Need for ESA					No studies were found that viewed a need for ESA.
Progression to end-stage kidney disease					No studies were found that viewed progression to end-stage kidney disease.
Patients requiring blood transfusion up to 108 weeks	Odds ratio: 1.26 (CI 95% 0.75–2.11) Based on data from 614 participants in one study	96 per 1000	118 per 1000	Very low Due to very serious risk of bias, due to serious imprecision[10]	Roxadustat (any dose) may worsen patients requiring blood transfusion up to 108 weeks.
		Difference: 22 more per 1000 (CI 95% 22 fewer–87 more)			
Health-related QoL					No studies were found that viewed health-related QoL.
Fatigue					No studies were found that viewed fatigue.
Change in hemoglobin levels from baseline up to 24 weeks in ESA-conditioned patients	Measured by: Scale: High better Based on data from 262 participants in one study	Mean	Mean	Very low Due to very serious risk of bias, due to serious indirectness, due to very serious imprecision[11]	Roxadustat (any dose) may have little or no difference on hemoglobin levels from baseline up to 24 weeks in ESA-conditioned patients.
		Difference: MD 0.12 lower (CI 95% 0.30 lower–0.06 lower)			

Risk of Bias: very serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, incomplete data and/or large loss to follow-up, selective outcome reporting, missing intention-to-treat analysis; **Indirectness: serious.** The included study was from only one non-South Asian country and was downgraded for lack of directness by one level; **Imprecision: very serious.** Wide confidence intervals, low number of patients, only data from one study; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, incomplete data and/or large loss to follow-up, selective outcome reporting, missing intention-to-treat analysis; **Imprecision: serious.** Wide confidence intervals, only data from one study; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious. Indirectness: serious.** The included study was from only one non-South-Asian country and was downgraded for lack of directness by one level; **Imprecision: very serious.** Wide confidence intervals, low number of patients, only data from one study; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, incomplete data and/or large loss to follow-up, selective outcome reporting, missing intention-to-treat analysis; **Imprecision: serious.** Only data from one study, wide confidence intervals; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, incomplete data and/or large loss to follow-up, selective outcome reporting, missing intention-to-treat analysis; **Imprecision: serious.** Wide confidence intervals, only data from one study; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, incomplete data and/or large loss to follow-up, selective outcome reporting, missing intention-to-treat analysis; **Imprecision: serious.** Wide confidence intervals, only data from one study; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, incomplete data and/or large loss to follow-up, selective outcome reporting, missing intention-to-treat analysis; **Imprecision: serious.** Wide confidence intervals, only data from one study; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, incomplete data and/or large loss to follow-up, selective outcome reporting, missing intention-to-treat analysis; **Imprecision: serious.** Only data from one study; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, incomplete data and/or large loss to follow-up, selective outcome reporting, missing intention-to-treat analysis; **Imprecision: serious.** Only data from one study; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, incomplete data and/or large loss to follow-up, selective outcome reporting, missing intention-to-treat analysis; **Imprecision: serious.** Only data from one study, wide confidence intervals; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, incomplete data and/or large loss to follow-up, selective outcome reporting, missing intention-to-treat analysis; **Indirectness: serious.** The included study was from only one non-South Asian country and was downgraded for lack of directness by one level; **Imprecision: very serious.** Only data from one study, low number of patients; **Publication bias: not serious.** Mostly commercially funded studies. ESA: Eythropoiesis-stimulating agents, NDD: Nondialysis dependent, CKD: Chronic kidney disease, MACE: Major adverse cardiovascular events, CI: Confidence interval, QoL: Quality of life, MD: Mean difference.

Table 15: Evidence to decision-making matrix for roxadustat as an alternative to ESA for anemia in NDD-CKD patients

Benefits and harms	Small net benefit or little difference between alternatives
Roxadustat decreased treatment emergent adverse up to 108 weeks in ESA-naïve patients by 8/1000 compared to darbepoetin alpha. However, evidence on this was uncertain. Almost 41% of GDG members (not including patients) would find such a scenario acceptable to switch to HIF-PHIs. In ESA-conditioned patients receiving roxadustat decreased all-cause mortality by 5/1000 compared to darbopoetin alpha. About 14% of GDG members (not including patients) would find such a scenario acceptable. Similarly, ESA-naïve patients receiving roxadustat decreased all-cause mortality up to 108 weeks by 12/1000 compared to darbepoetin alpha. Evidence on this was uncertain. About 58% of GDG members (not including patients) would find such a scenario acceptable. Roxadustat reduced incidences of MACE up to 108 weeks in ESA-naïve patients by 22/1000 compared to darbepoetin alpha. However, evidence on this was uncertain. All GDG members (not including patients) find such a cut-off acceptable for using HIF-PHIs. Similarly, roxadustat reduced incidences of MACE plus up to 108 weeks in ESA-naïve patients by 14/1000 compared to darbepoetin alpha. However, evidence on this was uncertain. About 88% of GDG members (not including patients) find such a cut-off acceptable for using HIF-PHIs. For ESA-naïve patients, roxadustat decreased the need for intravenous iron supplementation up to 36 weeks by 64/1000 as compared to darbepoetin alpha. However, evidence on this was uncertain. All GDG members (not including patients) find such a cut-off acceptable for using HIF-PHIs. For ESA-naïve patients, roxadustat decreased the need for bivalent oral iron supplementation up to 36 weeks by 62/1000 as compared to darbepoetin alpha. However, evidence on this was uncertain. All (100%) of the GDG members (not including patients) find such a cut-off acceptable for using HIF-PHIs. For ESA-naïve patients, roxadustat decreased the need for trivalent oral iron supplementation up to 36 weeks by 96/1000 as compared to darbepoetin alpha. However, evidence on this was uncertain. All (100%) of the GDG members (not including patients) find such a cut-off acceptable for using HIF-PHIs. Roxadustat may have had little or no difference on hemoglobin levels from baseline up to 24 weeks for ESA-conditioned patients as compared to darbepoetin alpha. However, evidence on this was uncertain. All GDG members (not including patients) find such a scenario acceptable to switch to HIF-PHIs. In the roxadustat group, there was 84/1000 more treatment emergent adverse events up to 52 weeks in ESA-conditioned patients as compared to darbepoetin alpha. Evidence on this was uncertain. All GDG members (not including patients) would find such a scenario unacceptable. Roxadustat increased the need for patients requiring blood transfusion up to 108 weeks by 22/1000 as compared to darbepoetin alpha group. Evidence on this was uncertain. All GDG members (not including patients) would find such a scenario unacceptable. None of the included studies examined the effect of roxadustat on health-related QoL, fatigue, and end-stage kidney disease. Overall, the panel judged that for roxadustat as compared to darbepoetin alpha, moderate benefits as well as moderate harm were anticipated, noting that there was very low certainty in the evidence base.	
Certainty of the evidence	Very low [Table 14]
Values and preferences	Substantial variability is expected or uncertain
Empirical examination of patients' values and preferences from South Asia is not available. This section is based on unstructured interactions with individual patients and caregivers and discussions with panel members. Our recommendation reflects a belief that patients and caregivers prefer oral drugs over subcutaneous injections for those who are not DD. However, the GDG also inferred that informed patient might be reluctant to use roxadustat due to the very low certainty of evidence and the lack of evidence on QoL and fatigue, which are of importance to patients.	
Resources	No important issues with the recommended alternative
Roxadustat is currently not available in India, so it is not possible to compare the cost at this time. It is administered orally, thereby requiring minimal resources as compared to darbepoetin alpha group which is injectable and requires refrigeration prior to administration. The ease of administration and easy storage for roxadustat can reduce the additional resource requirements.	
Equity	No important issues with the recommended alternative
Roxadustat does not need refrigeration (cold chain) as compared to darbepoetin alpha. It is thus more useful in remote areas with irregular supply of electricity and in equity groups who might not have refrigeration in their homes. Furthermore, as darbepoetin alpha requires injection, a certain level of health literacy may be needed on how to self-administer the treatment.	
Acceptability	No important issues with the recommended alternative
Roxadustat has a preferable route of administration for patients; patients either must self-administer ESA injections or make a hospital visit for the injection. However, ESAs have weekly/fortnightly dose requirements, whereas roxadustat should be taken daily or on alternate days. Both these factors can impact compliance and treatment adherence. ESAs may also be easier to supervise than roxadustat due to the differences in dose frequency requirements. Overall, for NDD patients, the oral nature of roxadustat was thought to be more acceptable by the GDG.	
Feasibility	Intervention is likely difficult to implement
Roxadustat can be orally administered and does not require cold chain, unlike darbepoetin alpha, which is relatively easy to administer and store. In addition, roxadustat may increase accessibility, particularly for non-dialysis patients, as it does not require hospital visitation or self-injection. As roxadustat is not yet approved in India or in any other South Asian country, the treatment is not feasible at the current time.	

ESA: Eythropoiesis-stimulating agents, NDD: Nondialysis dependent, CKD: Chronic kidney disease, MACE: Major adverse cardiovascular events, HIF PHI: Hypoxia-inducible factor prolyl hydroxylase inhibitor, QoL: Quality of life, GDG: Guideline development group

1.6 Vadadustat as an alternative to ESA

Table 16: Recommendation for vadadustat as an alternative to ESA for anemia in NDD-CKD patients

Recommendation for use in research setting only	This recommendation is evidence informed.
Vadadustat should not be used for NDD-CKD patients, except in the context of an approved randomized controlled trial. The panel recommends conduct of large head-to-head multicentric randomized controlled trials in the South Asian region on NDD-CKD patients and measuring critically important outcomes (as elucidated in this guideline) such that evidence base for vadadustat is improved.	

ESA: Eythropoiesis-stimulating agents, NDD: Nondialysis dependent, CKD: Chronic kidney disease

Table 17: Evidence profile for vadadustat as an alternative to ESA for anemia in NDD-CKD patients

Population: Anemia in non-dialysis-dependent chronic kidney disease
Intervention: Vadadustat (any dose)
Comparator: Darbepoetin Alpha

