Appendix 5- Summary of Findings

Summary of Findings 1: Desidustat as alternative to Erythropoietin Stimulating Agents (ESAs) for management of anaemia in dialysis dependent chronic kidney disease

Population: Adult patients (>18 years) of CKD with a diagnosis of anaemia on dialysis
Intervention: Desidustat (any dose)
Comparator: Epoetin alfa

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of 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 1 study	**36** per 1000	**20** per 1000	**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.
		Difference: **16 fewer per 1000** (CI 95% 30 fewer - 32 more)			
Need for iron supplementation					No studies were found that looked at need for iron supplementation.
Need for Erythropoietin Stimulating Agent					No studies were found that looked at need for ESA.
Incidences of MACE and MACE plus					No studies were found that looked at 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 1 study	**464** per 1000	**478** per 1000	**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
		Difference: **15 more per 1000** (CI 95% 80 fewer - 114 more)			
Patients requiring blood transfusion					No studies were found that looked at patients requiring blood transfusion.
Change in haemoglobin levels from baseline up to 16-24 weeks	Measured by: Scale: High better Based on data from 373 participants in 1 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 change in haemoglobin levels
		Difference: **MD 0.07 lower** (CI 95% -0.23 lower - 0.37 lower)			

					from baseline up to 16-24 weeks
Fatigue					No studies were found that looked at fatigue.
Quality of life assessed by SF-36 up to 24 weeks	Measured by: Short Form Health Survey-36 (SF-36) Scale: - High better Based on data from 346 participants in 1 study	Mean	Mean	**Very low** Due to very serious risk of bias, Due to serious imprecision [4]	We are uncertain whether Desidustat worsens quality of life assessed by SF-36 up to 24 weeks
		Difference: **MD -49.73 higher** (CI 95% -144.53 higher - 45.07 lower)			

1. **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: no serious.** The study is commercially funded.
2. **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: no serious.** The study is commercially funded.
3. **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: no serious.** The study is commercially funded.
4. **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: no serious.** The study is commercially funded.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Summary of Findings 2: Daprodustat as alternative to Erythropoietin Stimulating Agents (ESAs) for management of anaemia in dialysis dependent chronic kidney disease

Population: Adult patients (>18 years) of CKD with a diagnosis of anaemia on dialysis
Intervention: Daprodustat (any dose)
Comparator: ESA [rhEPO/Darbepoetin alpha/Epoetin alpha]

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of 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 1 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 need for iron supplementation [oral] up to 52 weeks.
		Difference: **21 fewer per 1000** (CI 95% 120 fewer - 99 more)			
Need for Erythropoietin Stimulating Agent (ESA)					No studies were found that looked at need for Erythropoietin Stimulating Agent (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 5 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 3 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 2 studies	**376** per 1000	**317** per 1000	**Moderate** Due to serious imprecision [4]	Daprodustat (any dose) probably decreases 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 4 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)			
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 1 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 haemoglobin levels from baseline up to 52 weeks	Measured by: Scale: High better Based on data from 3950 participants in 4 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 change in haemoglobin levels from baseline up to 52 weeks.
		Difference: **MD 0.02 lower** (CI 95% -0.14 lower - 0.18 higher)			
Quality of life					No studies were found that looked at quality of life.
Fatigue					No studies were found that looked at fatigue.

1. **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: no serious.** Mostly commercially funded studies.
2. **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: no serious.** Mostly commercially funded studies.
3. **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: no serious.** Mostly commercially funded studies.
4. **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: no serious.** Mostly commercially funded studies.
5. **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: no serious.** Mostly commercially funded studies.
6. **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: no serious.** Mostly commercially funded studies.
7. **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.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Summary of Findings 3: Enarodustat as alternative to Erythropoietin Stimulating Agents (ESAs) for management of anaemia in dialysis dependent chronic kidney disease

Population: Adult patients (>18 years) of CKD with a diagnosis of anaemia on dialysis
Intervention: Enarodustat (any dose)
Comparator: Darbepoetin alpha

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		Darbepoetin Alpha	Enarodustat any dose		
Need for Erythropoietin Stimulating Agent (ESA)					No studies were found that looked at need for Erythropoietin Stimulating Agent (ESA).
Incidences of MACE up to 52 weeks					No studies were found that looked at 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 1 study	**384** per 1000	**466** per 1000	**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 need for iron supplementation [oral] up to 24 weeks.
		Difference: **82 more per 1000** (CI 95% 63 fewer - 231 more)			
Adverse events up to 26 weeks	Odds ratio: 1.34 (CI 95% 0.57 - 3.15) Based on data from 173 participants in 1 study	**837** per 1000	**873** per 1000	**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.
		Difference: **36 more per 1000** (CI 95% 92 fewer - 105 more)			
Patients requiring blood transfusion					No studies were found that looked at patients requiring blood transfusion.
Change in haemoglobin levels from baseline up to 24 weeks	Measured by: Scale: - High better Based on data from 172 participants in 1 study	Mean	Mean	**Low** Due to serious indirectness, Due to serious imprecision [3]	Enarodustat (any dose) lowered the haemoglobin levels from baseline up to 24 weeks.
		Difference: **MD -0.12 lower** (CI 95% -0.33 lower - 0.09 higher)			
Quality of life					No studies were found that looked at quality of life.

