NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Roxadustat for treating symptomatic anaemia in chronic kidney disease

1 Recommendations

1.1 Roxadustat is recommended as an option for treating symptomatic anaemia associated with chronic kidney disease (CKD) in adults only if:

- they have stage 3 to 5 CKD with no iron deficiency and
- they are not on dialysis at the start of treatment and
- the company provides roxadustat according to the commercial arrangement (see section 2.3).

1.2 This recommendation is not intended to affect treatment with roxadustat that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Treatment for symptomatic anaemia associated with chronic kidney disease includes erythropoiesis stimulating agents (ESAs). Roxadustat is an alternative to ESAs.

A clinical trial comparing roxadustat with darbepoetin alfa (an ESA) shows that roxadustat works as well as darbepoetin alfa.

The cost effectiveness estimates for roxadustat are within what NICE normally considers an acceptable use of NHS resources. So roxadustat is recommended.

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2 Information about roxadustat

Marketing authorisation indication

2.1 Roxadustat (Evrenzo, Astellas Pharma) 'is indicated for treatment of adult patients with symptomatic anaemia associated with chronic kidney disease (CKD)'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for roxadustat.

Price

2.3 The list prices of roxadustat are:

- £59.24 per 12-tablet pack, each tablet contains 20 mg of roxadustat (excluding VAT; BNF online, accessed December 2021)
- £148.11 per 12-tablet pack, each tablet contains 50 mg of roxadustat (excluding VAT; BNF online, accessed December 2021)
- £207.35 per 12-tablet pack, each tablet contains 70 mg of roxadustat (excluding VAT; BNF online, accessed December 2021)
- £296.21 per 12-tablet pack, each tablet contains 100 mg of roxadustat (excluding VAT; BNF online, accessed December 2021)
- £444.32 per 12-tablet pack, each tablet contains 150 mg of roxadustat (excluding VAT; BNF online, accessed December 2021).

The company has a commercial arrangement (simple discount patient access scheme). This makes roxadustat available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by Astellas Pharma, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Anaemia associated with chronic kidney disease is associated with extreme fatigue and reduced quality of life

3.1 Anaemia is a serious condition defined by abnormally low levels of haemoglobin (Hb) or too few red blood cells in the blood. This reduces the ability of blood to carry oxygen around the body. Erythropoietin, a hormone produced by the kidneys in response to low oxygen levels, stimulates the bone marrow to produce red blood cells. However, kidneys that are not working properly make less erythropoietin, so anaemia is common in people with chronic kidney disease (CKD). CKD is characterised by the progressive loss of kidney function and is generally categorised into 5 stages based on decreasing kidney function. The prevalence and severity of anaemia increase as kidney disease worsens (6% of people with stage 1 CKD have anaemia compared with 34% and 43% of people with stage 4 and 5 CKD, respectively). People with CKD already face substantial challenges that affect their quality of life. Symptoms of CKD include fatigue, itching, swelling and sleep problems. These can affect many aspects of normal life and people's capacity to stay in work. Also, people with CKD experience stress and difficulties coming to terms with the diagnosis of an incurable, progressive disease and making difficult decisions about treatment, including dialysis. Anaemia further affects their quality of life. The patient expert explained that the symptoms of untreated anaemia are severe and disabling. For example, some people cannot drive, work, or even walk because of the extreme fatigue associated with anaemia. As a result, this can affect mental health. The patient expert added that people going into dialysis need relief from

anaemia-associated fatigue to make decisions about their treatment and manage their life around dialysis. The committee concluded that anaemia can be associated with extreme fatigue and has a considerable effect on quality of life for people with CKD.

People with anaemia in CKD would welcome an oral alternative to injectable erythropoiesis stimulating agents