Outcome Time frame	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Plain language summary
		Darbepoetin Alpha	Vadadustat any dose		
Adverse events beyond 52 weeks in ESA-naïve patients	Odds ratio: 0.91 (CI 95% 0.66–1.27) Based on data from 1748 participants in one study	916 per 1000	908 per 1000	Very low Due to serious risk of bias, due to very serious imprecision[1]	We are uncertain whether vadadustat (any dose) decreases adverse events beyond 52 weeks in ESA-naïve patients.
		Difference: 8 fewer per 1000 (CI 95% 38 fewer–17 more)			
Adverse events up to 52 weeks	Odds ratio: 0.77 (CI 95% 0.35–1.71) Based on data from 304 participants in one study	922 per 1000	901 per 1000	Very low Due to serious risk of bias, due to serious indirectness, due to very serious imprecision[2]	We are uncertain whether vadadustat (any dose) decreases adverse events up to 52 weeks in ESA-naïve and ESA-conditioned patients.
		Difference: 21 fewer per 1000 (CI 95% 117 fewer–31 more)			
Adverse events beyond 52 weeks in ESA-conditioned patients	Odds ratio: 1.14 (CI 95% 0.85–1.54) Based on data from 1723 participants in one study	877 per 1000	890 per 1000	Very low Due to serious risk of bias, due to very serious imprecision[3]	We are uncertain whether vadadustat (any dose) increases adverse events beyond 52 weeks in ESA-conditioned patients.
		Difference: 13 more per 1000 (CI 95% 19 fewer–40 more)			
Incidence of MACE beyond 52 weeks	Odds ratio: 1.10 (CI 95% 0.93–1.29) Based on data from 3521 participants in one study	199 per 1000	214 per 1000	Very low Due to serious risk of bias, due to very serious imprecision[4]	We are uncertain whether vadadustat (any dose) increases incidence of MACE beyond 52 weeks in ESA-naïve and ESA-conditioned patients.
		Difference: 16 more per 1000 (CI 95% 11 fewer–44 more)			
Incidence of MACE plus beyond 52 weeks	Odds ratio: 1.04 (CI 95% 0.89–1.21) Based on data from 3521 participants in one study	245 per 1000	252 per 1000	**Very low** Due to serious risk of bias, due to very serious imprecision[5]	We are uncertain whether vadadustat (any dose) increases incidence of MACE plus beyond 52 weeks.
		Difference: 7 more per 1000 (CI 95% 21 fewer–37 more)			
All-cause mortality beyond 52 weeks in ESA-conditioned patients	Odds ratio: 1.00 (CI 95% 0.77–1.29) Based on data from 1723 participants in one study	161 per 1000	161 per 1000	Very low Due to serious risk of bias, due to very serious imprecision[6]	We are uncertain if vadadustat (any dose) has little or no difference on all-cause mortality beyond 52 weeks in ESA-conditioned patients.
		Difference: 0 fewer per 1000 (CI 95% 32 fewer–37 more)			
All-cause mortality up to 52 weeks	Odds ratio: 0.34 (CI 95% 0.01–8.30) Based on data from 304 participants in one study	7 per 1000	2 per 1000	Very low Due to serious risk of bias, due to serious indirectness, due to very serious imprecision[7]	We are uncertain whether vadadustat (any dose) decreases all-cause mortality up to 52 weeks in ESA-naïve and ESA-conditioned patients.
		Difference: 5 fewer per 1000 (CI 95% 7 fewer–48 more)			
All-cause mortality beyond 52 weeks in ESA-naïve patients	Odds ratio: 1.08 (CI 95% 0.85–1.36) Based on data from 1748 participants in one study	**193** per 1000	**205** per 1000	**Very low** due to serious risk of bias, due to very serious imprecision[8]	We are uncertain whether vadadustat (any dose) increases all-cause mortality beyond 52 weeks in ESA-naïve patients.
		Difference: 12 more per 1000 (CI 95% 24 fewer–52 more)			

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Table 17: (Continued)

All-cause mortality beyond 52 weeks	Odds ratio: 1.01 (CI 95% 0.85–1.2) Based on data from 3521 participants in one study	177 per 1000	178 per 1000	Very low Due to serious risk of bias, due to very serious imprecision[9]	Vadadustat (any dose) may have little or no difference on all-cause mortality beyond 52 weeks in ESA-naïve and ESA-conditioned patients.
		Difference: 1 more per 1000 (CI 95% 22 fewer–28 more)			
Need for iron supplementation (oral) up to 52 weeks	Odds ratio: 1.26 (CI 95% 0.78–2.05) Based on data from 304 participants in one study	288 per 1000	337 per 1000	Very low Due to serious risk of bias, due to serious indirectness, due to very serious imprecision[10]	We are uncertain whether vadadustat (any dose) increases the need for iron supplementation (oral) up to 52 weeks in ESA-naïve and ESA-conditioned patients.
		Difference: 50 more per 1000 (CI 95% 48 fewer–165 more)			
Need for ESA					No studies were found that viewed a need for ESA.
Progression to end-stage kidney disease					No studies were found that viewed progression to end-stage kidney disease.
Patients requiring blood transfusion					No studies were found that viewed patients requiring blood transfusion.
Health-related QoL					No studies were found that viewed health-related QoL.
Fatigue					No studies were found that viewed fatigue.
Change in hemoglobin levels from baseline up to 52 weeks in ESA-naïve patients	Measured by: Scale: High better Based on data from 3780 participants in two studies	Mean	Mean	Very low Due to serious risk of bias, due to very serious inconsistency[11]	We are uncertain whether vadadustat (any dose) has little or no difference on hemoglobin levels from baseline up to 52 weeks in ESA-naïve patients.
		Difference: MD 0.00 lower (CI 95% 0.04 lower–0.05 lower)			

Risk of Bias: serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Imprecision: very serious.** Only data from one study, wide confidence intervals; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Indirectness: serious.** The included study was from only one non-South Asian country and was downgraded for lack of directness by one level; **Imprecision: very serious.** Wide confidence intervals, low number of patients, only data from one study; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Imprecision: very serious.** Wide confidence intervals, only data from one study; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Imprecision: very serious.** Wide confidence intervals, only data from one study; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Imprecision: very serious.** Only data from one study, wide confidence intervals; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Imprecision: very serious.** Only data from one study, wide confidence intervals; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Indirectness: serious.** The included study was from only one non-South Asian country and was downgraded for lack of directness by one level; **Imprecision: very serious.** Wide confidence intervals, low number of patients, only data from one study; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Imprecision: very serious.** Only data from one study, wide confidence intervals; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Indirectness: serious**. The included study was from only one non-South Asian country and was downgraded for lack of directness by one level; **Imprecision: very serious.** Low number of patients, wide confidence intervals, only

data from one study; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Inconsistency: very serious.** The magnitude of statistical heterogeneity was high, with I^2: 99 %, point estimates vary widely, the confidence interval of some of the studies do not overlap with those of the most included studies/ the point estimate of some of the included studies, the direction of the effect is not consistent between the included studies; **Publication bias: not serious.** Mostly commercially funded studies. ESA: Eythropoiesis-stimulating agents, NDD: Nondialysis dependent, CKD: Chronic kidney disease, CI: Confidence interval, MACE: Major adverse cardiovascular events, MD: Mean difference, QoL: Quality of life

Table 18: Evidence to decision table for vadadustat as an alternative to ESA for anemia in NDD-CKD patients

Benefits and harms	Small net benefit or little difference between alternatives
Vadadustat reduced adverse events for up to 52 weeks by 21/1000 as compared to darbepoetin alpha. However, evidence on this was uncertain. All GDG members (not including patients) find such a cut-off acceptable for using HIF-PHIs. Similarly, vadadustat reduced adverse events beyond 52 weeks in ESA-naïve patients by 8/1000 as compared to darbepoetin alpha. However, evidence on this was uncertain. Almost 41% of GDG members (not including patients) find such a cut-off acceptable for using HIF-PHIs. Vadadustat decreased all-cause mortality for up to 52 weeks by 5/1000 as compared to darbepoetin alpha. Evidence on this was uncertain. About 14% of GDG members (not including patients) would find such a scenario acceptable for using HIF-PHIs. Vadadustat had little or no difference on all-cause mortality beyond 52 weeks in ESA-conditioned patients. However, evidence on this was uncertain. About 14% of GDG members (not including patients) find such a scenario acceptable to switch to HIF-PHIs. Vadadustat had little or no difference on all-cause mortality beyond 52 weeks. However, evidence on this was uncertain. About 14% of GDG members (not including patients) find such a scenario acceptable to switch to HIF-PHIs. Vadadustat had little or no difference in hemoglobin levels from baseline up to 52 weeks as compared to darbepoetin alpha. However, evidence on this was uncertain. All GDG members (not including patients) find such a scenario acceptable to switch to HIF-PHIs In the group that received vadadustat, there were 13/1000 more adverse events beyond 52 weeks for ESA-conditioned patients as compared to darbepoetin alpha. Evidence on this was uncertain. About 97% of GDG members (not including patients) would find such a scenario unacceptable. Vadadustat increased incidences of MACE beyond 52 weeks by 16/1000 as compared to darbepoetin alpha. Evidence on this was uncertain. All GDG members (not including patients) find such a scenario unacceptable to switch to HIF-PHIs. Vadadustat increased incidences of MACE plus beyond 52 weeks by 7/1000 as compared to darbepoetin alpha. Evidence on this was uncertain. About 81% GDG members (not including patients) find such a scenario unacceptable to switch to HIF-PHIs. Vadadustat increases the incidence of all-cause mortality beyond 52 weeks in ESA-naïve patients by 12/1000 as compared to darbepoetin alpha. However, evidence on this was uncertain. All GDG members (not including patients) find such a scenario unacceptable to switch to HIF-PHIs.	
In the group that received vadadustat, there were 50/1000 more patients who needed oral iron supplementation up to 52 weeks as compared to darbepoetin alpha. Evidence on this was uncertain. All GDG members (not including patients) find such a scenario unacceptable to switch to HIF-PHIs. There were no included studies that examined health-related QoL, fatigue, need for blood transfusion, progression to end-stage kidney disease, or need for ESA as outcomes. Overall, the panel judged that the anticipated benefits and anticipated harm were both moderate when comparing vadadustat to darbepoetin alpha, noting that there was very low certainty in the evidence base.	
Certainty of the evidence	Very low [Table 17]
Values and preferences	Substantial variability is expected or uncertain
Empirical examinations of patients' values and preferences from South Asia are not available. This section is based on unstructured interactions with individual patients and caregivers and discussions with panel members. Our recommendation reflects a belief that patients and caregivers prefer oral drugs over subcutaneous injections for those who are not DD. However, the GDG also inferred that the informed patient might be reluctant to use vadadustat due to the very low certainty of evidence and the lack of evidence on QoL and fatigue, which are of importance to patients.	
Resources	No important issues with the recommended alternative
Vadadustat is currently not available in India, so it is not possible to compare the cost. It is administered orally, thereby requiring minimal resources as compared to darbepoetin alpha which is injectable and requires refrigeration prior to administration. The ease of administration and easy storage for vadadustat can reduce the additional resource requirements.	
Equity	No important issues with the recommended alternative
Vadadustat does not need refrigeration (cold chain) as compared to darbepoetin alpha. It is thus more useful in remote areas with irregular supply of electricity and in equity groups, who might not have refrigeration in their homes. Furthermore, as darbepoetin alpha requires injection, a certain level of health literacy may be needed on how to self-administer the treatment.	
Acceptability	No important issues with the recommended alternative

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Table 18: (Continued)

Vadadustat has a preferable route of administration for patients; patients either must self-administer ESA injections or make a hospital visit for the injection. However, ESAs have weekly/fortnightly dose requirements, whereas vadadustat should be taken daily or on alternate days. Both these factors can impact compliance and treatment adherence. ESAs may also be easier to supervise than vadadustat due to the differences in dose frequency requirements. Overall, for NDD patients, the oral nature of vadadustat was thought to be more acceptable by the GDG.	
Feasibility	Intervention is likely difficult to implement
Vadadustat can be orally administered and does not require cold chain, unlike darbepoetin alpha, which is relatively easy to administer and store. In addition, vadadustat may increase accessibility, particularly for non-dialysis patients, as it does not require hospital visitation or self-injection. As vadadustat is not yet approved in India or any other South Asian country, the treatment is not feasible at the current time.	