Fatigue					No studies were found that looked at fatigue.
All-cause mortality up to 26 weeks	Based on data from 173 participants in 1 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.

1. **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: no serious.** The study is commercially funded.
2. **Risk of Bias: no 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: no serious.** The study is commercially funded.;
3. **Risk of Bias: no 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: no serious.** The study is commercially funded.;
4. **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: no serious.** The study is commercially funded.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Summary of Findings 4: Molidustat as alternative to Erythropoietin Stimulating Agents (ESAs) for management of Anaemia in dialysis dependent chronic kidney disease

Population: Adult patients (>18 years) of CKD with a diagnosis of anaemia on dialysis
Intervention: Molidustat (any dose)
Comparator: ESA [Epoetin alpha/Epoetin beta/ Darbepoetin alpha]

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of 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 1 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 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 2 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 Erythropoietin Stimulating Agent (ESA) up to 52 weeks	Odds ratio: 8.15 (CI 95% 1.06 - 62.93) Based on data from 229 participants in 1 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 need for Erythropoietin Stimulating Agent (ESA) up to 52 weeks.
		Difference: **84 more per 1000** (CI 95% 1 more - 440 more)			
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 1 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 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 1 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 2 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 1 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
		Difference: **21 more per 1000**			

		(CI 95% 31 fewer - 195 more)			blood transfusion up to 20 weeks.
Change in haemoglobin levels from baseline up to 36 weeks	Measured by: Scale: High better Based on data from 379 participants in 2 studies	Mean	Mean	**Low** Due to serious risk of bias, Due to serious imprecision [8]	We are uncertain whether Molidustat (any dose) lowered the haemoglobin levels from baseline up to 36 weeks.
		Difference: **0.17 lower (MD)** (CI 95% -0.43 lower - 0.10 higher)			
Quality of life					No studies were found that looked at quality of life.
Fatigue					No studies were found that looked at fatigue.

1. **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: no serious.** Mostly commercially funded studies.
2. **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) .
3. **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: no serious.** Mostly commercially funded studies.
4. **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) .
5. **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: no serious.** Mostly commercially funded studies.
6. **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);
7. **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.** Low number of patients, only data from one study, wide confidence intervals; **Publication bias: no serious.** Mostly commercially funded studies.
8. **Risk of Bias: serious.** Missing intention-to-treat analysis; **Imprecision: serious.** Low number of patients, only data from one study; **Publication bias: no serious.** Mostly commercially funded studies.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Summary of Findings 5: Roxadustat as alternative to Erythropoietin Stimulating Agents (ESAs) for management of Anaemia in dialysis dependent chronic kidney disease

Population: Adult patients (>18 years) of CKD with a diagnosis of anaemia on dialysis
Intervention: Roxadustat (any dose)
Comparator: ESA [Epoetin alpha/Darbepoetin alpha]

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		ESA [Epoetin Alpha/Darbepoetin Alpha]	Roxadustat		
All-cause mortality up to 6-52 weeks	Odds ratio: 1.11 (CI 95% 0.76 - 1.62) Based on data from 1715 participants in 6 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 up to 6-52 weeks.
		Difference: **8 more per 1000** (CI 95% 18 fewer - 44 more)			
All-cause mortality up to 108-209 weeks	Odds ratio: 1.13 (CI 95% 0.96 - 1.33) Based on data from 3974 participants in 3 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 up to 108-209 weeks.
		Difference: **18 more per 1000** (CI 95% 6 fewer - 44 more)			
Need for iron supplementation up to 6-52 weeks	Odds ratio: 0.57 (CI 95% 0.16 - 2.05) Based on data from 1215 participants in 3 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 need for iron supplementation up to 6-52 weeks.
		Difference: **107 fewer per 1000** (CI 95% 413 fewer - 94 more)			
Need for Erythropoietin Stimulating Agent (ESA) up to 6-52 weeks	Odds ratio: 13.38 (CI 95% 0.75 - 238.31) Based on data from 916 participants in 2 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 Erythropoietin Stimulating Agent (ESA) up to 6-52 weeks
		Difference: **0 fewer per 1000** (CI 95% 0 - 0)			
Need for iron supplementation up to 52-208 weeks	Odds ratio: 0.56 (CI 95% 0.13 - 2.46) Based on data from 2940 participants in 2 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 up to 52-208 weeks.
		Difference: **103 fewer per 1000** (CI 95% 238 fewer - 211 more)			
Need for Erythropoietin Stimulating Agent (ESA) up to 208 weeks	Odds ratio: 20.29 (CI 95% 4.89 - 84.25)	**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 Erythropoietin
		Difference: **37 more per 1000** (CI 95% 8 more - 142 more)			

