NICE National Institute for Health and Care Excellence

NICE guidance

Vadadustat for treating symptomatic anaemia in adults having dialysis for chronic kidney disease

Technology appraisal guidance
Published: 23 January 2025

www.nice.org.uk/guidance/ta1035

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Vadadustat is recommended, within its marketing authorisation, as an option for treating symptomatic anaemia caused by chronic kidney disease in adults having maintenance dialysis. Vadadustat is only recommended if the company provides it according to the commercial arrangement.

1.2 If people with the condition and their healthcare professional consider vadadustat and erythropoiesis stimulating agents (ESAs) to be suitable treatments, after discussing the advantages and disadvantages of all the options, the least expensive should be used. Administration costs, dosages, price per dose and commercial arrangements should all be taken into account.

Why the committee made these recommendations

Standard treatment for symptomatic anaemia caused by chronic kidney disease in adults having maintenance dialysis is ESAs with iron. Vadadustat could be offered with iron instead of ESAs.

Clinical trial evidence shows that vadadustat increases haemoglobin levels, but not more than ESAs. But vadadustat costs less than ESAs, on average. So, it is recommended.

2 Information about vadadustat

Marketing authorisation indication

2.1 Vadadustat (Vafseo, MEDICE) is indicated for 'the treatment of symptomatic anaemia associated with chronic kidney disease (CKD) in adults on chronic maintenance dialysis'.

Dosage in the marketing authorisation

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

Price

2.3 The list prices of vadadustat are:

- £148.59 per 28-tablet pack of 150-mg tablets (excluding VAT; company submission)
- £520.08 per 98-tablet pack of 150-mg tablets (excluding VAT; company submission)
- £297.19 per 28-tablet pack of 300-mg tablets (excluding VAT; company submission)
- £1,040.16 per 98-tablet pack of 300-mg tablets (excluding VAT; company submission)
- £445.78 per 28-tablet pack of 450-mg tablets (excluding VAT; company submission)
- £1,560.23 per 98-tablet pack of 450-mg tablets (excluding VAT; company submission).

Annual treatment cost starts from £3,872.65 at the starting dosage of 300 mg per day (excluding VAT).

2.4 The company has a commercial arrangement. This makes vadadustat available to the NHS with a discount. The size of the discount is commercial in confidence.

3 Committee discussion

The evaluation committee considered evidence submitted by MEDICE, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Impact on quality of life

3.1 Anaemia is a serious condition defined by abnormally low levels of haemoglobin 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. But 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. Around 5% of adults have stage 3 to 5 CKD, increasing to 34% of adults aged 75 or older. The prevalence and severity of anaemia increase as kidney disease worsens. Stage 5 kidney disease is typically dialysis dependent. Up to 90% of people with dialysis-dependent CKD develop anaemia. People with CKD already face substantial challenges that affect their quality of life. Anaemia significantly contributes to the burden of CKD. Symptoms of CKD include fatigue, itching, swelling and sleep problems, which can affect many aspects of normal life and people's capacity to stay in work. Symptoms of anaemia include tiredness, breathlessness, low appetite, lethargy, palpitations, low cognition and concentration, and reduced libido. These symptoms can be an obstacle to being in employment. A patient expert explained that the extreme fatigue can be very sudden, 'hitting you like a wave'. Another expert noted the significant impact of anaemia on life, including on mental health and feeling like a burden to others. They noted that brain fog and not being able to do basic things like going to the bathroom, changing clothes, and other everyday tasks can cause a lot of stress. The committee concluded that anaemia has a considerable effect on quality of life for people with CKD.