HIF PHI: Hypoxia-inducible factor prolyl hydroxylase inhibitor, ESA: Eythropoiesis-stimulating agents, NDD: Nondialysis dependent, CKD: Chronic kidney disease, MACE: Major adverse cardiovascular events, GDG: Guideline development group

2. Recommendations for HIF-PHIs for Treatment of Anemia in Dialysis-Dependent Chronic Kidney Disease patients

2.1 Desidustat as an alternative to ESAs

Table 19: Recommendation for desidustat as an alternatives to ESA for anemia in DD-CKD patients

Consensus Statement	This is a consensus statement, which implies that there is not enough evidence to give an evidence-informed recommendation, but the panel still regarded it as important to provide a statement to support practice decisions
The panel consensus was that desidustat might be offered an alternative to ESAs in DD patients with CKD who do not prefer ESAs. When offering desidustat, it should be thoroughly explained to the patients about the potential benefits and harms, including the very low certainty of evidence on its effectiveness and safety. Patients should be iron replete before the initiation of therapy.	
Recommendation for future research	This recommendation is evidence informed.
The panel recommends conducting large multicentric trials in the South Asian region on DD-CKD patients and measuring critically important outcomes (as elucidated in this guideline) such that evidence base for desidustat is improved. Considering feasibility, acceptability, and equity considerations, and that the drug is already licensed in India, non-industry research funders should prioritize such trials. (This recommendation is evidence-informed.) Robust Phase IV studies in approved markets are also required to establish long-term safety and risk-benefit ratio. Cost-benefit analysis should be done to understand the relative cost of desidustat with ESAs.	

DD: Dialysis-Dependent, CKD: Chronic kidney disease, ESA: Eythropoiesis-stimulating agents, CKD: Chronic kidney disease

Table 20: Evidence profile for desidustat as an alternative to ESA for anemia in DD-CKD patients

Population: Anemia in dialysis-dependent chronic kidney disease Intervention: Desidustat Comparator: Epoetin alfa					
Outcome **Time frame**	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence**	**Plain language summary**
		Epoetin Alpha	**Desidustat**		
All-cause mortality up to 26 weeks	Odds ratio: 0.56 (CI 95% 0.16–1.95) Based on data from 392 participants in one study	36 per 1000	20 per 1000 Difference: 16 fewer per 1000 (CI 95% 30 fewer–32 more)	Very low Due to very serious risk of bias, due to very serious imprecision[1]	We are uncertain whether desidustat (any dose) decreases all-cause mortality up to 26 weeks in comparison with ESAs.
Need for iron supplementation					No studies were found that viewed the need for iron supplementation.
Need for ESA					No studies were found that viewed the need for ESA.
Incidences of MACE and MACE plus					No studies were found that viewed incidences of MACE and MACE plus.
Treatment emergent adverse events up to 26 weeks	Odds ratio: 1.06 (CI 95% 0.72–1.58) Based on data from 392 participants in one study	464 per 1000	478 per 1000 Difference: 15 more per 1000 (CI 95% 80 fewer–114 more)	Very low Due to very serious risk of bias, due to very serious imprecision[2]	We are uncertain whether desidustat (any dose) increases treatment emergent adverse events up to 26 weeks.

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Table 20: (Continued)

Patients requiring blood transfusion					No studies were found that viewed patients requiring blood transfusion.
Change in hemoglobin levels from baseline up to 16–24 weeks	Measured by: Scale: High better Based on data from 373 participants in one study	Mean	Mean	Very low Due to very serious risk of bias, due to serious imprecision[3]	Desidustat may have little or no difference compared with ESAs on changes in hemoglobin levels from baseline up to 16–24 weeks.
		Difference: MD 0.07 lower (CI 95% 0.23 lower–0.37 lower)			
Fatigue					No studies were found that viewed fatigue.
QoL assessed by SF-36 up to 24 weeks	Measured by: SF-36 Scale: High better Based on data from 346 participants in one study	Mean	Mean	Very low Due to very serious risk of bias, due to serious imprecision[4]	We are uncertain whether desidustat worsens QoL assessed by SF-36 up to 24 weeks.
		Difference: MD 49.73 higher (CI 95% 144.53 higher–45.07 lower)			

Risk of Bias: very serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Imprecision: very serious.** Wide confidence intervals, only data from one study, low number of patients, 95% CI of the included study overlaps line of no effect (i.e., CI includes 1.0) rate; **Publication bias: not serious.** The study is commercially funded. **Risk of Bias: very serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, missing intention-to-treat analysis; **Imprecision: very serious.** Only data from one study, wide confidence intervals, low number of patients, 95% CI of the included study overlaps line of no effect (i.e., CI includes 1.0) rate; **Publication bias: not serious.** The study is commercially funded. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Imprecision: very serious.** Low number of patients, only data from one study, and inadequate optimal information size (OIS); Publication bias: not serious. The study is commercially funded. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Imprecision: very serious.** Only data from one study, low number of patients, and inadequate optimal information size (OIS); **Publication bias: not serious.** The study is commercially funded. DD: Dialysis-Dependent, CKD: Chronic kidney disease, ESA: Eythropoiesis-stimulating agents, CI: Confidence interval, MACE: Major adverse cardiovascular events, MD: Mean difference, SF 36: Short Form 36 Health Survey, QoL: Quality of life

Table 21: Evidence to decision table for desidustat as an alternative to ESA for anemia in DD-CKD patients

Benefits and harms	Small net benefit or little difference between alternatives
Desidustat improved QoL assessed by SF-36 up to 24 weeks. But evidence on this was uncertain. All GDG members (not including patients) are comfortable using HIF-PHIs over ESAs in a scenario where there is evidence of improved QoL for HIF-PHI. Desidustat reduced all-cause mortality up to 26 weeks by 16/1000. However, evidence on this was uncertain. About 64% of GDG members (not including patients) find such a cut-off acceptable for using HIF-PHIs. Desidustat had little or no difference for hemoglobin levels from baseline up to 16–24 weeks. However, evidence on this was uncertain. All GDG members (not including patients) find such a scenario acceptable to switch to HIF-PHIs. In the group that received desidustat, there were 15/1000 more treatment emergent adverse events up to 26 weeks compared to ESAs. Evidence on this was uncertain. About 97% of GDG members (not including patients) would find such a scenario unacceptable. There is no evidence on fatigue, incidences of MACE and MACE plus, patient requiring blood transfusion, need for iron supplements (oral/IV), and need for ESA from the trials. All these outcomes were thought to be critical for decision-making. Overall, the panel judged that the anticipated benefits and harms of desidustat over HIF-PHIs were small, but there was very low certainty in the evidence. There is some concern regarding the lack of robust evidence on cardiovascular safety in DD-CKD patients with anemia.	
Certainty of the evidence	Very low [Table 20]
Values and preferences	Substantial variability is expected or uncertain
Empirical examinations of patients' values and preferences from South Asia are not available. This section is based on unstructured interactions with individual patients and caregivers and discussions with panel members. Subcutaneous ESA administration is challenging due to its invasive nature; its use has a learning curve and there are logistic issues (refrigeration). Use of HIF-PHIs might have concerns around pill burden and adherence in some patients. However, some patients might prefer injections because of the need to limit fluid intake	
Resources	No important issues with the recommended alternative
There was no empirical assessment of costs for resources. The direct price of sesidustat (which is available in India) for a month is substantially lower than that of the ESAs. Additionally, desidustat does not need refrigeration and can be administered orally (compared to subcutaneously when given at home or intravenously during hemodialysis). Overall, it is likely to have resource savings. The assessment is based on opinions of GDG members collected through a survey.	

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Table 21: (Continued)

Equity	No important issues with the recommended alternative
Desidustat does not need refrigeration and can be administered orally (unlike ESA). DD patients of CKD undergoing hemodialysis however can be administered ESA during hospital visits, irrespective of health literacy status or affordability. For those undergoing peritoneal dialysis, oral drugs will probably increase equity more.	
Acceptability	Important issues or potential issues not investigated
There are no qualitative studies on preference of South Asian patients with DD-CKD with respect to the acceptability of HIF-PHIs. Patients with hemodialysis might get ESAs intravenously, thus not requiring additional pricks through subcutaneous routes. However, there are concerns around polypharmacy on the use of HIF-PHIs.	
Feasibility	No important issues with the recommended alternative
There are no formal studies on facilitators and barriers to the use of HIF-PHIs in South Asia. The panel adjudged that desidustat, which is licensed for use in India, because of its oral route of administration, is a feasible intervention.	

DD: Dialysis-Dependent, CKD: Chronic kidney disease, ESA: Eythropoiesis-stimulating agents, MACE: Major adverse cardiovascular events, SF 36: Short Form 36 Health Survey, QoL: Quality of life, HIF PHI: Hypoxia-inducible factor prolyl hydroxylase inhibitor, GDG: Guideline development group

2.2 Daprodustat as an alternative to ESAs

Table 22: Recommendation for daprodustat as an alternative to ESA for anemia in DD-CKD patients

Weak recommendation	This recommendation is evidence informed. The drug is currently not licensed in India, and any additional evidence with concerns on safety or effectiveness which might be available to regulators has not been appraised.
The GDG suggests that when available, daprodustat might be considered as an alternative to ESAs for correcting and maintaining hemoglobin level in DD patients with chronic kidney disease. Patients should be iron replete before the initiation of therapy.	

DD: Dialysis-Dependent, CKD: Chronic kidney disease, ESA: Eythropoiesis-stimulating agents, GDG: Guideline development group

Table 23: Evidence profile for daprodustat as an alternative to ESA for anemia in DD-CKD patients

Population: Anemia in dialysis-dependent chronic kidney disease
Intervention: Daprodustat
Comparator: ESA (rhEPO/darbepoetin alpha/epoetin alpha)

Outcome **Time frame**	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence**	**Plain language summary**
		ESA (rhEPO/ darbepoetin alpha/epoetin alpha)	**Daprodustat**		
Need for iron supplementation (oral) up to 52 weeks.	Odds ratio: 0.91 (CI 95% 0.55–1.52) Based on data from 267 participants in one study	343 per 1000	322 per 1000	Very low Due to serious indirectness, due to very serious imprecision[1]	We are uncertain whether daprodustat (any dose) decreases the need for iron supplementation (oral) up to 52 weeks.
		Difference: 21 fewer per 1000 (CI 95% 120 fewer–99 more)			
Need for ESA					No studies were found that viewed the need for ESA.
All-cause mortality up to 52 weeks	Odds ratio: 0.98 (CI 95% 0.82–1.16) Based on data from 4035 participants in five studies	166 per 1000	163 per 1000	Low Due to serious risk of bias, due to serious imprecision[2]	Daprodustat (any dose) may have little or no difference on all-cause mortality up to 52 weeks.
		Difference: 3 fewer per 1000 (CI 95% 26 fewer–22 more)			
Incidences of MACE up to 52 weeks	Odds ratio: 0.95 (CI 95% 0.82–1.11) Based on data from 3691 participants in three studies	239 per 1000	230 per 1000	Low Due to serious risk of bias, due to serious imprecision[3]	Daprodustat (any dose) may decrease incidence of MACE up to 52 weeks.
		Difference: 9 fewer per 1000 (CI 95% 34 fewer–19 more)			
Need for iron supplementation (IV) up to 52 weeks	Odds ratio: 0.77 (CI 95% 0.53–1.13) Based on data from 674 participants in two studies	376 per 1000	317 per 1000	Moderate Due to serious imprecision[4]	Daprodustat (any dose) probably decreases the need for iron supplementation (IV) up to 52 weeks.
		Difference: 59 fewer per 1000 (CI 95% 134 fewer–29 more)			
Adverse events up to 52 weeks	Odds ratio: 1.05 (CI 95% 0.73–1.50) Based on data from 3945 participants in four studies	843 per 1000	849 per 1000	Low Due to serious risk of bias, due to serious imprecision[5]	Daprodustat (any dose) may have little or no difference on adverse events up to 52 weeks.
		Difference: 6 more per 1000 (CI 95% 46 fewer–47 more)			

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Table 23: (Continued)

Patients requiring blood transfusion up to 52 weeks	Odds ratio: 0.86 (CI 95% 0.73–1.01) Based on data from 2964 participants in one study	183 per 1000	162 per 1000	Low Due to serious risk of bias, due to serious imprecision[6]	Daprodustat (any dose) may decrease patients requiring blood transfusion up to 52 weeks.
		Difference: 21 fewer per 1000 (CI 95% 42 fewer–1 more)			
Change in hemoglobin levels from baseline up to 52 weeks	Measured by: Scale: High better Based on data from 3950 participants in four studies	(Mean)	(Mean)	Low Due to serious risk of bias, due to serious imprecision[7]	Daprodustat (any dose) probably has little or no difference on changes in hemoglobin levels from baseline up to 52 weeks.
		Difference: MD 0.02 lower (CI 95% 0.14 lower–0.18 higher)			
QoL					No studies were found that viewed QoL.
Fatigue					No studies were found that viewed fatigue.