3.2 Anaemia is carefully monitored in people with CKD. NICE's guideline on chronic kidney disease: assessment and management recommends maintaining Hb between 100 g/litre and 120 g/litre for adults and avoiding Hb levels above 120 g/litre because of an increased risk of death and serious cardiovascular adverse events. Anaemia associated with CKD may be treated with iron therapy, erythropoiesis stimulating agents (ESAs), or both. NICE's guideline recommends that ESA treatment not be started without also managing iron deficiency. The clinical experts confirmed that people with anaemia must have sufficient iron levels (iron replete) before starting treatment with ESAs. Iron therapy can be given orally or intravenously depending on the severity of CKD, dialysis status or previous response to treatment. Treatment with ESAs is offered to adults, children and young people with anaemia who are likely to benefit in terms of quality of life and physical function. NICE's guideline on chronic kidney disease recommends a Hb level of 110 g/litre or lower for starting anaemia treatment. Clinical experts indicated that the level of haemoglobin at which it is appropriate to start treatment with ESAs is individualised, but they are likely to start treatment at Hb levels lower than 95 g/litre to 105 g/litre. The committee discussed whether ESAs were interchangeable and could be considered equally effective (a 'class effect'). The clinical experts explained that while some differences exist in the frequency of administration, the effectiveness of ESAs was similar. The committee concluded that ESAs could be considered as a class. Current ESAs are injectable analogues of erythropoietin that can be given subcutaneously, intravenously, or through the haemodialysis machine. For people who are not on haemodialysis, including those on peritoneal

dialysis, ESAs are typically self-administered. People have training to learn how to self-inject and to dispose of sharps. However, many people with anaemia find injecting themselves unpleasant and difficult, while some have to rely on others to give them their injections. Many people manage subcutaneous injections because of the high prevalence of people with diabetes on insulin among people with CKD and anaemia. In general, the patient and clinical experts noted that ESAs are well-established products that improve quality of life for people with anaemia. The patient expert highlighted that treatment-related adverse events are important to patients. They noted that people may be less likely to take medications that might have adverse effects that can affect quality of life. The committee concluded that people with anaemia would welcome an oral treatment if it is safe, particularly those who find it difficult to inject ESAs.

The company's positioning of roxadustat in the treatment pathway is appropriate

3.3 Roxadustat has a marketing authorisation for treating symptomatic anaemia associated with CKD in adults. The company positioned roxadustat as an alternative to ESAs for treating symptomatic anaemia associated with stage 3 to 5 CKD in people with no iron deficiency and who are not on dialysis at the start of treatment. It added that roxadustat would only be offered to people who are not on dialysis (including peritoneal dialysis), but people starting roxadustat would be able to continue treatment if they went on to dialysis. Also, switching from ESAs to roxadustat for people who are on dialysis and whose anaemia is stable on ESAs should only be considered if there is a valid clinical reason. This is because of cardiovascular disease safety concerns based on advice from the European Medicines Agency and the Medicines and Healthcare products Regulatory Agency (MHRA). Also, there is no clinical trial evidence of switching treatment from ESAs to roxadustat in people with anaemia associated with CKD who are not on dialysis. Clinical experts stated that they would start ESA treatment based on the presence of

anaemia symptoms if people had sufficient iron levels. They added that anaemia associated with stage 1 or 2 CKD is usually effectively treated with iron therapy alone, while ESAs are reserved for stage 3 to 5 CKD. They also confirmed that because intravenous iron and some ESAs are administered through the dialysis machine, the main benefit of roxadustat as an oral treatment would be for treating anaemia in people not on dialysis. The clinical experts explained the importance of avoiding blood transfusion because of the potential impact of developing antibodies that may affect the success of future kidney transplants. The committee was aware that some people cannot have treatment with ESAs because of chronic inflammation, cancer, adverse reactions, anaemia that does not respond adequately to ESAs or because they are not able to self-inject. However, the company had not presented any evidence for roxadustat in people whose anaemia cannot be treated with ESAs. The committee concluded that the position of roxadustat in the treatment pathway broadly represented where it would be used in clinical practice.

Clinical effectiveness

DOLOMITES is the only clinical trial that reflects the decision problem

3.4 The company identified 4 multicentre, randomised controlled trials of roxadustat in people with anaemia and stage 3 to 5 CKD who were not on dialysis at the start of treatment. Three trials (ALPS, ANDES, and OLYMPUS) compared roxadustat with placebo, while the fourth study (DOLOMITES) compared roxadustat with darbepoetin alfa, an ESA. The DOLOMITES study was a phase 3, open-label, non-inferiority trial in 28 countries including the UK. It included people with symptomatic anaemia and stage 3, 4 or 5 CKD who were not on dialysis and had Hb levels less than 105 g/litre at the start of treatment. Although lower than the 110 g/litre threshold recommended in NICE's guideline on chronic kidney disease for starting anaemia treatment, the committee recalled that this reflects UK practice (see section 3.2). The DOLOMITES trial excluded people who could not take ESAs, had cancer, had anaemia caused by

conditions other than CKD or who had chronic inflammatory conditions that could impact erythropoiesis (making red blood cells). It also excluded people who had ESAs, intravenous iron, or a red blood cell transfusion 12, 6 and 8 weeks before study randomisation, respectively. The primary end point was Hb response after 24 weeks of treatment, defined as:

- An Hb level of 110 g/litre or more and change from baseline Hb of 10 g/litre or more in people with Hb greater than 80 g/litre at baseline without rescue therapy.
- Change from baseline Hb of 20 g/litre or more in people with Hb of 80 g/litre or less at baseline without rescue therapy.

The DOLOMITES was designed as a non-inferiority trial, with no plan to test the primary end point for superiority. Secondary outcomes included change from baseline in Hb level, low-density lipoprotein cholesterol and mean arterial pressure, time to first hypertension event and intravenous iron infusion, and health-related quality-of-life measures such as the SF-36, EQ-5D-5L visual analogue scale (VAS) and the Functional Assessment of Cancer Therapy – Anemia (FACT-An) scale. With respect to baseline characteristics, 95% to 96% of people in the DOLOMITES trial were described as being white, compared with about 87% in clinical practice. The company confirmed that the roxadustat trials had different requirements for iron repletion. As a result, about half of the people in the DOLOMITES trial had sufficient iron levels compared with clinical practice, when iron repletion is needed to start treatment with ESA. The committee noted that both roxadustat and darbepoetin alfa arms included similar proportions of people who did not have sufficient iron levels. The company stated that oral iron was encouraged in the roxadustat arm of the DOLOMITES trial both for supporting erythropoiesis and as the first line treatment for iron deficiency. But in the darbepoetin alfa arm either oral or intravenous iron could be given for iron deficiency according to local practice. The company did not present any evidence for people who cannot take ESAs. The committee concluded that DOLOMITES is the only

trial that reflects the decision problem, and it is likely to be generalisable to NHS clinical practice.

Roxadustat is non-inferior compared with darbepoetin alfa

3.5 The company defined non-inferiority as the lower limit of the 2-sided 95% confidence interval (non-inferiority margin) being greater than -15% difference in the proportion of people whose anaemia responded to treatment between roxadustat and darbepoetin alfa. Results from the DOLOMITES trial showed that after 24 weeks, 256 people (90%) randomised to have roxadustat and 213 people (78%) randomised to have darbepoetin alfa achieved the primary end point. The difference was 12% (95% confidence interval 5.7% to 17.4%) and non-inferiority was met. All measures of quality of life (SF-36, EQ-5D-5L VAS and FACT-An) and all other secondary end points were non-inferior for roxadustat compared with darbepoetin alfa, while a decreased need for intravenous iron was superior. The trial presented no results on length of life. The committee agreed that roxadustat is non-inferior compared with darbepoetin alfa.

The company's revised approach using only DOLOMITES trial data is acceptable

3.6 To compare roxadustat with ESAs as a class, the company initially combined data from the roxadustat arms of the darbepoetin alfa-controlled DOLOMITES and all placebo-controlled trials to estimate clinical parameters for roxadustat. Data for darbepoetin alfa as proxy for the clinical effectiveness of all ESAs was based on the DOLOMITES trial alone. The company considered combining the roxadustat arms to be appropriate. However, it could not explain to the committee's satisfaction how it had done this. The ERG was concerned that the company's pooling approach removed the benefits of randomisation of the trials. Therefore, the results of the pooled analyses were likely to be biased. The committee agreed with the ERG that using combined roxadustat data did not outweigh the benefits of using the head-to-head trial data from the

DOLOMITES trial. It considered that the company's approach to combining roxadustat data was not appropriate. The committee appreciated the importance of using data, when available, in the absence of potentially less biased approaches. However, for decision making, the committee preferred analyses only using data from DOLOMITES. After consultation, the company updated its base case to use only DOLOMITES trial data to determine the clinical effectiveness of roxadustat and darbepoetin alfa. The ERG confirmed that the company applied the change correctly. The committee concluded that the company's revised approach using only DOLOMITES trial data was acceptable for decision making.