Clinical management

Treatment pathway and comparator

3.2 When people with dialysis-dependent CKD develop anaemia, they are usually offered intravenous or subcutaneous erythropoiesis stimulating agents (ESAs) alongside intravenous or oral iron. ESAs can be short acting, taken up to 3 times per week, or long acting, taken weekly or monthly. Clinical experts noted that the effect of ESAs is broadly the same, and that the choice of ESA is usually based on cost, which may be subject to locally negotiated contracts. The committee considered ESAs as a class, that is, it considered all ESAs to be equally effective and safe. For people having haemodialysis, ESAs and iron are usually taken intravenously as part of dialysis. For people having peritoneal dialysis, ESAs are usually subcutaneous, either self-injected or injected by a carer or healthcare professional and iron is either oral or intravenous. The pathway for ESA treatment is well established. The clinical experts noted that a person with anaemia may have already started taking roxadustat before they became dialysis dependent, in line with NICE technology appraisal guidance TA807. They noted that patient choice is important and if people taking roxadustat start dialysis, some may choose to stay on roxadustat, an oral tablet taken 3 times per week, because it is familiar and easy to take. Other people still taking roxadustat, such as those who are starting haemodialysis, may prefer an ESA to remove the small burden of an oral tablet and because of the relative ease of administration of an intravenous injection with haemodialysis. If a person's anaemia is 'ESA resistant' (when the blood does not contain target haemoglobin levels despite usual doses of ESA, or needs increasingly higher doses to maintain haemoglobin concentration), they may be offered short-term rescue therapy. This may involve an additional ESA or red blood cell transfusion. The clinical experts noted a lack of evidence about the use of red blood transfusions in the UK, but their impression was that they are less commonly used in the UK than other countries. They also tend to be avoided in people who may be eligible for a kidney transplant. The committee concluded that ESAs are the most relevant comparator.

Positioning in the treatment pathway

3.3 The company positioned vadadustat as an alternative to ESAs, or as an option for anaemia that is resistant to ESAs. The clinical experts noted that most people having haemodialysis, whether in a clinic or at home, will have intravenous ESAs as part of their dialysis. So, an additional daily oral treatment may not be needed or desirable for people who already have a relatively high pill burden. They noted that the oral administration of vadadustat could benefit people who are unable to take ESAs because of needle phobia, or people who are having peritoneal dialysis who are unable to self-inject ESAs. It was not possible to quantify how many people having peritoneal dialysis need help with ESA injections, but the clinical experts noted it was likely to be a small proportion. Vadadustat could also be an option for people whose anaemia is ESA resistant. ESAs could also be used after vadadustat if a person's anaemia does not respond adequately to vadadustat. But transferring from one treatment to another was not directly addressed in the evidence base. The committee concluded that an oral option for treating anaemia would be welcome for some people. It confirmed that the company's positioning of vadadustat in the treatment pathway was appropriate.

Clinical effectiveness

Data sources

3.4 The main clinical evidence was from 2 trials: INNO$_2$VATE-incident and INNO$_2$VATE-prevalent. Both trials were non-inferiority randomised controlled trials comparing vadadustat with darbepoetin alfa (an ESA). People in the trials had treatment for up to 182 weeks, followed by an additional 4-week follow-up period for safety. The INNO$_2$VATE-incident trial included 369 people with anaemia who had recently started dialysis treatment for CKD, whereas INNO$_2$VATE-prevalent included 3,554 people with anaemia whose maintenance dialysis treatment for CKD had already been established. Both trials had similar key primary and secondary outcomes: change in average haemoglobin level between baseline and the primary efficacy period (PEP; 24 to 36 weeks), and then change in average haemoglobin level between baseline and the secondary efficacy period (SEP; 40 to 52 weeks). For the INNO$_2$VATE-prevalent trial, both outcomes were

'maintaining' haemoglobin levels, whereas for the $INNO_2VATE$-incident trial, the first (change in average haemoglobin at the PEP) was considered to be 'correction' of haemoglobin levels and the second (change in average haemoglobin at the SEP) was considered to be 'correction' and 'maintenance'.

