NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Roxadustat for treating anaemia in chronic kidney disease

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using roxadustat in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: January 2022

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using roxadustat in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 16 February 2022

Second appraisal committee meeting: to be confirmed

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 Roxadustat is not recommended, within its marketing authorisation, for treating symptomatic anaemia associated with chronic kidney disease in adults.

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. However, the clinical-effectiveness estimates for roxadustat combined results from this trial and trials comparing roxadustat with placebo. This way of estimating the clinical effectiveness of roxadustat compared with ESAs is inappropriate and means the cost-effectiveness estimates are uncertain. These estimates are also likely to be higher than what NICE normally considers acceptable. So, roxadustat is not recommended.

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.

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, which would have applied if the technology had been recommended.

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 and 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, when the body's iron stores are full) 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 ESA 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 of 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 injection 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 and 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 ESA 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 the proposed positioning for roxadustat does not include people on dialysis (including peritoneal dialysis). This is because of cardiovascular disease safety concerns based on advice from the European Medicines Agency and Medicines and Healthcare products Regulatory Agency (MHRA). Also, there is no clinical trial evidence of switching treatment from ESA 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

theSF-36, EQ-5D-5L visual analogue scale 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. However, the company stated that oral iron was encouraged in the roxadustat arm of the DOLOMITES trial, but not in the darbepoetin alfa arm. The committee reasoned that reduced oral iron use is likely to underestimate the absolute effectiveness of darbepoetin alfa because erythropoiesis needs adequate iron stores. 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 proportions of responders between roxadustat and darbepoetin alfa. Results from the DOLOMITES trial showed that after 24 weeks, 256 (90%) of people randomised to have roxadustat and 213 (78%) of people 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 did not combine data from all roxadustat trials appropriately

3.6 To compare roxadustat with ESAs as a class, the company 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 because it considered that the baseline characteristics, dose, dosing schedule and delivery of roxadustat were similar across trials). In addition, it stated that the statistical models it used accounted for differences in baseline characteristics that could affect outcomes (for example, age, sex, cardiovascular disease, type 2 diabetes and estimated glomerular filtration rate), while unique study identifiers (ALPS, ANDES, OLYMPUS, and DOLOMITES) for each trial controlled for nesting effects. However, the company could not clarify 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. This was because people were no longer drawn randomly from the same population, and effect modifiers and prognostic factors may not be balanced between the roxadustat and darbepoetin alfa arms. The ERG also highlighted that there may be effect modifiers and prognostic factors that were not measured (or known), for which the company could not account. 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 noted that it may have been more appropriate to combine data to provide a baseline for roxadustat efficacy compared with placebo and to obtain and apply the relative effects from the DOLOMITES study to estimate the efficacy of darbepoetin alfa. The committee also discussed generating a network meta-analysis using the roxadustat trials and trial that compared ESAs with placebo. It concluded

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 using data only from the DOLOMITES trial.

Cost effectiveness

The company's economic model includes more health states than necessary

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 based the probability of being in each health state on the pooled roxadustat trials data. 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 had 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. The ERG noted that the during the company's own model validation, experts indicated that a model with health states based on Hb levels below the NICE guideline target range, within the target range (100 to 120 g/L; see section 3.2) and above the target range might reflect the condition. One of the clinical experts attending the committee meeting agreed. The committee 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 committee concluded that the company's economic model broadly reflects anaemia being based on Hb, but likely includes more health states than necessary.

Transition probabilities between health states are uncertain and do not reflect the DOLOMITES trial data

3.8 In its model, the company distributed people across Hb health states over the lifetime time horizon. The company 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 and noted that the company had not presented it with results from a model that did not include this interaction. The ERG was concerned that the distribution of people in the first cycle and the multinomial regression model were based on the inappropriately pooled roxadustat trials data (see section 3.5). Also, the committee considered it highly speculative that the effects seen during the roxadustat clinical trials would last indefinitely over the 25-year time horizon. The committee considered it inappropriate to extrapolate undiminished benefits for roxadustat over 25 years based only on 12 weeks of data, rather than for the entire length of the DOLOMITES trial (36 weeks). Using the entire length of DOLOMITES would also be associated with uncertainty over such a long period of extrapolation. The committee wanted to see scenarios that altered this assumption. Also, the committee noted that the model (from which the company concluded that roxadustat was superior to ESAs) was inconsistent with the 36 weeks of data from the DOLOMITES trial that showed non-inferiority of roxadustat compared with darbepoetin alfa. The company did not model a stopping rule for roxadustat (or ESAs) when haemoglobin levels exceed those recommended by the regulators for ESAs (120 g/litre; MHRA recombinant human erythropoietins: new advice for prescribing) or if Hb levels are above 130 g/litre for roxadustat as stated in the DOLOMITES trial protocol. One clinical expert indicated that they would titrate the dose of roxadustat down if Hb level reached around 125 g/litre in clinical practice. The committee concluded that the transition probabilities between health

states estimated by the company are uncertain because they do not reflect the DOLOMITES trial data.

Utility values

The committee prefer health-state utilities estimated using a multiplicative approach

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). For the Hb level utility reductions, the company obtained the utility values from the pooled roxadustat trials data, which 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 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 concluded that it would prefer health-state utilities estimated using a multiplicative approach.