Cost effectiveness

The company's economic model broadly reflects anaemia and is acceptable for decision making

3.7 The company used a cohort health-state transition model to estimate the cost effectiveness of roxadustat compared with ESAs, with effectiveness measured in quality-adjusted life years (QALYs). The company assumed that roxadustat improves quality of life but does not make people live any longer compared with ESAs. The model included 8 health states based on Hb level categories (that is, below 70 g/litre, 70 to 79.9 g/litre, 80 to 89.9 g/litre, 90 to 99.9 g/litre, 100 to 109.9 g/litre, 110 to 119.9 g/litre, 120 to 129.9 g/litre and 130 g/litre and above) and a death health state. The company stated that it chose the 8 Hb categories from 2 published studies: a microsimulation cost-effectiveness model of Hb level targets for treating anaemia in the US (Yarnoff et al. 2016) and an observational study assessing the relationship between Hb level and health-related quality of life (Finklestein et al. 2009). The company initially based the probability of being in each health state on the pooled roxadustat trials data. But, it changed to DOLOMITES trial only data after the first committee meeting. Hb levels determined treatment dose, the proportion of people having iron therapy, iron therapy dose and the frequency of red

blood cell transfusions. It modelled the impact of dialysis on survival and health-related quality of life implicitly. It did the same for the impact of treatment-related adverse events on survival and health-related quality of life. The company acknowledged that it did not include renal transplant. It stated that it modelled adverse events based on anaemia treatment and not for each health state because of insufficient data. The model included a 25-year time horizon, which the company considered to cover lifetime length. The ERG was concerned that the company had not fully justified the Hb categories used to define health states. For instance, Yarnoff et al. took the Hb categories directly from another study of transfusion burden in anaemia in the US (Lawler et al. 2010) without further justification. Finkelstein et al. showed that the impact of Hb increases only for levels below 110 g/litre, 110 to below 120 g/litre, 120 to below 130 g/litre and 130 g/litre and above. It was unclear to the ERG why and how each health state would differ in terms of health-related quality of life, costs, and survival. For example, the model by Yarnoff et al. models quality-of-life impact through Hb levels, but this modelling does not confirm that a change of 10 g/litre in Hb has a meaningful effect on quality of life. The patient expert highlighted that people with anaemia are not aware of changes in Hb levels. They further explained that people notice improvements in quality of life, such as feeling less tired, when their Hb levels increased above 90 g/litre. At the second committee meeting, 1 clinical expert advised that increases of 10 g/litre in Hb do not show noticeable differences in quality of life. The ERG noted that during the company's own model validation, experts indicated that a model with health states based on Hb levels below, within and above the NICE guideline target range might reflect the condition. The target Hb range in the NICE guideline is 100 g/litre to 120 g/L (see section 3.2). One of the clinical experts attending the first committee meeting agreed. The committee, at its first meeting, concluded that having 8 health states overcomplicates the model and there is not enough data for each health state to identify differences between them. The company did not revise its

model to include fewer health states after the first committee meeting. So it was unclear to the committee whether reducing the number of health states would have an impact on the cost-effectiveness estimates. The committee concluded that the company's economic model broadly reflects anaemia being based on Hb, but including 8 health states may overcomplicate the model.

Transition probabilities between health states are uncertain

3.8 In its model, the company distributed people across Hb health states over the lifetime time horizon. The company initially based the probability of being in each health state for the first cycle of the model on the pooled roxadustat trials. Because each cycle in the model is 3 months, the company used the data from the first 12 weeks of the pooled roxadustat trials to distribute people across the Hb health states in the first cycle. The company used a multinomial logistic regression model to distribute people after the first cycle. The regression model included several covariates such as treatment type (placebo, ESA or roxadustat), time (log[time+1]), history of cardiovascular disease at baseline, history of type 2 diabetes at baseline, unique study identifier (ALPS, ANDES, OLYMPUS, and DOLOMITES), and an interaction between treatment type and time. The committee questioned why the company had chosen to include an interaction between treatment type and time. It noted that the company had not presented it with results from a model excluding this interaction. After consultation, the company revised its modelling approach to use only DOLOMITES trial data to inform the distribution of people across health states over the lifetime horizon. Also, it stated that all available DOLOMITES trial data was included in the regression model for long-term extrapolation, including data from people who had up to 104 weeks of roxadustat treatment. The ERG was concerned that the company had not provided enough details of the methodology behind the regression model based on DOLOMITES only trial data. This included the statistical analysis plan for the regression model, diagnostic plots or how the additional long-term DOLOMITES data was incorporated. The committee

noted that the long-term extrapolations were uncertain and considered that the effects seen in the DOLOMITES trial might not last indefinitely over the 25-year time horizon. So, at the second committee meeting, the committee preferred the scenario analysis when roxadustat and ESA have equal efficacy in month 25 of the model (that is, immediately after the end of the DOLOMITES trial). The committee concluded that the transition probabilities between health states estimated by the company remained uncertain because of the insufficient information on the regression model.