Trial results

3.5 The proportion of people who had an average haemoglobin level within the geography-specific target range (haemoglobin level of 100 g/litre to 110 g/litre in the US and 100 g/litre to 120 g/litre outside of the US) at the PEP (24 to 36 weeks) was higher in the darbepoetin alfa treatment arm than in the vadadustat arm in both trials (odds ratio [OR] 0.6, 95% confidence interval [CI] 0.40 to 0.96 for $INNO_2VATE$-incident and OR 0.9, 95% CI 0.76 to 1.00 for $INNO_2VATE$-prevalent). During the SEP, this remained true for the $INNO_2VATE$-prevalent trial (OR 0.8, 95% CI 0.68 to 0.91). But there was no difference between treatments in the proportion of people who had an average haemoglobin level within the geography-specific target range in the $INNO_2VATE$-incident trial (OR 1, 95% CI 0.64 to 1.59).

The primary efficacy outcome, average haemoglobin level from baseline to the PEP (24 to 36 weeks), showed a small benefit for darbepoetin alfa in both trials (least squares mean -3.1 g/litre, 95% CI -5.3 to -1.0 for $INNO_2VATE$-incident and least squares mean -1.7 g/litre, 95% CI -2.3 to -1.0 for $INNO_2VATE$-prevalent). The secondary efficacy outcome, average haemoglobin level from baseline to the SEP (40 to 52 weeks) showed a small benefit for darbepoetin alfa for the $INNO_2VATE$-prevalent trial but no difference for the $INNO_2VATE$-incident trial (least squares mean -1.8 g/litre, 95% CI -2.5 to -1.2 for $INNO_2VATE$-prevalent and least squares mean -0.7 g/litre, 95% CI -3.4 to 1.9 for $INNO_2VATE$-incident). When the results were pooled (see section 3.6), both the naive comparison and fixed effects meta-analyses showed a small benefit for darbepoetin alfa for both the primary and secondary outcomes. But the confidence intervals were wider for the results from the meta-analysis (average haemoglobin level from baseline to the PEP: least squares mean with naive: -1.8 g/litre, 95% CI -2.4 to -1.2 and mean difference with meta-analysis: -1.8 g/litre, -2.7 to -1.0; average haemoglobin level from baseline to the SEP: least squares mean with naive: -1.7 g/litre, 95% CI -2.4 to -1.1 and mean difference with meta-analysis: -1.7 g/litre, 95% CI -2.7 to -0.8).

But any results showing a benefit for darbepoetin alfa were within the company's pre-specified non-inferiority margin (-7.5 to 7.5 g/litre), so showed that vadadustat was non-inferior.

There was no difference between treatments in the primary safety endpoint, time to first major adverse cardiovascular event (MACE; hazard ratio [HR] 0.96, 95% CI 0.833 to 1.113). As the confidence interval for the hazard ratio included the value of 1, this meant that there was no statistical difference between the vadadustat and darbepoetin alfa treatment groups for the time to first MACE. The company did not provide this outcome by trial, only pooled using a naive comparison. The committee concluded that there was insufficient evidence to conclude that there were statistical or clinically meaningful differences between treatments in MACEs.

The company noted that the trials were non-inferiority trials and were not designed to detect if one treatment was better than the other. The clinical experts considered that any differences between treatments were not clinically important. The committee concluded that there was insufficient evidence to conclude that there were clinically meaningful differences between treatments.

Pooling of trials

3.6 The company pooled individual patient data from the $INNO_2VATE$-incident and $INNO_2VATE$-prevalent trials using a 'treat-as-one-trial' method. In this naive approach, the individual patient data from both trials was combined, not adjusting for any differences between the trials. These pooled results were used in the company's model. The company acknowledged that there were some differences in baseline characteristics between the trials such as time on dialysis, but noted that many characteristics were similar, including age, sex, type of dialysis, comorbidities and the cause of CKD. It also noted that the trial design, dosing and objectives were pre-specified and consistent between trials, and that the intention to pool was also pre-specified. The company considered that the pooled population reflected the whole eligible population for vadadustat.