Indirectness: serious. The included study was from only one country which is not in South Asia and was downgraded for lack of directness by one level; **Imprecision: very serious**. Only data from one study, low number of patients, the 95% CI of the included study overlaps line of no effect (i.e., CI includes 1.0) rate, wide confidence intervals; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, selective outcome reporting; **Imprecision: serious.** The 95% CI of the included study overlaps line of no effect (i.e., CI includes 1.0) rate, wide confidence intervals; **Publication bias: not serious**. Mostly commercially funded studies. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, selective outcome reporting; **Imprecision: serious.** The 95% CI of the included study overlaps line of no effect (i.e., CI includes 1.0) rate; **Publication bias: not serious.** Mostly commercially funded studies. **Imprecision: serious.** The 95% CI of the included study overlaps line of no effect (i.e., CI includes 1.0) rate, wide confidence intervals; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, selective outcome reporting; Imprecision: serious. The 95% CI of the included studies overlaps line of no effect (i.e., CI includes 1.0) rate, wide confidence intervals; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: serious.** Selective outcome reporting, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: serious.** Only data from one study, wide confidence intervals; **Publication bias: not serious.** Mostly commercially funded studies. Risk of Bias: serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, selective outcome reporting; **Imprecision: serious.** Wide confidence intervals, 95% CI of the included study overlaps line of no effect. DD: Dialysis-Dependent, CKD: Chronic kidney disease, ESA: Eythropoiesis-stimulating agents, MACE: Major adverse cardiovascular events, QoL: Quality of life, HIF PHI: Hypoxia-inducible factor prolyl hydroxylase inhibitor, GDG: Guideline development group, rhEPO: epoetins or their biosimilars or darbepoetin, CI: Confidence interval

Table 24: Evidence profile for daprodustat as an alternative to ESA for anemia in DD-CKD patients

Benefits and harms	Substantial net benefits of the recommended alternative
Daprodustat probably decreased the need for intravenous iron supplementation with the estimate for difference reported as 59 fewer per 1000 compared to ESAs. All GDG members (not including patients) would find such a scenario acceptable. Daprodustat decreased the need for oral iron supplementation up to 52 weeks by 21/1000. However, evidence on this was uncertain. About 64% of GDG members (not including patients) would find such a scenario acceptable. Patients requiring blood transfusion up to 52 weeks was reduced by 21/1000 for patients receiving daprodustat. About 85% of GDG members (not including patients) would find such a scenario acceptable. In the group receiving daprodustat, there were 9/1000 fewer incidences of MACE up to 52 weeks compared to ESAs. About 19% of GDG members (not including patients) would find such a scenario acceptable. Daprodustat probably resulted in little or no difference in changes in hemoglobin levels from baseline up to 52 weeks. GDG members (not including patients) find such a scenario acceptable to switch to HIF-PHIs. Daprodustat may have little or no difference on adverse events. About 41% of GDG members (not including patients) find such a scenario acceptable to switch to HIF-PHIs. Daprodustat may have little or no difference on all-cause mortality up to 52 weeks. Almost 14% of GDG members (not including patients) find such a scenario acceptable to switch to HIF-PHIs. There was no data available in included studies that examined health-related QoL, fatigue, or need for ESA. All these outcomes were thought to be critical for decision-making. Overall, the panel judged that the desirable benefits of daprodustat in comparison to ESAs to be moderate with moderate certainty of evidence for the outcomes of change in hemoglobin and use of intravenous iron supplementation. The harms of daprodustat were comparable to those for ESAs (trivial/no harm), but evidence on this was of low or very low certainty.	
Certainty of the evidence	Low [Table 23]
Values and preferences	Substantial variability is expected or uncertain

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Table 24: (Continued)

Empirical examinations of patients' values and preferences from South Asia are not available. This section is based on unstructured interactions with individual patients and caregivers and discussions with panel members. Subcutaneous ESA administration is challenging due to its invasive nature; its use has a learning curve; and there are logistic issues (refrigeration). Use of HIF-PHIs might have concerns around pill burden and adherence in some patients. However, some patients might prefer injections because of the need to limit fluid intake	
Resources	Important issues or potential issues not investigated
Daprodustat is currently not available in South Asia, so it is not possible to compare the cost currently. Although daprodustat does not need refrigeration and can be administered orally (unlike ESAs), this may not be of added benefit for DD patients as they would already be undertaking regular hospital visits for dialysis. In this case, they can receive the intervention during hospital visits, which is unlikely to require extra resources from the patient. The assessment is based on opinions of GDG members collected through survey.	
Equity	No important issues with the recommended alternative
Daprodustat does not need refrigeration and can be administered orally (unlike ESAs). DD patients would already be undertaking hospital visits; thereby, no extra resource is required for administering oral drug. Hence, it is less likely to decrease equity. Furthermore, patients who are DD do not require a certain level of health literacy to learn how to self-administer the treatment.	
Acceptability	Important issues or potential issues not investigated
There are no qualitative studies on the preferences of South Asian patients with DD-CKD with respect to the acceptability of HIF-PHIs. Patients with hemodialysis might get ESAs intravenously, thus not requiring additional pricks through subcutaneous routes. However, there are concerns around polypharmacy on the use of HIF-PHIs.	
Feasibility	Intervention is likely difficult to implement
There are no formal studies on facilitators and barriers to use of HIF-PHIs in South Asia. The panel adjudged that daprodustat, although preferred because of its oral route of administration, is not licensed by the national drug regulators in India or any other South Asian country. As such, it is currently not feasible.	

DD: Dialysis-Dependent, CKD: Chronic kidney disease, ESA: Eythropoiesis-stimulating agents, MACE: Major adverse cardiovascular events, HIF PHI: Hypoxia-inducible factor prolyl hydroxylase inhibitor, GDG: Guideline development group

2.3 Enarodustat as an alternative to ESAs

Table 25: Recommendations for enarodustat as an alternative to ESA for DD-CKD patients

Recommendation for use in research setting only	This recommendation is evidence informed.
Enarodustat should not be used for DD-CKD patients, except in the context of an approved randomized controlled trial. The panel recommends conducting large head-to-head multicentric randomized controlled trials in the South Asian region on DD-CKD patients and measuring critically important outcomes (as elucidated in this guideline) such that the evidence base for enarodustat is improved.	

DD: Dialysis-Dependent, CKD: Chronic kidney disease, ESA: Eythropoiesis-stimulating agents

Table 26:Evidence profile for enarodustat as an alternative to ESA for DD-CKD patients

Population: Anemia in dialysis-dependent chronic kidney disease Intervention: Enarodustat (any dose) Comparator: Darbepoetin alpha					
Outcome **Time frame**	**Study results and measurements**	**Absolute effect estimates**		**Certainty of evidence**	**Plain language summary**
		Darbepoetin alpha	**Enarodustat any dose**		
Need for ESA					No studies were found that viewed at the need for ESA.
Incidences of MACE up to 52 weeks					No studies were found that viewed incidences of MACE up to 52 weeks.
Need for iron supplementation (oral) up to 24 weeks	Odds ratio: 1.40 (CI 95% 0.76–2.56) Based on data from 172 participants in one study	384 per 1000	466 per 1000 Difference: 82 more per 1000 (CI 95% 63 fewer–231 more)	Very low Due to serious risk of bias, due to serious indirectness, due to very serious imprecision[1]	We are uncertain whether enarodustat (any dose) increases the need for iron supplementation (oral) up to 24 weeks.
Adverse events up to 26 weeks	Odds ratio: 1.34 (CI 95% 0.57–3.15) Based on data from 173 participants in one study	837 per 1000	873 per 1000 Difference: 36 more per 1000 (CI 95% 92 fewer–105 more)	Very low Due to serious indirectness, due to very serious imprecision[2]	We are uncertain whether enarodustat (any dose) increases adverse events up to 26 weeks.

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Table 25: (Continued)

Patients requiring blood transfusion				No studies were found that viewed patients requiring blood transfusion.
Change in hemoglobin levels from baseline up to 24 weeks	Measured by: Scale: High better Based on data from 172 participants in one study	Mean: Mean Difference: MD 0.12 lower (CI 95% -0.33 lower–0.09 higher)	Low Due to serious indirectness, due to serious imprecision[3]	Enarodustat (any dose) lowered the hemoglobin levels from baseline up to 24 weeks.
QoL				No studies were found that viewed QoL.
Fatigue				No studies were found that viewed fatigue.
All-cause mortality up to 26 weeks	Based on data from 173 participants in one study	No deaths were reported in either enarodustat any dose or darbepoetin alpha group	Very low Due to serious risk of bias, due to serious indirectness, due to serious imprecision[4]	There were no patients who experienced all-cause mortality up to 26 weeks, so we were unable to determine whether enarodustat (any dose) made a difference.

Risk of Bias: serious. Missing intention-to-treat analysis; **Indirectness: serious.** The included study was from only one country which is not in South Asia and was downgraded for lack of directness by one level; Imprecision: very serious. The 95% CI of the included study overlaps line of no effect (i.e., CI includes 1.0) rate, only data from one study, low number of patients, wide confidence intervals; **Publication bias: not serious.** The study is commercially funded. **Risk of Bias: not serious.** Missing intention-to-treat analysis; Indirectness: serious. The included study was from only one country which is not in South Asia and was downgraded for lack of directness by one level; **Imprecision: very serious.** The 95% CI of the included study overlaps line of no effect (i.e., CI includes 1.0) rate only data from one study, low number of patients, wide confidence intervals; **Publication bias: not serious.** The study is commercially funded. **Risk of Bias: not serious.** Missing intention-to-treat analysis; **Indirectness: serious.** The included study was from only one country which is not in South Asia and was downgraded for lack of directness by one level; **Imprecision: serious.** Only data from one study, low number of patients, the 95% CI of the included study overlaps line of no effect; **Publication bias: not serious.** The study is commercially funded.; **Risk of Bias: serious.** Missing intention-to-treat analysis; **Indirectness: serious.** The included study was from only one country which is not in South Asia and was downgraded for lack of directness by one level; **Imprecision: serious.** Low number of patients, only data from one study; **Publication bias: not serious.** The study is commercially funded. DD: Dialysis-Dependent, CKD: Chronic kidney disease, ESA: Eythropoiesis-stimulating agents, MACE: Major adverse cardiovascular events, CI: Confidence interval, QoL: Quality of life, MD: Mean difference

Table 27: Evidence to decision table for enarodustat as an alternative to ESA for DD-CKD patients