Utility values

The company's revised base case using a multiplicative approach to estimate health-state utilities is acceptable

3.9 The company estimated health-state utilities using general population utility values adjusted for age and sex and subtracting disutility for CKD, type of dialysis (haemodialysis and peritoneal dialysis), Hb level, and treatment-related adverse events. It sourced the general population utilities and disutilities for CKD, type of dialysis and adverse events from literature or NICE's technology appraisal guidance on tolvaptan for autosomal dominant polycystic kidney disease (TA358). Acting on the committee's preference to use a single source of data, for the Hb level utility reductions, the company obtained the utility values from the DOLOMITES trial data. This used the EQ-5D-5L instrument cross-walked to EQ-5D-3L levels values. It then used a generalised linear mixed model to estimate utility values for each Hb level controlling for history of cardiovascular disease and presence or absence of type 2 diabetes at baseline. The company initially assumed that the utility reductions are additive based on previous studies that also used this approach (for example, Yarnoff et al. 2010 and Glenngard et al. 2018). However, the ERG highlighted that the company did not explore any alternative approaches to health-state utility estimation such as multiplicative, or minimum or maximum values. The literature suggests that a multiplicative approach might be preferable when multiple factors can affect overall

utility. The committee noted that with high disutility values, using an additive approach would lead to implausibly low health-state utility values in some cases. It stated that it would prefer health-state utilities estimated using a multiplicative approach. After consultation the company updated its base case to include a multiplicative approach to estimate health-state utilities. The ERG confirmed that the company applied the change correctly. The committee concluded that the company's revised approach was acceptable for decision making.

The company's approach to modelling harms and costs of Hb level over 120 g/litre is uncertain, but the impact on cost effectiveness is likely to be low

3.10 The company used utility reductions for CKD, dialysis and adverse events from published sources and estimated utility reductions for each Hb level based on roxadustat trial data (see section 3.9). The committee noted that the sources for disutilities for CKD, type of dialysis and adverse events dated as far back as 1999. It was unclear whether these values reflect current values or whether they were generalisable to CKD because they were taken from TA358 on polycystic kidney disease (see section 3.9). The committee also considered that the utility reductions applied by the company were high (for example, a utility reduction of 0.35 for a mild stroke, which is the same as the utility reduction applied for people who were on haemodialysis). The patient expert added that it is unlikely for dialysis to reduce utility to that extent. This is because people are aware that dialysis is a treatment approach that extends life compared with an adverse event such as stroke, which is irreversible and disabling and can potentially make people ineligible for kidney transplant. At the first meeting, the committee recalled regulatory advice to avoid sustained Hb levels greater than 120 g/litre, because of an increased risk of cardiovascular disease. It noted that the company did not reflect this in its modelling. The committee was particularly concerned that the company included lower roxadustat doses and costs, reduced iron and blood

transfusion use, and not included disutility and costs for Hb levels over 120 g/litre in the model. It considered that this modelling would overestimate the cost effectiveness of treatment with roxadustat. The committee concluded that the utility reductions for type of dialysis and Hb level do not reflect patient and clinical experience. After consultation, the company included a scenario analysis exploring the impact of capturing harms and costs for higher Hb levels. It did so by including Hb-specific event probabilities for stroke, heart attack and vascular access thrombosis. The company sourced the probability of stroke caused by Hb levels from published literature, but used the same value for heart attack and vascular access thrombosis in the absence of published data for these events. The ERG and the committee were unclear whether the harms and costs of these events were applied to Hb levels over 120 g/litre or 130 g/litre. The committee considered it good practice to apply the harms and costs to Hb levels over 120 g/litre. It indicated that it preferred this assumption be included in the base case, rather than as a scenario analysis. Also, it highlighted that the company had not adequately captured the consequences of Hb levels over 120 g/litre because it did not include all relevant harms and costs. Also, the committee recalled there were few disincentives in the model for Hb going above the target range. It concluded that the company's approach to modelling harms and costs of Hb levels over 120 g/litre was uncertain, but it considered that the impact on cost effectiveness was likely to be low.