The EAG considered it inappropriate to pool the trials because the study populations and, therefore, treatment aims and the geographical locations of the studies differed. The EAG noted that naive pooling did not take into account

between-trial variation and led to a narrower confidence interval. It pointed out that the results were dominated by the $INNO_2VATE$-prevalent trial because it was almost 10 times larger. The EAG did scenario analyses by trial which showed some differences in results between the trial populations. But it considered the results should be treated with caution because some data that was included in the model (treatment discontinuation parametric models and haemoglobin transition matrices) were only provided by the company for a pooled population. A clinical expert noted that people who are starting on dialysis but do not yet have the dialysis optimised are at higher risk of cardiovascular events and mortality. So, it is important to increase haemoglobin slowly to avoid risk of stroke and mortality. The company confirmed that people who were not on dialysis were excluded from both trials. The clinical experts thought that the results reported for the treatment being used as maintenance were more likely to be valid and informative than results reported for the treatment being used to correct haemoglobin. The EAG subsequently noted that any differences between treatment during the PEP for the $INNO_2VATE$-incident trials were, therefore, unlikely to be clinically important. The committee noted, and the EAG agreed, that this supported the argument to pool data from the $INNO_2VATE$-incident and $INNO_2VATE$-prevalent trials. The committee concluded that it was acceptable to pool the results from the trials, but thought that analyses should be adjusted to account for differences between participants in the trials.

Economic model

Company and EAG's modelling approach

3.7 The company aimed to create a simpler model than that used for the appraisal on roxadustat (TA807), which had 8 states based on different haemoglobin levels. The company's model used 3 main health states: dialysis dependent, transplant and death, and had substates based on occurrence of MACE. Haemoglobin levels were used in the model to calculate utilities. The distribution of people among different haemoglobin level thresholds was based on the $INNO_2VATE$ trials. The company applied a weighted average of disutilities associated with each haemoglobin level threshold. It considered the use of MACE in the model transitions to best reflect the clinical course of CKD and the impact of MACE on

costs and quality of life, and ensured the INNO$_2$VATE trials were predominantly used to populate the model. The EAG considered the company's model to be overly complex for the decision problem, particularly since it was based on MACE but without evidence of a difference in MACE within the trials (the HR CI crossed 1: 0.833 to 1.113). It noted the company model disassociated haemoglobin level from the model structure, when impact on anaemia was a key trial aim, and also from the primary and secondary outcomes. It noted that haemoglobin level in the company model did not interact with mortality, costs, or treatment discontinuation, and that haemoglobin was only used for utility decrements. It also noted that the company used the UK renal registry (UKRR) which includes data from people from the start of dialysis, but that the company had not adjusted data from the registry appropriately to align with the trial in which people had a median time to dialysis of 2.4 years.

The EAG modified the model structure, removing MACE substates and using haemoglobin levels in the substates. It used 1 of the main trial outcomes in the model: improvement of haemoglobin levels from baseline to the end of the SEP at 52 weeks. The EAG preferred using a meta-analysis with a random effects model to pool the trials (see section 3.6). It did not have the data to include this in the model, so it used the results from the company's naive pooling method. The EAG noted that the transitions between the 3 main health states in its model used data from the UKRR, resulting in no differences between arms, which was in line with the EAG's clinical expert opinion that there is little functional difference between treatments. Transitions between substates were based on INNO$_2$VATE trial data up to week 52, but then it used the transition matrices from cycle 4 for the rest of the 42-year time horizon. The EAG also adjusted the UKRR data before incorporating the INNO$_2$VATE trial data to ensure the data aligned in terms of time on dialysis. The committee agreed that there was no evidence to support differences in MACE. It concluded that it preferred the EAG model structure based on haemoglobin substates because there was no difference in MACE, so it was not appropriate to base a model on this outcome. It also preferred the EAG's approach to adjusting for the time on dialysis of the UKRR data before applying it to the INNO$_2$VATE trial data.