	Based on data from 2106 participants in 1 study				Stimulating Agent (ESA) up to 208 weeks.
Treatment emergent adverse events up to 6-52 weeks	Odds ratio: 1.45 (CI 95% 1.08 - 1.96) Based on data from 1715 participants in 6 studies	**786** per 1000	**841** per 1000	**Moderate** Due to serious risk of bias [7]	Roxadustat (any dose) may increase treatment emergent adverse events up to 6- 52 weeks.
		Difference: **56 more per 1000** (CI 95% 13 more - 92 more)			
Treatment emergent adverse events up to 108- 209 weeks	Odds ratio: 1.05 (CI 95% 0.85 - 1.28) Based on data from 2935 participants in 2 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 of decreases treatment emergent adverse events up to 108- 209 weeks.
		Difference: **6 more per 1000** (CI 95% 22 fewer - 29 more)			
Patients requiring blood transfusion 6 to 52 weeks	Odds ratio: 0.58 (CI 95% 0.42 - 0.82) Based on data from 821 participants in 2 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)			
Patients requiring blood transfusion 58 to 108 weeks	Odds ratio: 0.87 (CI 95% 0.65 - 1.17) Based on data from 1869 participants in 2 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 haemoglobin levels from baseline up to 6-52 weeks	Measured by: Scale: High better Based on data from 5553 participants in 9 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 haemoglobin levels from baseline up to 6-52 weeks.
		Difference: **0.21 lower (MD)** (CI 95% 0.11 lower - 0.32 higher)			
Quality of life assessed by EQ-5D-5L VAS	Measured by: Scale: High better Based on data from 783 participants in 1 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 quality of life 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 1 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
		Difference: **2.41 higher (MD)** (CI 95% -1.68 lower - 6.51 higher)			

				score at 28 weeks.
Incidence of MACE up to 6 weeks	Based on data from 96 participants in 1 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 [14]	There were no participants who experienced MACE up to 6 weeks, so we were unable to determine whether Roxadustat (any dose) made a difference.

1. **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: no serious.** Mostly commercially funded studies.
2. **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: no serious.** Mostly commercially funded studies;
3. **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: no serious.** Mostly commercially funded studies.
4. **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: no serious.** Mostly commercially funded studies.
5. **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: no serious.** Mostly commercially funded studies.
6. **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: no serious.** Mostly commercially funded studies.
7. **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: no serious.** Mostly commercially funded studies.
8. **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: no serious.** Mostly commercially funded studies.
9. **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: no serious.** Mostly commercially funded studies.
10. **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: no serious.** Mostly commercially funded studies.
11. **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.
12. **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: no serious.** Mostly commercially funded studies.
13. **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: no serious.** Mostly commercially funded studies.
14. **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: no serious.** Mostly commercially funded studies.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Summary of Findings 6: Vadadustat as alternative to Erythropoietin Stimulating Agents (ESAs) for management of Anaemia in dialysis dependent chronic kidney disease

Population: Adult patients (>18 years) of CKD with a diagnosis of anaemia on dialysis
Intervention: Vadadustat (any dose)
Comparator: Darbepoetin alpha

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		Darbepoetin Alpha	Vadadustat		
Need for iron supplementation					No studies were found that looked at 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 1 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 1 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 Erythropoietin Stimulating Agent (ESA) in incident dialysis	Odds ratio: 1.75 (CI 95% 0.83 - 3.71) Based on data from 265 participants in 1 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 need for Erythropoietin
		Difference: **59 more per 1000**			

group up to 116 weeks		(CI 95% 15 fewer - 183 more)			Stimulating Agent (ESA) in an incident dialysis group up to 116 weeks.
Incidences of MACE up to 116 weeks	Odds ratio: 0.93 (CI 95% 0.79 - 1.10) Based on data from 3902 participants in 1 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 Erythropoietin Stimulating Agent (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 1 study	**175** per 1000	**209** per 1000	**Low** Due to very serious risk of bias[5]	Vadadustat may increase need for Erythropoietin Stimulating Agent (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 1 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 1 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 1 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 1 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 3 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)			
Quality of life					

					No studies were found that looked at quality of life.
Fatigue					No studies were found that looked at fatigue.

1. **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: no serious.** Mostly commercially funded studies.
2. **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: no serious.** Mostly commercially funded studies.
3. **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: no serious.** Mostly commercially funded studies.
4. **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: no serious.** Mostly commercially funded studies.
5. **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: no serious.** Mostly commercially funded studies.
6. **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: no serious.** Mostly commercially funded studies.
7. **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: no serious.** Mostly commercially funded studies.
8. **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: no serious.** Mostly commercially funded studies.
9. **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: no serious.** Mostly commercially funded studies.
10. **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: no serious.** Mostly commercially funded studies.

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