Benefits and harms	Small net benefit or little difference between alternatives
Enarodustat lowered the hemoglobin levels from baseline up to 24 weeks by 12/1000 compared to darbepoetin alpha. However, evidence on this was uncertain. All GDG members (not including patients) find such a scenario unacceptable to switch to HIF-PHIs. In the group that received enarodustat, there was 36/1000 more risk of adverse events up to 26 weeks compared to darbepoetin alpha. Evidence on this was uncertain. All GDG members (not including patients) would find such a scenario unacceptable. Enarodustat increased the need for oral iron supplementation up to 24 weeks as compared to darbepoetin alpha by 82/1000. Evidence on this was uncertain. All GDG members (not including patients) would find such a scenario unacceptable. There were no patients who experienced all-cause mortality up to 26 weeks; thus it is uncertain to determine whether enarodustat made a difference as compared to darbepoetin alpha. None of the included studies measured health-related QoL, fatigue, incidences of MACE and MACE plus, need for blood, and ESA as outcomes. Overall, compared to darbepoetin alpha, the panel judged desirable anticipated effects for enarodustat to be trivial and harm to be moderate, noting that there was very low certainty in the evidence base. There is substantial concern regarding the lack of robust evidence on cardiovascular safety in DD-CKD patients with anemia.	
Certainty of the evidence	Very low [Table 26]
Values and preferences	Substantial variability is expected or uncertain
Empirical examinations of patients' values and preferences from South Asia are not available. This section is based on unstructured interactions with individual patients and caregivers and discussions with panel members. Subcutaneous ESA administration is challenging due to its invasive nature, its use has a learning curve, and there are logistic issues (refrigeration). Use of HIF-PHIs might have concerns around pill burden and adherence in some patients. However, some patients might prefer injections because of the need to limit fluid intake.	
Resources	Important issues or potential issues not investigated

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Table 27: (Continued)

Enarodustat is currently not available in India, so it is not possible to compare the cost at this time. Although it does not need refrigeration and can be administered orally (unlike darbepoetin alpha), this may not be of added benefit for DD patients as they would already be undertaking regular hospital visits for dialysis. In this case, they can receive the intervention during hospital visits, which is unlikely to require extra resources from the patient	
Equity	Important issues or potential issues not investigated
Although enarodustat does not need refrigeration and can be administered orally (unlike darbepoetin alpha), this is less likely to decrease equity for DD patients, as they would already have regular hospital visits for dialysis purposes. In this case, it would put minimal additional strain to have darbepoetin alpha administered.	
Acceptability	Important issues or potential issues not investigated
There are no qualitative studies on preference of South Asian patients with DD-CKD with respect to the acceptability of HIF-PHIs. Patients with hemodialysis might get ESAs intravenously, thus not requiring additional pricks through subcutaneous routes. However, there are concerns around polypharmacy on the use of HIF-PHIs.	
Feasibility	Intervention is likely difficult to implement
There are no formal studies on facilitators and barriers to the use of HIF-PHIs in South Asia. The panel adjudged that enarodustat, although preferred because of its oral route of administration, is not licensed by the national drug regulators in India or any other South Asian country. As such, it is probably not feasible.	

DD: Dialysis-Dependent, CKD: Chronic kidney disease, ESA: Eythropoiesis-stimulating agents, MACE: Major adverse cardiovascular events, HIF PHI: Hypoxia-inducible factor prolyl hydroxylase inhibitor

2.4 Molidustat as an alternative to ESAs

Table 28: Recommendation for molidustat as an alternative to ESA for DD-CKD patients

Recommendation for use in research setting only	This recommendation is evidence informed.
Molidustat should not be used for DD-CKD patients, except in the context of an approved randomized controlled trial. The panel recommends conducting large head-to-head multicentric randomized controlled trials in the South Asian region on DD-CKD patients and measuring critically important outcomes (as elucidated in this guideline) such that evidence base for molidustat is improved.	

DD: Dialysis-Dependent, CKD: Chronic kidney disease, ESA: Eythropoiesis-stimulating agents

Table 29: Evidence profile for molidustat as an alternative to ESA for DD-CKD patients

Population: Anemia in dialysis-dependent chronic kidney disease
Intervention: Molidustat
Comparator: ESA (epoetin alpha/epoetin beta/darbepoetin alpha)

Outcome Time frame	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence**	**Plain language summary**
		ESA (epoetin alpha/ epoetin beta/ darbepoetin alpha)	**Molidustat**		
Need for iron supplementation (oral) up to 52 weeks	Odds ratio: 3.45 (CI 95% 0.99–12.05) Based on data from 229 participants in one study	39 per 1000	122 per 1000	Very low Due to serious risk of bias, due to serious indirectness, due to very serious imprecision[1]	We are uncertain whether molidustat (any dose) increases the need for iron supplementation (oral) up to 52 weeks.
		Difference: 84 more per 1000 (CI 95% 0–289 more)			
All-cause mortality up to 52 weeks	Odds ratio: 0.56 (CI 95% 0.10–3.04) Based on data from 428 participants in two studies	17 per 1000	9 per 1000	Very low Due to serious risk of bias, due to very serious imprecision[2]	We are uncertain whether molidustat (any dose) decreases all-cause mortality up to 52 weeks.
		Difference: 7 fewer per 1000 (CI 95% 15 fewer–33 more)			
Need for ESA up to 52 weeks	Odds ratio: 8.15 (CI 95% 1.06–62.93) Based on data from 229 participants in one study	13 per 1000	96 per 1000	Very low Due to serious risk of bias, due to serious indirectness, due to very serious imprecision[3]	We are uncertain whether molidustat (any dose) increases the need for ESA up to 52 weeks.
		Difference: 84 more per 1000 (CI 95% 1 more–440 more)			

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Table 29: (Continued)

Need for iron supplementation (IV) up to 52 weeks	Odds ratio: 0.96 (CI 95% 0.54–1.69) Based on data from 229 participants in one study	632 per 1000	622 per 1000	Very low Due to serious risk of bias, due to serious indirectness, due to very serious imprecision[4]	We are uncertain whether molidustat (any dose) decreases the need for iron supplementation (IV) up to 52 weeks.
		Difference: 10 fewer per 1000 (CI 95% 151 fewer–112 more)			
Incidences of MACE up to 52 weeks	Odds ratio: 1.25 (CI 95% 0.24–6.60) Based on data from 229 participants in one study	26 per 1000	32 per 1000	Very low Due to serious risk of bias, due to serious indirectness, due to very serious imprecision[5]	We are uncertain whether molidustat (any dose) increases incidences of MACE up to 52 weeks.
		Difference: 6 more per 1000 (CI 95% 20 fewer–124 more)			
Treatment emergent adverse event up to 52 weeks	Odds ratio: 1.24 (CI 95% 0.62–2.45) Based on data from 428 participants in two studies	881 per 1000	901 per 1000	Very low Due to serious risk of bias, due to very serious imprecision[6]	We are uncertain whether molidustat increases treatment emergent adverse event up to 52 weeks.
		Difference: 21 more per 1000 (CI 95% 60 fewer–67 more)			
Patients requiring blood transfusion up to 20 weeks	Odds ratio: 1.47 (CI 95% 0.34–6.38) Based on data from 199 participants in one study	48 per 1000	69 per 1000	Very low Due to very serious risk of bias, due to very serious imprecision[7]	We are uncertain whether molidustat (any dose) increases patients requiring blood transfusion up to 20 weeks.
		Difference: 21 more per 1000 (CI 95% 31 fewer–195 more)			
Change in hemoglobin levels from baseline up to 36 weeks	Measured by: Scale: High better Based on data from 379 participants in two studies	Mean	Mean	Low due to serious risk of bias, due to serious imprecision[8]	We are uncertain whether molidustat (any dose) lowered the hemoglobin levels from baseline up to 36 weeks.
		Difference: 0.17 lower (MD) (CI 95% 0.43 lower–0.10 higher)			
QoL					No studies were found that viewed QoL.
Fatigue					No studies were found that viewed fatigue.

Risk of Bias: serious. Missing intention-to-treat analysis; **Indirectness: serious.** The included study was from only one country which is not in South Asia and was downgraded for lack of directness by one level; **Imprecision: very serious.** Wide confidence intervals, low number of patients, only data from one study, the 95% CI of the included study overlaps line of no effect (i.e., CI includes 1.0) rate; Publication bias: not serious. Mostly commercially funded studies. **Risk of Bias: serious.** Missing intention-to-treat analysis; **Imprecision: very serious.** Wide confidence intervals, low number of patients, the 95% CI of the included study overlaps line of no effect (i.e., CI includes 1.0). **Risk of Bias: serious.** Missing intention-to-treat analysis; **Indirectness: serious.** The included study was from only one country which is not in South Asia and was downgraded for lack of directness by one level; **Imprecision: very serious.** Only data from one study, low number of patients, wide confidence intervals, the 95% CI of the included study overlaps line of no effect (i.e., CI includes 1.0) rate; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: serious.** Missing intention-to-treat analysis; **Indirectness: serious.** The included study was from only one country which is not in South Asia and was downgraded for lack of directness by one level; **Imprecision: very serious.** Wide confidence intervals, low number of patients, only data from one study, the 95% CI of the included study overlaps line of no effect (i.e., CI includes 1.0). **Risk of Bias: serious.** Missing intention-to-treat analysis; I**ndirectness: serious.** The included study was from only one country which is not in South Asia and was downgraded for lack of directness by one level; **Imprecision: very serious.** Wide confidence intervals, low number of patients, only data from one study, the 95% CI of the included study overlaps line of no effect (i.e., CI includes 1.0) rate; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: serious.** Missing intention-to-treat analysis; **Imprecision: very serious.** Wide confidence intervals, low number of patients, the 95% CI of the included study overlaps line of no effect (i.e., CI includes 1.0). **Risk of Bias: very serious.** Missing intention-to-treat analysis, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; I**mprecision: very serious.** Low number of patients, only data from one study, wide confidence intervals; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: serious.** Missing intention-to-treat analysis; **Imprecision: serious.** Low number of patients, only data from one study; **Publication bias: not serious.** Mostly commercially funded studies. DD: Dialysis-Dependent, CKD: Chronic kidney disease, ESA: Eythropoiesis-stimulating agents, MACE: Major adverse cardiovascular events, HIF PHI: Hypoxia-inducible factor prolyl hydroxylase inhibitor, CI: Confidence interval, MD: Mean difference, QoL: Quality of life

Table 30: Evidence profile for molidustat as an alternative to ESA for DD-CKD patients