Treatment discontinuation

3.8 The company's model assumed that no people stopped treatment after 52 weeks. The company noted that treatment discontinuation in the first year of the trial would be sufficient to capture stopping treatment because of adverse events or suboptimal haemoglobin levels. The EAG noted that the trial data at 3 years showed that some people stopped treatment after 52 weeks, and that people are also likely to stop treatment beyond 52 weeks in clinical practice. It considered that not all relevant treatment costs were captured in the model. It also noted that the reason that most people stopped treatment in the first year in the trials was because 'subject no longer wants to receive study drug', not because of adverse events or suboptimal haemoglobin levels. The clinical experts at the meeting noted that there were many reasons why people would stop treatment after a year, so the model should allow for this. The committee concluded that the company's assumption that people do not stop treatment after 52 weeks was not accurate in the trial and unlikely to represent clinical practice.

The EAG preferred to use parametric survival models extrapolated from trial data to inform the number of people on treatment per cycle. The company provided a scenario at the clarification stage using parametric survival models for treatment discontinuation. In this approach, it censored people who had a transplant or died, which removed these individuals from the population at risk of stopping treatment at the point of transplant or death, so they were no longer at risk of stopping treatment. In the EAG base case, where it had also removed people at cycle 2 in line with the stopping rule (see section 3.9), it considered transplant and death to be events, meaning that people who had a transplant or died were considered to have stopped treatment. Both the company and EAG preferred the Weibull distribution for extrapolating time to treatment discontinuation for both treatment arms. The company noted that it had not considered transplant or death to be events. This was because it considered this to be double counting, because both were already accounted for in each model cycle. The EAG agreed that treating transplant and death as events would be double counting in the company's model, but it was appropriate in the EAG model where these were applied separately. The committee considered that the company's approach potentially overestimated treatment discontinuation, because people who had a transplant or died were removed from the denominator at the point of transplant

or death. The committee concluded that there was uncertainty about treatment discontinuation. It preferred the EAG's approach of using parametric models, but also considered that the company could explore transplant and death being treated as competing risks in a multi-state model, governing all transitions in the model. It agreed with the use of a Weibull extrapolation method in the company and EAG approaches, but noted that alternative parametric models would need to be assessed for their appropriateness if a competing risks modelling approach was taken.

Stopping rule

3.9 The company had applied a stopping rule for vadadustat when there was an inadequate response to treatment at cycle 1 (week 13). The EAG noted that applying this at cycle 1 was not in line with the stopping rule in the marketing authorisation, which is at 24 weeks. The EAG considered it more appropriate to apply the stopping rule from cycle 2 (26 weeks). It noted that with the half cycle correction, cycle 1 was week 7 and cycle 2 was week 20. The committee concluded that the stopping rule should be applied as done by the EAG, because this aligned with the marketing authorisation.

Treatment waning

3.10 The company assumed a difference in treatment effect in terms of MACE beyond the 3-year trial data up until 5 years. From this point onwards (from cycle 20), it assumed equal efficacy between treatments, and it applied the transition probabilities for ESAs to vadadustat. This treatment effect waning was applied to MACE but not haemoglobin or quality of life. The company considered this a conservative approach, which was validated with clinical experts. It noted that waning is often used in technology appraisals up to 5 years. The company's scenario that removed treatment effect waning decreased the incremental cost-effectiveness ratio (ICER). The EAG was unclear of the rationale for incorporating waning, particularly when it was applied to MACE but not haemoglobin levels. The EAG removed treatment effect waning from its base case because MACE was excluded from its model. Because the committee preferred the EAG's model structure (see section 3.7), it did not need to consider the appropriateness of the

company's approach to treatment effect waning in terms of MACE.