Costs in the economic model

Costs of hospitalisations should be based on hospitalisation rates measured directly from the DOLOMITES trial

3.11 The company modelled frequency of hospitalisations indirectly based on adverse events seen in the roxadustat trials, rather than directly based on frequency of hospitalisations. It did so to avoid double counting the costs and quality-of-life effects associated with hospitalisations and adverse events. Also, the company indicated that there was not enough data to

model hospitalisations based on Hb level and that roxadustat was not expected to affect hospitalisation rates. This is despite the company showing different rates of hospitalisations between roxadustat (58%) and darbepoetin alfa (52%) in the DOLOMITES trial. The ERG highlighted that the company's approach was not in line with NICE's guide to the methods of technology appraisal, which states that indirect (surrogate) outcomes should be used only when direct outcomes are not available. It added that the company should explore both expected and unexpected effects associated with roxadustat. The committee recognised that it is possible for the company to model hospitalisations directly and avoid double counting, because the company knows which hospitalisations were because of adverse events. The committee understood that hospitalisations from causes other than adverse events made up about a third of all hospitalisations and emphasised the need to measure hospitalisations directly. After consultation, the company provided additional justification for modelling hospitalisations indirectly based on adverse events. It calculated and presented the incident rate ratios for hospitalisations from adverse events and other causes, which showed that there were no significant differences in hospitalisations between roxadustat and ESA. The committee accepted that there were no significant differences in hospitalisations between roxadustat and ESA and considered that their inclusion was likely to have a small impact on cost effectiveness. However, it preferred that the company's approach had been in line with NICE guidance. The committee concluded that the costs of hospitalisations should be based on hospitalisation rates measured directly from the DOLOMITES trial.

The company's revised base case should include additional adverse events

3.12 The company chose major adverse cardiovascular events as the only adverse events in its economic model. It included stroke, heart attack and vascular access thrombosis. It considered these more important than other adverse events because they can lead to death and reduce health-

related quality of life, have a high prevalence in people with CKD, and contribute to high healthcare resource use. The company indicated that its own 3 experts agreed with its choice of adverse events. It considered other adverse events to have no impact on model outcomes because they had a low incidence or similar rates between the roxadustat and darbepoetin alfa arms. However, the ERG noted that some adverse events differed in incidence by 2% to 4% between roxadustat and darbepoetin alfa:

- peripheral oedema (15% compared with 12%)
- hyperkalaemia (12% compared with 14%)
- nausea (11% compared with 9%)
- hyperphosphatemia (9% compared with 5%)
- muscle spasms (8% compared with 5%)
- dyspnoea (7% compared with 4%)
- headache (7% compared with 4%)
- insomnia (6% compared with 3%).

The patient expert indicated that specific adverse events such as insomnia, headache and nausea are important for patients because they can affect quality of life and whether people will take roxadustat as intended. At the first committee meeting, the company presented exploratory analyses including additional adverse events that occurred in more than 3% of the DOLOMITES population and were of grade 3 or higher severity. These included cardiac failure, pneumonia, and hypertension. It considered that these adverse events had a minor impact on the cost effectiveness of roxadustat. Despite this, the committee considered that the company model should have included a wider range of adverse events, particularly those that are important to patients and could impact quality of life. After consultation, the company provided additional justification to exclude adverse events from modelling. It showed that the rates of adverse events that were of grade 3 or higher severity in DOLOMITES were similar between roxadustat and darbepoetin

alfa. However, the committee recalled that certain adverse events such as nausea and headache affect quality of life even at grade 2 severity. The patient expert reiterated that adverse events are important because they can affect adherence to treatment. They added that if patients stop taking their anaemia medication because of adverse events then this would reduce their Hb levels and in turn affect their quality of life. The committee understood that rates of adverse events of grade 2 or higher severity were similar between roxadustat and darbepoetin alfa. So it considered that their exclusion from the modelling was likely to have a small impact on cost effectiveness. However, it considered it good practice to explore the impact of all relevant adverse events and concluded that the company's revised base case should have included additional adverse events.