Benefits and harms	Small net benefit or little difference between alternatives
Molidustat reduced all-cause mortality up to 52 weeks by 7/1000. However, evidence on this was uncertain. About 14% of GDG members (not including patients) find such a cut-off acceptable for using HIF-PHIs. Molidustat reduced the need for intravenous iron supplementation up to 52 weeks by 10/1000, but evidence on this was uncertain. Almost 27% of GDG members (not including patients) are comfortable using HIF-PHIs over ESAs. Molidustat lowered hemoglobin levels from baseline up to 36 weeks. However, evidence on this was uncertain. All GDG members (not including patients) find such a scenario acceptable to switch to HIF-PHIs. Molidustat increased the need for blood transfusion up to 20 weeks by 21/1000 compared to ESAs. However, evidence on this was uncertain. All GDG members (not including patients) find such a scenario unacceptable to switch to HIF-PHIs. Compared to ESA, molidustat increased the risk of treatment emergent adverse events up to 52 weeks by 21/1000. Evidence on this was uncertain. All GDG members (not including patients) would find such a scenario unacceptable. In the group that received molidustat, there was 6/1000 more incidences of MACE up to 52 weeks compared to the group that received ESAs. Evidence on this was uncertain. About 81% of GDG members (not including patients) would find such a scenario unacceptable. Uncertain evidence also reported an increased need for oral iron supplementation up to 52 weeks by 84/1000 in the molidustat group as compared to the ESA group. All GDG members (not including patients) would find such a scenario unacceptable. There was increased need for ESA up to 52 weeks by 84/1000 in the molidustat group as compared the ESA group. However, evidence on this was uncertain. None of the included studies measured health-related fatigue as an outcome. Overall, the panel judged that the desirable anticipated effects of molidustat compared to ESA were small and that there were moderate harms, noting that there was very low certainty in the evidence base.	
Certainty of the evidence	Very low [Table 29]
Values and preferences	Substantial variability is expected or uncertain
Empirical examinations of patients' values and preferences from South Asia are not available. This section is based on unstructured interactions with individual patients and caregivers and discussions with panel members. Subcutaneous ESA administration is challenging due to its invasive nature, its use has a learning curve, and there are logistic issues (refrigeration). Use of HIF-PHIs might have concerns around pill burden and adherence in some patients. However, some patients might prefer injections because of the need to limit fluid intake	
Resources	Important issues or potential issues not investigated
Molidustat is currently not available in India, so it is not possible to compare the cost at this time. Although molidustat does not need refrigeration and can be administered orally (unlike ESAs), this may not be of added benefit for DD patients, as they would already be undertaking regular hospital visits for dialysis. In this case, they can receive the intervention during hospital visits, which is unlikely to require extra resources from the patient.	
Equity	No important issues with the recommended alternative
Although molidustat does not need refrigeration and can be administered orally (unlike ESAs), this is less likely to decrease equity for DD patients, as they would already have to make regular hospital visits for dialysis purposes. In this case, it would put minimal additional strain to have ESA administered.	
Acceptability	Important issues or potential issues not investigated
There are no qualitative studies on preference of South Asian patients with DD-CKD with respect to the acceptability of HIF-PHIs. Patients with hemodialysis might get ESAs intravenously, thus not requiring additional pricks through subcutaneous routes. However, there are concerns around polypharmacy on the use of HIF-PHIs.	
Feasibility	Intervention is likely difficult to implement
There are no formal studies on facilitators and barriers to the use of HIF-PHIs in South Asia. The panel adjudged that molidustat, although preferred because of its oral route of administration, is not licensed by the national drug regulators in India or in any other South Asian country. As such, it is probably not feasible.	

DD: Dialysis-Dependent, CKD: Chronic kidney disease, ESA: Eythropoiesis-stimulating agents, HIF PHI: Hypoxia-inducible factor prolyl hydroxylase inhibitor, GDG: Guideline development group, MACE: Major adverse cardiovascular events

2.5 Roxadustat as an alternative to ESA

Table 31: Recommendation for roxadustat as an alternative to ESA for DD-CKD patients

Recommendation for use in research setting only	This recommendation is evidence informed.
Roxadustat should not be used for DD-CKD patients, except in the context of an approved randomized controlled trial. The panel recommends conducting large head-to-head multicentric randomized controlled trials in the South Asian region on DD-CKD patients and measuring critically important outcomes (as elucidated in this guideline) such that evidence base for roxadustat is improved.	

DD: Dialysis-Dependent, CKD: Chronic kidney disease, ESA: Eythropoiesis-stimulating agents

Table 32: Evidence profile for roxadustat as an alternative to ESA for DD-CKD patients

Population: Anemia in dialysis-dependent chronic kidney disease Intervention: Roxadustat Comparator: ESA (epoetin alpha/darbepoetin alpha)					
Outcome **Time frame**	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence**	**Plain language summary**
		ESA (epoetin alpha/ darbepoetin alpha)	**Roxadustat**		
All-cause mortality from 6 to 52 weeks	Odds ratio: 1.11 (CI 95% 0.76–1.62) Based on data from 1715 participants in six studies	82 per 1000	90 per 1000	Low Due to serious risk of bias, due to serious imprecision[1]	We are uncertain whether roxadustat (any dose) increases all-cause mortality from 6 to 52 weeks.
		Difference: 8 more per 1000 (CI 95% 18 fewer–44 more)			
All-cause mortality from 108 to 209 weeks	Odds ratio: 1.13 (CI 95% 0.96–1.33) Based on data from 3974 participants in three studies	171 per 1000	189 per 1000	Very low Due to very serious risk of bias, due to serious imprecision[2]	We are uncertain whether roxadustat (any dose) increases all-cause mortality from 108 to 209 weeks.
		Difference: 18 more per 1000 (CI 95% 6 fewer–44 more)			
Need for iron supplementation from 6 to 52 weeks	Odds ratio: 0.57 (CI 95% 0.16–2.05) Based on data from 1215 participants in three studies	793 per 1000	685 per 1000	Very low Due to serious risk of bias, due to serious inconsistency, due to serious imprecision[3]	We are uncertain whether roxadustat (any dose) decreases the need for iron supplementation from 6 to 52 weeks.
		Difference: 107 fewer per 1000 (CI 95% 413 fewer–94 more)			
Need for ESA from 6 to 52 weeks	Odds ratio: 13.38 (CI 95% 0.75–238.31) Based on data from 916 participants in two studies	0 per 1000	0 per 1000	Very low Due to very serious risk of bias, due to very serious imprecision[4]	We are uncertain whether roxadustat (any dose) increases the need for ESA from 6 to 52 weeks.
		Difference: 0 fewer per 1000 (CI 95% 0–0)			
Need for iron supplementation from 52 to 208 weeks	Odds ratio: 0.56 (CI 95% 0.13–2.46) Based on data from 2940 participants in two studies	288 per 1000	184 per 1000	**Very low** Due to very serious risk of bias, due to serious inconsistency, due to serious imprecision[5]	We are uncertain whether roxadustat (any dose) decreases need for iron supplementation from 52 to 208 weeks.
		Difference: 103 fewer per 1000 (CI 95% 238 fewer–211 more)			
Need for ESA up to 208 weeks	Odds ratio: 20.29 (CI 95% 4.89–84.25) Based on data from 2106 participants in one study	2 per 1000	39 per 1000	Very low Due to very serious risk of bias, due to serious imprecision[6]	We are uncertain whether roxadustat increases need for ESA up to 208 weeks.
		Difference: 37 more per 1000 (CI 95% 8 more–142 more)			
Treatment emergent adverse events from 6 to 52 weeks	Odds ratio: 1.45 (CI 95% 1.08–1.96) Based on data from 1715 participants in six studies	786 per 1000	841 per 1000	Moderate Due to serious risk of bias[7]	Roxadustat (any dose) may increase treatment emergent adverse events from 6 to 52 weeks.
		Difference: 56 more per 1000 (CI 95% 13 more–92 more)			
Treatment emergent adverse events from 108 to 209 weeks	Odds ratio: 1.05 (CI 95% 0.85–1.28) Based on data from 2935 participants in two studies	849 per 1000	855 per 1000	Very low Due to very serious risk of bias, due to serious imprecision[8]	We are uncertain whether roxadustat (any dose) increases or decreases treatment emergent adverse events from 108 to 209 weeks.
		Difference: 6 more per 1000 (CI 95% 22 fewer–29 more)			
Patients requiring blood transfusion 6–52 weeks	Odds ratio: 0.58 (CI 95% 0.42–0.82) Based on data from 821 participants in two studies	202 per 1000	128 per 1000	Very low Due to very serious risk of bias, due to serious imprecision[9]	We are uncertain whether roxadustat (any dose) decreases patients requiring blood transfusion from 6 to 52 weeks.
		Difference: 74 fewer per 1000 (CI 95% 106 fewer–30 fewer)			

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Table 32: (Continued)

Patients requiring blood transfusion from 58 to 108 weeks	Odds ratio: 0.87 (CI 95% 0.65–1.17) Based on data from 1869 participants in two studies	93 per 1000	82 per 1000	Very low Due to serious risk of bias, due to serious inconsistency, due to serious imprecision[10]	We are uncertain whether roxadustat (any dose) decreases patients requiring blood transfusion from 58 to 108 weeks.
		Difference: 11 fewer per 1000 (CI 95% 31 fewer–14 more)			
Change in hemoglobin levels from baseline from 6 to 52 weeks	Measured by: Scale: High better Based on data from 5553 participants in nine studies	Mean	Mean	Low Due to serious risk of bias, due to serious publication bias[11]	We are uncertain whether roxadustat (any dose) increases change in hemoglobin levels from baseline from 6 to 52 weeks.
		Difference: 0.21 lower (MD) (CI 95% 0.11 lower–0.32 higher)			
QoL assessed by EQ-5D-5L VAS	Measured by: Scale: High better Based on data from 783 participants in one study	Mean	Mean	Very low Due to very serious risk of bias, due to serious imprecision[12]	We are uncertain whether roxadustat (any dose) improves QoL assessed by EQ-5D-5L VAS.
		Difference: 1.42 higher (MD) (CI 95% 1.21 lower–4.04 higher)			
Fatigue measured by FACT—total score at 28 weeks	Measured by: Scale: High better Based on data from 783 participants in one study	Mean	Mean	Very low Due to very serious risk of bias, due to serious imprecision[13]	We are uncertain whether roxadustat (any dose) increases fatigue measured by FACT—total score at 28 weeks.
		Difference: 2.41 higher (MD) (CI 95% 1.68 lower–6.51 higher)			
Incidence of MACE up to 6 weeks	Based on data from 96 participants in one study	No incidence of MACE was reported in either Roxadustat or ESA (epoetin alpha/darbepoetin alpha) group		Very low Due to very serious risk of bias, due to serious indirectness, due to serious imprecision[13]	There were no participants who experienced MACE up to 6 weeks, so we were unable to determine whether roxadustat (any dose) made a difference.

Risk of Bias: serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: serious.** Wide confidence intervals, the 95% CI of the included study overlaps line of no effect (i.e., CI includes 1.0) rate; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, selective outcome reporting; **Imprecision: serious.** Wide confidence intervals, wide confidence intervals, the 95% CI of the included study overlaps line of no effect (i.e., CI includes 1.0) rate; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Inconsistency: serious.** The magnitude of statistical heterogeneity was high with I^2 55 %; **Imprecision: serious.** Wide confidence intervals, the 95% CI of the included study overlaps line of no effect (i.e., CI includes 1.0) rate; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Missing intention-to-treat analysis, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: very serious.** Wide confidence intervals, the 95% CI of the included study overlaps line of no effect (i.e., CI includes 1.0) rate, low number of patients; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, selective outcome reporting; **Inconsistency: serious.** The magnitude of statistical heterogeneity was high with I^2: 98%, the confidence interval of some of the studies do not overlap with those of most included studies/the point estimate of some of the included studies; **Imprecision: serious.** Wide confidence intervals, the 95% CI of the included study overlaps line of no effect (i.e., CI includes 1.0) rate; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, selective outcome reporting; **Imprecision: serious.** Wide confidence intervals, the 95% CI of the included study overlaps line of no effect (i.e., CI includes 1.0) rate; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Indirectness: serious.** The included study was from countries other than South Asia and was downgraded for lack of directness by one level; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, selective outcome reporting; **Imprecision: serious.** Wide confidence intervals, the 95% CI of the included study overlaps line of no effect (i.e., CI includes 1.0) rate, wide confidence intervals; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Missing intention-to-treat analysis, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: serious.** Due to less events (< 400) and inadequate optimal information size (OIS); **Publication bias: not serious.** Mostly

commercially funded studies. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Inconsistency: serious.** The magnitude of statistical heterogeneity was high with I^2:56 %; **Imprecision: serious.** Wide confidence intervals, the 95% CI of the included study overlaps line of no effect (i.e., CI includes 1.0) rate; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Publication bias: serious.** Mostly commercially funded studies, asymmetrical funnel plot. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, selective outcome reporting, missing intention-to-treat analysis; **Imprecision: serious.** Only data from one study, low number of patients, wide confidence intervals, the 95% CI of the included study overlaps line of no effect; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Missing intention-to-treat analysis; inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, selective outcome reporting; **Imprecision: serious.** Wide confidence intervals; low number of patients, only data from one study; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Missing intention-to-treat analysis, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, incomplete data and/or large loss to follow-up; **Indirectness: serious.** The included study was not from South Asian country and was downgraded for lack of directness by one level; **Imprecision: serious.** Low number of patients, only data from one study; **Publication bias: not serious.** Mostly commercially funded studies. DD: Dialysis-Dependent, CKD: Chronic kidney disease, ESA: Eythropoiesis-stimulating agents, MACE: Major adverse cardiovascular events, HIF PHI: Hypoxia-inducible factor prolyl hydroxylase inhibitor, FACT: Functional assessment of cancer therapy (measure of fatigue), CI: Confidence interval, MD: Mean difference