Utility reductions for type of dialysis and Hb level are uncertain and do not reflect patient and clinical experience

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 the utility reductions applied by the company to be 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 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. The committee was aware of regulatory advice to avoid sustained Hb levels greater than 120 g/litre, because of an increased risk of cardiovascular disease and noted that the company did not reflect this in its modelling. It was particularly concerned that company included lower roxadustat doses and costs, reduced iron and blood transfusion use, and no disutility for Hb levels over 120 g/L in the model. It considered that this modelling would overestimate the cost effectiveness of a treatment which would increase Hb levels over 120 g/L. The committee concluded that utility reductions for type of dialysis and Hb level do not reflect patient and clinical experience.

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 too little 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. It concluded that the costs of hospitalisations should be based on hospitalisation rates measured directly from the DOLOMITES trial.

The model 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. The company 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. The company explored 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. The committee concluded that the company model should include a wider range of adverse events, particularly those that are important to patients and could impact quality of life.

The estimated costs of roxadustat 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 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. 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 that it had not assumed treatment stops in the economic model, despite the DOLOMITES trial having a stopping rule for roxadustat (see section 3.8). Clinical experts indicated that the decision whether or not to stop treatment depends on how well anaemia is managed. They stated that they would change dosages so that Hb levels stay within a safe range (that is, between 100 g/litre and 120 g/litre) instead of stopping treatment (see section 3.8). One clinical expert added that there would no administration costs or additional burden associated with roxadustat in clinical practice. This is because it is an oral treatment and people already take oral tablets for other conditions. The committee concluded that the estimated costs of roxadustat are appropriate. But it recognised that they came from the pooled data and preferred that, when possible, data on effectiveness, utility and costs reflect the same data source.

The costs of ESAs are uncertain

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 the TUNE study, an observational retrospective study of medical records in the UK population. However, the company acknowledged that there is uncertainty around the distribution of ESA in clinical practice because there are no clear or reliable sources to inform this parameter. Clinical experts pointed out that some hospitals or 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. The committee concluded that administration costs should be included, but the overall costs of ESA are uncertain. It also concluded that it would like to see scenario analyses with different distributions of ESA.

Cost-effectiveness estimates

The company and the ERG's cost-effectiveness estimates are very different

3.15 In the company's base-case analysis, roxadustat was both more effective and less expensive than ESAs. The committee recalled that the DOLOMITES trial showed non-inferiority, in line with its objective. The company's analysis was based on the list price of each type of ESAs. The ERG's analysis was based only on the DOLOMITES trial data for the effectiveness of roxadustat and ESA, and included the confidential NHS commercial medicines unit price for each type of ESA. The ERG's analyses suggested that roxadustat was more effective than ESAs, but the incremental QALY gain was smaller than in the company's analyses. Also, instead of costing less than ESAs, the incremental cost of roxadustat was higher than ESAs. The ERG's incremental cost-

effectiveness estimate (ICER) was more than £4,000,000 per QALY gained. The exact results cannot be reported because of the confidential price for each ESA. The committee appreciate that the absolute estimates of differences in effectiveness between roxadustat were very small, and further changes based on different assumptions meant that the estimates of incremental cost effectiveness were unstable. The committee concluded that the estimates were generated from a model that did not reflect its preferred assumptions (see section 3.16).

The company's and the ERG's analyses do not reflect the committee's preferred assumptions

3.16 The committee noted that the clinical and cost-effectiveness modelling assumptions made by the company and the ERG were flawed. In particular, the committee considered that analyses should be based only on the DOLOMITES trial (see section 3.6) in the absence of a network meta-analysis. Also, transition probabilities should reflect all the data from the DOLOMITES trial (see section 3.8). The committee concluded it would prefer to see analyses using:

- DOLOMITES only trial data or data from a network meta-analysis using trials of ESA compared with placebo (see section 3.6).
- Full justification for using 8 health states or using fewer health states (see section 3.7).
- Health states which reflect the harms and costs of having Hb levels over 120 g/L (see section 3.10)
- Health-state transition probabilities based on data from the entire 36 weeks of the DOLOMITES trial (see section 3.8).
- Justification of the regression model used to extrapolate beyond the trial period (see section 3.8).
- Health-state utilities estimated using multiplicative approach (see section 3.9).
- Hospitalisation costs based on hospitalisation rates measured directly from the DOLOMITES trial (see section 3.11).

- ESA administration costs for people who start having peritoneal dialysis.
- A model that includes additional adverse events (see section 3.12).
- 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).

3.17 The committee would also like to see scenario analyses in which:

- The benefits of roxadustat do not last indefinitely over the 25-year time horizon.
- Different distributions of ESA are used.

Innovation

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

3.18 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. 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.

Equalities

There are no equalities issues identified for roxadustat

3.19 No equalities issues were identified during scoping, submission or technical engagement.

Other factors

3.20 NICE's advice about end of life treatments for people with a short life expectancy did not apply, because there is no evidence that people who have roxadustat live longer than those who have ESAs.

Conclusion

Roxadustat is not recommended

3.21 The committee had not seen cost-effectiveness estimates based on its preferred modelling assumptions. Of those the committee did see, the scenarios most closely aligned with its assumptions generated cost-effectiveness estimates that greatly exceed what would be considered cost effective. The committee concluded that it could not recommend roxadustat for treating symptomatic anaemia associated with chronic kidney disease in adults.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler

Chair, appraisal committee

December 2021

Issue date: January 2022

5 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.

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

Eleanor Donegan
Technical adviser

Thomas Feist
Project manager

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