The estimated costs of roxadustat in the company's revised approach are appropriate

3.13 The company estimated costs of roxadustat based on body weight, Hb levels, and 2 separate treatment phases (correction and maintenance) to account for dose changes made in clinical practice. Starting doses are based on weight, and dose changes are based on response to treatment and changes in Hb levels. The correction phase lasted up to 3 months from starting treatment and corresponded with the first cycle of the model. The maintenance phase started immediately after the correction phase. The company initially estimated the average roxadustat dosage for each Hb level in the correction phase based on data including body weight from people in all roxadustat trials. However, after consultation, the company estimated roxadustat dosages for the correction phase only from the DOLOMITES trial data. For the maintenance phase, it extrapolated the average weekly dose using a generalised linear mixed model and controlled for history of cardiovascular disease and presence of type 2 diabetes at baseline. The company confirmed at the first committee meeting that it had not assumed treatment stops in the economic model, despite the DOLOMITES trial having a stopping rule for roxadustat for Hb levels above 130 g/litre. Clinical experts indicated that the decision

whether to stop treatment depends on how well anaemia is managed. They stated that they would titrate the dose of roxadustat down if Hb levels reached around 125 g/litre so that Hb levels stay within a safe range (that is, between 100 g/litre and 120 g/litre) rather than stopping treatment (see section 3.8). After consultation, the company revised its base case to include a stopping rule for roxadustat at Hb levels over 130 g/litre. It applied the stopping rule only to roxadustat treatment costs in this health state, because Hb levels over 130 g/litre are not associated with a utility benefit in the model. However, the ERG was concerned that this adjustment implicitly assumed that the stopping rule affects only roxadustat costs and not its clinical effectiveness or other model parameters. The committee found the application of the stopping rule uncertain because roxadustat would not be completely stopped in clinical practice. Instead the dosage would be adjusted or temporarily withheld until Hb levels reach the target range according to the instructions in the summary of product characteristics for roxadustat and clinical expert feedback. However, the committee concluded that the estimated costs of roxadustat in the company's revised approach are appropriate because they are based only on the DOLOMITES trial data.

The overall costs of ESAs are uncertain, but the company's revised approach is appropriate

3.14 The prices of ESAs reflect confidential arrangements between companies and the NHS. The company estimated costs of ESAs using the same approach as for the costs of roxadustat (see section 3.13). It used only data from the DOLOMITES trial to determine the average weekly doses for the correction and maintenance phases. In line with clinical guidance and practice, the company assumed a class effect (see section 3.2) and included all 5 ESAs available in the UK in the model. To determine equivalent doses between ESAs, the company used darbepoetin alfa as a reference and applied a 'dose conversion' factor for each ESA based on their weekly dose from the BNF. The company took the list price of the different types of ESA from the BNF. It estimated the proportions of

people with anaemia having each ESA from TUNE, an unpublished observational retrospective study of medical records in the UK population. However, the company acknowledged that there is uncertainty around the distribution of ESAs in clinical practice because there are no clear or reliable sources to inform this parameter. Clinical experts pointed out that some hospitals or NHS trusts purchase and prescribe only 1 type of ESA, rather than a basket of different types of ESAs as used in the company model. The company included drug administration costs for 20% of people who have ESAs. One clinical expert confirmed that people do incur costs associated with ESA administration and that the proportion of people estimated by the company is reasonable. After consultation, the company revised its modelling approach to include administration costs for people on peritoneal dialysis. However, it did not include a stopping rule for ESAs when Hb levels exceed those recommended by the regulators (120 g/litre; MHRA recombinant human erythropoietins: new advice for prescribing). The company indicated that it considered the ESA dosing data from DOLOMITES to reflect clinical practice and any stopping rules. This is because the dosing of darbepoetin alfa was based on its summary of product characteristics, which already includes dose adjustments and temporary stops if Hb levels exceed 120 g/litre. The committee agreed that the stopping rule for ESAs was already accounted for in the dosage data from DOLOMITES. It concluded that the company's revised approach was acceptable for decision making, but the overall costs of ESAs are uncertain.