Table 33: Evidence to decision table for roxadustat as an alternative to ESA for DD-CKD patients

Benefits and harms	Important harms
Roxadustat improved QoL assessed by EQ-5D-5L VAS by a mean difference of 1.42, but evidence on this was uncertain. All GDG members (not including patients) are comfortable using HIF-PHIs in a scenario where there is evidence of better QoL for roxadustat as compared to ESAs. Roxadustat reduced the need for blood transfusion between 6 and 52 weeks by 74/1000. However, evidence on this was uncertain. All GDG members (not including patients) find such a cut-off acceptable for using HIF-PHIs. Similarly, roxadustat reduced the need for blood transfusion between 52 and 108 weeks by 11/1000. However, evidence on this was also uncertain. Only about 6% of GDG members (not including patients) find such a cut-off acceptable for using HIF-PHIs. In the group that received roxadustat, the need for iron supplementation from 6 to 52 weeks was decreased by 107/1000 as compared to the group that received ESAs. Evidence on this was uncertain. All GDG members (not including patients) would find such a scenario acceptable. Similarly, roxadustat decreased the need for iron supplementation by 103/1000 from 52 to 208 weeks compared to ESAs. However, evidence on this was uncertain. All GDG members (not including patients) find such a cut-off acceptable for using HIF-PHIs. Roxadustat increases hemoglobin levels from baseline from 6 to 52 weeks as compared to ESAs. However, evidence on this was uncertain. All GDG members (not including patients) find such a scenario acceptable to switch to HIF-PHIs. Roxadustat may have resulted in little or no difference on treatment adverse events at 108–209 weeks. About 41% of GDG members (not including patients) find such a scenario acceptable to switch to HIF-PHI. Roxadustat may have had little or no difference on need for ESA between 6 and 52 weeks with uncertain evidence. Roxadustat may have increased risk of treatment emergent adverse events at 6–52 weeks by 56/1000 compared to ESAs (low certainty). All of the GDG members (not including patients) find such a cut-off unacceptable for using HIF-PHIs. Uncertain evidence reports that roxadustat increased the risk of all-cause mortality at 6–52 weeks by 8/1000 compared to ESAs. Almost 86% of GDG members (not including patients) find such a cut-off unacceptable for using HIF-PHIs. Roxadustat increased the risk of all-cause mortality at 108–209 weeks by 18/1000 compared to ESAs. However, evidence on this was uncertain. All GDG members (not including patients) find such a cut-off unacceptable for using HIF-PHIs. Roxadustat increased need for ESA by 37/1000 up to 208 weeks compared to ESAs. However, evidence on this was uncertain. Roxadustat worsened fatigue measured by FACT score at 28 weeks compared to ESAs, but evidence on this was uncertain. There were no participants who experienced the incidence of MACE up to 6 weeks, so it was not possible to determine whether Roxadustat made a difference. Overall, the panel judged that the desirable anticipated effects and harm of roxadustat (compared to ESAs) were both comparable, noting there was a very low certainty in the evidence base.	
Certainty of the evidence	Very low [Table 32]
Values and preferences	Substantial variability is expected or uncertain
Empirical examinations of patients' values and preferences from South Asia are not available. This section is based on unstructured interactions with individual patients and caregivers and discussions with panel members. Subcutaneous ESA administration is challenging due to its invasive nature, its use has a learning curve, and there are logistic issues (refrigeration). Use of HIF-PHIs might have concerns around pill burden and adherence in some patients. However, some patients might prefer injections because of the need to limit fluid intake.	
Resources	No important issues with the recommended alternative

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Table 33: (Continued)

Roxadustat is currently not available in India, so it is not possible to compare the cost. Although Roxadustat does not need refrigeration and can be administered orally (unlike ESAs), this may not be of added benefit for DD patients, as they would already be undertaking regular hospital visits for dialysis. In this case, they can receive the intervention during hospital visits, which is unlikely to require extra resources from the patient.	
Equity	No important issues with the recommended alternative
Although roxadustat does not need refrigeration and can be administered orally (unlike ESAs), this is less likely to decrease equity for DD patients, as they would already have to have regular hospital visits for dialysis purposes. In this case, it would put minimal additional strain to have ESA administered.	
Acceptability	Important issues or potential issues not investigated
There are no qualitative studies on preference of South Asian patients with DD-CKD with respect to the acceptability of HIF-PHIs. Patients with hemodialysis might get ESAs intravenously, thus not requiring additional pricks through subcutaneous routes. However, there are concerns around polypharmacy on the use of HIF-PHIs.	
Feasibility	Intervention is likely difficult to implement
There are no formal studies on facilitators and barriers to use of HIF-PHIs in South Asia. The panel adjudged that roxadustat, although preferred because of its oral route of administration, is not licensed by national drug regulators in India or any other South Asian country. As such, it is currently not feasible.	

DD: Dialysis-Dependent, CKD: Chronic kidney disease, ESA: Eythropoiesis-stimulating agents, MACE: Major adverse cardiovascular events, GDG: Guideline development group, HIF PHI: Hypoxia-inducible factor prolyl hydroxylase inhibitor, FACT: Functional assessment of cancer therapy (measure of fatigue)

2.6 Vadadustat as an alternative to ESA

Table 34: Recommendations for vadadustat as an alternative to ESA in DD-CKD patients

Recommendation for use in research setting only	This recommendation is evidence informed.
Vadadustat should not be used for DD-CKD patients, except in the context of an approved randomized controlled trial. The panel recommends conducting large head-to-head multicentric randomized controlled trials in the South Asian region on DD-CKD patients and measuring critically important outcomes (as elucidated in this guideline) such that evidence base for vadadustat is improved.	

DD: Dialysis-Dependent, CKD: Chronic kidney disease, ESA: Eythropoiesis-stimulating agents

Table 35: Evidence profile for vadadustat as an alternative to ESA in DD-CKD patients

Population: Anemia in dialysis-dependent chronic kidney disease Intervention: Vadadustat Comparator: Darbepoetin alpha					
Outcome **Time frame**	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence**	**Plain language summary**
		Darbepoetin alpha	**Vadadustat**		
Need for iron supplementation					No studies were found that viewed the need for iron supplementation.
All-cause mortality up to 116 weeks	Odds ratio: 1.00 (CI 95% 0.83–1.21) Based on data from 3902 participants in one study	129 per 1000	129 per 1000	Very low Due to very serious risk of bias, due to serious imprecision[1]	We are uncertain whether vadadustat has little or no difference on all-cause mortality up to 116 weeks.
		Difference: 0 fewer per 1000 (CI 95% 20 fewer–23 more)			
All-cause mortality up to 52 weeks	Odds ratio: 2.00 (CI 95% 0.18–22.28) Based on data from 323 participants in one study	6 per 1000	11 per 1000	Very low Due to serious risk of bias, due to very serious imprecision, due to serious indirectness[2]	We are uncertain whether vadadustat increases all-cause mortality up to 52 weeks.
		Difference: 6 more per 1000 (CI 95% 5 fewer–113 more)			
Need for ESA in incident dialysis group up to 116 weeks	Odds ratio: 1.75 (CI 95% 0.83–3.71) Based on data from 265 participants in one study	93 per 1000	152 per 1000	Very low Due to very serious risk of bias, due to serious indirectness, due to very serious imprecision[3]	We are uncertain whether vadadustat increases the need for ESA in an incident dialysis group up to 116 weeks.
		Difference: 59 more per 1000 (CI 95% 15 fewer–183 more)			

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Table 35: (Continued)

Incidences of MACE up to 116 weeks	Odds ratio: 0.93 (CI 95% 0.79–1.10) Based on data from 3902 participants in one study	193 per 1000	181 per 1000	Very low Due to very serious risk of bias, due to serious imprecision[4]	We are uncertain whether vadadustat decreases incidences of MACE up to 116 weeks.
		Difference: 11 fewer per 1000 (CI 95% 34 fewer–15 more)			
Need for ESA in prevalent dialysis group up to 116 weeks	Odds ratio: 1.25 (CI 95% 1.03–1.51) Based on data from 2792 participants in one study	175 per 1000	209 per 1000	Low Due to very serious risk of bias[5]	Vadadustat may increase need for ESA in prevalent dialysis group up to 116 weeks.
		Difference: 35 more per 1000 (CI 95% 4 more–68 more)			
Any adverse event in incident dialysis group up to 116 weeks	Odds ratio: 0.88 (CI 95% 0.50–1.55) Based on data from 365 participants in one study	855 per 1000	838 per 1000	Very low Due to very serious risk of bias, due to very serious imprecision[6]	We are uncertain whether vadadustat decreases any adverse events in an incident dialysis group up to 116 weeks.
		Difference: 17 fewer per 1000 (CI 95% 108 fewer–46 more)			
Any adverse event in prevalent dialysis group up to 116 weeks	Odds ratio: 0.91 (CI 95% 0.74–1.12) Based on data from 3537 participants in one study	893 per 1000	883 per 1000	Very low Due to very serious risk of bias, due to serious imprecision[7]	We are uncertain whether vadadustat decreases any adverse event in prevalent dialysis group up to 116 weeks.
		Difference: 9 fewer per 1000 (CI 95% 32 fewer–10 more)			
Adverse event up to 52 weeks	Odds ratio: 0.37 (CI 95% 0.10–1.40) Based on data from 323 participants in one study	981 per 1000	950 per 1000	Very low Due to serious risk of bias, due to serious indirectness, due to serious imprecision[8]	We are uncertain whether vadadustat decreases any adverse event up to 52 weeks.
		Difference: 31 fewer per 1000 (CI 95% 143 fewer–5 more)			
Incidence of MACE plus up to 116 weeks	Odds ratio: 0.92 (CI 95% 0.79–1.07) Based on data from 3902 participants in one study	230 per 1000	215 per 1000	Very low Due to very serious risk of bias, due to serious imprecision[9]	We are uncertain whether vadadustat decreases incidence of MACE plus (expanded MACE) up to 116 weeks.
		Difference: 14 fewer per 1000 (CI 95% 39 fewer–12 more)			
Change in hemoglobin levels from baseline up to 52 weeks	Measured by: Scale: High better Based on data from 4243 participants in three studies	Mean	Mean	Low Due to very serious risk of bias[10]	Vadadustat may decrease hemoglobin levels from baseline up to 52 weeks.
		Difference: 0.15 lower (MD) (CI 95% 0.24 lower–0.07 lower)			
QoL					No studies were found that viewed QoL.
Fatigue					No studies were found that viewed fatigue.