Cost-effectiveness estimates

The company did not address all of committee's preferred assumptions, but the likely impact on cost effectiveness is small

3.15 The committee discussed the company's base case, revised after consultation. It noted how the company attempted to address its preferences from its first meeting, namely:

- Using only DOLOMITES trial data for clinical effectiveness estimates for roxadustat and ESAs (see section 3.6).
- Clarifying that health-state transition probabilities are based on 36-week data from DOLOMITES and also include some 104-week follow-up data (see section 3.8).
- Health-state utilities estimated using a multiplicative approach (see section 3.9).
- Health states that reflect the harms and costs of having Hb levels over 120 g/litre (see section 3.10).
- ESA administration costs for people who start having peritoneal dialysis.
- Roxadustat costs that reflect the DOLOMITES trial (see section 3.13).
- A model that reflects the stopping rule in DOLOMITES and other regulatory recommendations for safety (see section 3.8 and section 3.13).

The ERG acknowledged that the company's revised base case incorporates its and the committee's preferred assumptions. So it considered its preferred base case the same as the company's revised base case. The ERG's analysis also included the confidential NHS Commercial Medicines Unit price for each ESA. However, the ERG highlighted that the company's revised base case excluded some committee preferred assumptions such as:

- Providing full justification for using 8 health states or using fewer health states (see section 3.7).
- Justifying and providing full details of the regression model used to extrapolate beyond the trial period (see section 3.8).
- Including hospitalisation costs based on hospitalisation rates measured directly from the DOLOMITES trial (see section 3.11).
- Including additional adverse events that impact adherence to treatment and health-related quality of life (see section 3.12).

The committee did not agree with the updated preferences for the harms and costs of Hb levels over 120 g/litre in the company's revised base case (see section 3.10). It also considered that the exclusion of its preferred assumptions highlighted by the ERG increased the uncertainty of the cost-effectiveness estimate. However, it noted that the impact of including the harms and costs of Hb levels over 120 g/litre and its remaining preferred assumptions in the revised base case was likely to be small. The committee was willing to accept this uncertainty specifically for this appraisal. But, it considered it good practice to adequately capture the harms and costs of Hb levels over 120 g/litre, and to include or explore all its preferred assumptions in the base case for future hypoxia-inducible factor inhibitors similar to roxadustat. The committee concluded that the company had not addressed all its preferred assumptions adequately but considered the likely impact on cost effectiveness to be small.

The ICERs for roxadustat are within what NICE considers an acceptable use of NHS resources

3.16 Applying confidential discounts for ESAs, and considering its preferences, the committee noted that the ERG's and company's incremental cost-effectiveness estimates (ICERs) were within what NICE considers an acceptable use of NHS resources. Because of the confidential discounts for ESAs, the ICERs or incremental costs cannot be reported here. The committee was satisfied that roxadustat is similarly effective to ESA and that overall, the costs are similar.

Innovation

Roxadustat has a novel mechanism of action, but has not shown superiority to ESAs, and all benefits are captured in the modelling

3.17 The committee noted that roxadustat is a first-in-class oral hypoxia-inducible factor prolyl hydroxylase inhibitor, which provides an additional treatment for anaemia associated with CKD. However, it was aware that roxadustat was shown only to be non-inferior to current treatment. The

patient expert indicated that roxadustat's oral administration is a step-change compared with injectable ESAs, even though this might affect whether people will take roxadustat as intended. Having an oral alternative might reduce costs associated with ESA administration and reduce the need for cold-chain storage and special sharps disposals. Roxadustat might also simplify management of anaemia by reducing the need for iron transfusions. The committee recalled that the company already included fewer iron infusions and costs of ESA administration costs in its economic model (see section 3.13). So, the committee concluded that roxadustat did not meet NICE's criteria to be considered an innovative treatment.

Conclusion

Roxadustat is recommended as an option for treating symptomatic anaemia associated with chronic kidney disease

3.18 The committee was satisfied that roxadustat is similarly effective to ESAs and that overall, the costs are similar. So, it was able to recommend roxadustat as an option for treating symptomatic anaemia associated with chronic kidney disease.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources

for it within 2 months of the first publication of the final appraisal document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has symptomatic anaemia associated with chronic kidney disease and the doctor responsible for their care thinks that roxadustat is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Review of guidance

5.1 The guidance on this technology will be considered for review 3 years after publication. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Charles Crawley
Chair, appraisal committee
March 2022

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

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NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

George Braileanu
Technical lead

Rufaro Kausi
Technical adviser

Thomas Feist
Project manager

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