Risk of Bias: very serious. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Imprecision: serious.** The 95% CI of the included study overlaps line of no effect (i.e., CI includes 1.0) rate, wide confidence intervals; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: serious.** Missing intention-to-treat analysis; **Indirectness: serious.** The included study was from non-South Asian countries and was downgraded for lack of directness by one level; **Imprecision: very serious.** Due to less events (< 400) and inadequate optimal information size (OIS), the 95% CI of the included study overlaps line of no effect, wide confidence intervals; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Missing intention-to-treat analysis; inadequate concealment of allocation during randomization process, resulting in potential for selection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Indirectness: serious.** The included study was from non-South Asian countries and was downgraded for lack of directness by one level; **Imprecision: very serious.** Due to less events (< 400) and inadequate optimal information size (OIS), the 95% CI of the included study overlaps line of no effect, wide confidence intervals; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Missing intention-to-treat analysis, inadequate concealment of allocation during randomization process, resulting in potential for selection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: serious.** Only data from one study, the 95% CI of the included study overlaps line of no effect (i.e., CI includes 1.0) rate; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, inadequate/lack

of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; missing intention-to-treat analysis; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; missing intention-to-treat analysis; **Imprecision: very serious.** Due to less events (< 400) and inadequate optimal information size (OIS), the 95% CI of the included study overlaps line of no effect (i.e., CI includes 1.0) rate, wide confidence intervals; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; missing intention-to-treat analysis; **Imprecision: serious.** The 95% CI of the included study overlaps line of no effect (i.e., CI includes 1.0) rate, wide confidence intervals; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: serious.** Missing intention-to-treat analysis; **Indirectness: serious.** The included study was from non-South Asian country and was downgraded for lack of directness by one level; **Imprecision: serious.** Due to less events (< 400) and inadequate optimal information size (OIS), wide confidence intervals, the 95% CI of the included study overlaps line of no effect (i.e. CI includes 1.0) rate; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Missing intention-to-treat analysis, inadequate concealment of allocation during randomization process, resulting in potential for selection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: serious.** The 95% CI of the included study overlaps line of no effect (i.e., CI includes 1.0) rate; **Publication bias: not serious.** Mostly commercially funded studies. **Risk of Bias: very serious.** Missing intention-to-treat analysis; inadequate concealment of allocation during randomization process, resulting in potential for selection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Publication bias: not serious.** Mostly commercially funded studies.
DD: Dialysis-Dependent, CKD: Chronic kidney disease, ESA: Eythropoiesis-stimulating agents, MACE: Major adverse cardiovascular events, QoL: Quality of life, GDG: Guideline development group, CI: Confidence interval

Table 36: Evidence to decision table for vadadustat as an alternative to ESA in DD-CKD patients

Benefits and harms	Small net benefit or little difference between alternatives
Vadadustat decreased incidences of MACE up to 116 weeks by 11/1000 as compared to darbepoetin alpha. However, evidence on this is uncertain. Almost 88% of GDG members (not including patients) find such a cut-off acceptable for using HIF-PHIs. Vadadustat decreases incidences of MACE plus up to 116 weeks by 14/1000 as compared to darbepoetin alpha. Almost 88% of GDG members (not including patients) find such a cut-off acceptable for using HIF-PHIs. However, evidence on this was uncertain. In the group that received vadadustat, there was 17/1000 less adverse events in incident dialysis group up to 116 weeks as compared to darbepoetin alpha. Evidence on this is uncertain. About 94% of GDG members (not including patients) would find such a scenario acceptable. In the group that received vadadustat, there was 9/1000 less adverse events in prevalent dialysis group up to 116 weeks as compared to darbepoetin alpha. Evidence on this is uncertain. Almost 41% of GDG members (not including patients) would find such a scenario acceptable. Vadadustat reduced adverse events up to 52 weeks by 31/1000 as compared to darbepoetin alpha. Evidence on this was uncertain. All GDG members (not including patients) would find such a scenario acceptable. Vadadustat lowered hemoglobin levels from baselines up to 52 weeks as compared to darbepoetin alpha. All GDG members (not including patients) find such a scenario acceptable to switch to HIF-PHI. There was no difference on all-cause mortality up to 116 weeks. Only 14% of GDG members (not including patients) find such a scenario acceptable to switch to HIF-PHIs. Vadadustat increases all-cause mortality up to 52 weeks by 6/1000. However, evidence on this is uncertain. About 86% of GDG members (not including patients) find such a cut-off unacceptable for using HIF-PHIs. It is uncertain if vadadustat increases the need for ESA in incident dialysis group up to 116 weeks by 59/1000 as compared to darbepoetin alpha. Similarly, it was uncertain if vadadustat increases the need for ESA in the prevalent dialysis group up to 116 weeks by 35/1000 as compared to Darbepoetin. None of the included studies examined the need for iron supplementation, QoL, and fatigue as an outcome. Overall, the panel judged that the desirable anticipated effects to be comparable and there were small harms, noting there was very low certainty on the evidence base for it. There is concern on the lack of evidence on the need for iron supplementation, QoL, and fatigue in DD-CKD patients with anemia.	
Certainty of the evidence	Very low [Table 35]
Values and preferences	Substantial variability is expected or uncertain
Empirical examinations of patients' values and preferences from South Asia are not available. This section is based on unstructured interactions with individual patients and caregivers and discussions with panel members. Subcutaneous ESA administration is challenging due to its invasive nature, its use has a learning curve, and there are logistic issues (refrigeration). Use of HIF-PHIs might have concerns around pill burden and adherence in some patients. However, some patients might prefer injections because of the need to limit fluid intake	
Resources	Important issues or potential issues not investigated

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Table 36: (Continued)

Vadadustat is currently not available in India, so it is not possible to compare the cost at this time. Although vadadustat does not need refrigeration and can be administered orally (unlike darbepoetin alpha), this may not be of added benefit for DD patients, as they would already be undertaking regular hospital visits for dialysis. In this case, they can receive the intervention during hospital visits, which is unlikely to require extra resources from the patient.	
Equity	No important issues with the recommended alternative
Although vadadustat does not need refrigeration and can be administered orally (unlike darbepoetin alpha), this is less likely to decrease equity for DD patients, as they would already have to make regular hospital visits for dialysis purposes. In this case, it would put minimal additional strain to have darbepoetin alpha administered.	
Acceptability	Important issues or potential issues not investigated
There are no qualitative studies on preference of South Asian patients with DD-CKD with respect to acceptability of HIF-PHIs. Patients with hemodialysis might get ESAs intravenously, thus not requiring additional pricks through subcutaneous routes. However, there are concerns around polypharmacy on the use of HIF-PHIs.	
Feasibility	Intervention is likely difficult to implement
There are no formal studies on facilitators and barriers to the use of HIF-PHIs in South Asia. The panel adjudged that vadadustat, although preferred because of its oral route of administration, is not licensed by the national drug regulators in India or any other South Asian country. As such, it is probably not feasible.	

DD: Dialysis-Dependent, CKD: Chronic kidney disease, ESA: Eythropoiesis-stimulating agents, MACE: Major adverse cardiovascular events, HIF PHI: Hypoxia-inducible factor prolyl hydroxylase inhibitor, QoL: Quality of life, GDG: Guideline development group

Updating procedure

As evidence on HIF-PHIs is currently evolving, the guidelines will be updated to reflect the current research. The panel will review the evidence after three years and update based on the appraisal of new evidence, as relevant.

Financial support and sponsorship

The George Institute for Global Health India received an unrestricted institutional grant from Zydus Lifesciences Ltd for the guideline development. Logistic support including funding for meetings, was provided by Zydus. The funder has no role in any part of the guideline development.

Conflicts of interest

The Conflicts of Interest (COIs) were managed in according with a COI policy which was adopted by the steering committee. The COI policy was adapted from a conflict of interest management policy[1] formulated by Meta-Research and Evidence Synthesis Unit at George Institute for Global Health, India.

K. Shah reports being commissioned for research through an organization and employment in an organization with potential financial interest—Nephrocare Health Services Pvt. Ltd.

M. Sahay has been on the advisory board of Astra Zeneca, Boehringer Ingelheim, and Novo Nordisk; has been support for attending meetings for the Indian Society of Nephrology, Southern Chapter, Indian Society of Organ Transplant and International Society of Nephrology; has received payment for lectures by Astra Zeneca, Boehringer Ingelheim, and Novo Nordisk; has received a grant for medical education and research in Telangana in two projects; was a national leader in Otsuka Visterra Study; and was a PHI coauthor for a 2016 study.

M. Tiwaskar has received payment for lectures (Astra Zeneca, Lupin, Boehringer Ingelheim, Cipla, Glenmark, Merck, Sun, Novo Nordisk, Torrent), payment for expert testimony (Astra Zeneca, Lupin, Boehringer Ingelheim, Cipla, Glenmark, Merck, Sun, Novo Nordisk, Torrent), and payment for participation on a Data Safety Monitoring Board, Advisory Board, or Guideline Panel (Novo Nordisk, Glenmark, Boehringer Ingelheim, Cipla).

N. Prasad reported being a member of the National Dialysis Program.

P. Verma reported unspecified honoraria for educational events.

S. Gang reported being commissioned for research for roxudastat.

S. Alexander reported being commissioned for research for roxudastat.

T. Jeloka was the principal investigator for Anemia Studies in Chronic Kidney Disease: Erythropoiesis via a Novel Prolyl Hydroxylase Inhibitor Daprodustat-Dialysis (ASCEND-D), ASCEND, DREAM, and DREAM D studies; has received payment for lectures by Astra Zeneca; received support to attend a Zydus meeting in Delhi; has received consultation fees from Zydus for transplant products promotion; has served on the Astra Zeneca Advisory Board and Guideline Panel; and had worked as panel with Astra Zeneca for an unpublished and disputed study on HIF-PHI.

[1] Kaur M, Tyagi J, Bhaumik S. Policy for managing conflict of interests during development of clinical practice guidelines: a template Version January 2022. Meta-research & Evidence Synthesis Unit, The George Institute for Global Health, India

U. Khanna has received funding from Astra Zeneca for roxadustat; has received support for attending meetings for Astra Zeneca, has stocks in Astra Zeneca; has received consultation fees; and has received payment for participation on a data safety, monitoring board, advisory board, or guideline panel for Astra Zeneca.
U. Anandh received payment for lectures on dapagliflozin from Astra Zeneca in 2020/2021.
V. Kher reported receiving grants from Novartis and Genzyme (Sanofi); received payment for lectures (Novartis, Roche, Astellas, Torrent, Reddy's, Intas, JB pharmaceuticals, Panacea, Sanofi Aventis, Biocon, Pfizer, Johnson and Johnson, Astra Zeneca); received support for attending meetings (Novartis, Astellas, Reddy's, Intas, Panacea); received consultation fees or payment for board participation (Torrent pharmaceuticals, Novartis, Roche, Panacea, Sanofi Aventis, Intas, Astellas, Reddy's, Biocon, JB, GSK, RPG Life Sciences, Astra Zeneca); has received writing assistance or other services (Cipla, JB, Astra Zeneca, Sanofi); and has had leadership roles in related organizations (Kidney Health Education and Research Society India, kidney education and research network, regional coordinator research at South Asia International Society of Nephrology, Advisory board member of the *Indian Journal of Nephrology* and *Indian Journal of Transplantation*).
V. Jha reported having provided scientific leadership on the Trial Steering Committee for Daprodustat and reports consulting fee/honoraria from Bayer, Astra Zeneca, Boehringer Ingelheim, Biocryst, Vera, Visterra, Otsuka, Novartis, Astra Zeneca, Chinook, Biocryst and Alpine under the policy of all payments going to the organization.
All other contributors report no conflicts of interest.

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