Rescue therapy

3.11 Rescue therapy during the trials included ESAs or red blood cell transfusion. These were categorised in the trials as 'narrow' or 'broad-on-treatment'. 'Narrow' rescue therapy included ESA therapy for low haemoglobin (less than 95 g/litre) or worsening anaemia symptoms, or red blood cell transfusion therapy given for low haemoglobin or moderate to severe anaemia symptoms. The definition for 'broad-on-treatment' rescue therapy included the 'narrow' definition of rescue therapy but also included any additional use of ESAs or red blood cell transfusion (such as for acute or severe loss of blood). The company used narrow rescue therapy in its model because it considered that this captured the scope better, specifically in relation to anaemia from CKD. It noted that the broad-on-treatment definition included situations unrelated to anaemia such as ESA therapy after accidents and operations. The EAG considered that the definitions of rescue therapy were not clear, so it preferred using the broad-on-treatment definition which was more likely to capture all instances of rescue therapy used for anaemia symptoms in the trials. The clinical experts had said that red blood cell transfusion is not as commonly used in the UK as in other countries (see section 3.2). It would have preferred to see estimates of UK transfusion rates and thresholds. Since transfusion rates in the UK are likely to be conservative, the committee concluded that the narrow definition of rescue therapy should be used in the model because it was likely to better reflect rescue therapy used in the UK.

Survival extrapolation

3.12 The company preferred to use a logarithmic regression to extrapolate survival beyond the trial evidence in its model. It explained that as there were very few data points in the UKRR, its clinical experts had said that the linear regression fit was not appropriate, and also because assumptions about the number at risk were needed. So, it considered a logarithmic regression to be a pragmatic approach. The EAG preferred to use parametric models to extrapolate survival in the model, which enabled censoring of people that did not experience the event or were lost to follow up, or who completed the study and survived. The

committee considered the company's approach to be too simplistic and preferred the EAG's use of parametric survival curves.

Utility values

Source of utility values

3.13 The company used EQ-5D data from Liem et al. (2008) for the 'no MACE' substates. Liem et al. (2008) was a meta-analysis of utility values for people with end-stage renal disease that was also used in TA807, but it did not provide utility values for people with anaemia. The EAG preferred to use a more recent study, Cooper et al. (2020), which was a systematic review of health-related quality of life scores of people with CKD. It reported utility values for people who were dialysis dependent and after transplant by CKD stage, but this study also did not provide utility values for people with anaemia. The EAG used the utility data from Cooper et al. (2020) in its model. At the clarification stage, the company used Cooper et al. (2020) in a scenario analysis, resulting in the ICER decreasing. The company noted that the Cooper et al. (2020) study was not returned in its literature search but was content to accept its use in the model. The committee concluded it preferred to use Cooper et al. (2020) as the source of utility data because it was the most recent study.

Utility decrements

3.14 The company applied utility decrements for different haemoglobin cohorts in its model. It used a utility decrement of -0.0114 for every 1 g/dL decrease in haemoglobin from a reference of 13 g/dL from Yarnoff et al. (2016). The company applied additive disutilities for each 10 g/litre (1 g/dL) decrease in haemoglobin level (a haemoglobin level of less than 70 g/litre had a fixed utility) and then mean disutility was estimated for each category. The EAG noted that NICE prefers a multiplicative approach to utility adjustments (section 4.3.7 of NICE's health technical evaluation manual) and that this was also preferred for TA807. But it noted that because the source of utilities provided disutility between 1 haemoglobin level only and there was no reference utility to calculate a

multiplicative approach, it was content with an additive approach. The EAG also noted that the company used Sullivan et al. (2011) for the disutilities that it applied for each MACE, based on the type and frequency of MACE events in the trials. It noted that Sullivan et al. (2011) reported a large decrement with thromboembolic events but that the company excluded this disutility from the model. The EAG noted that because it was a large decrement, it considered that it was important to include. The committee noted that the thromboembolic event decrement only applied to the company's model with MACE substates. But, because the committee preferred the EAG's model with haemoglobin substates, the use of this decrement was not relevant. The committee concluded that it preferred a multiplicative approach to adjusting utilities in line with NICE's preferred approach. But it accepted the additive approach on this occasion, because the multiplicative approach was not possible as there was no reference utility.

Costs

Resource use

3.15 The company used different versions of Personal Social Services Research Unit (PSSRU) prices from 2019, 2020 and 2021, sometimes inflated to 2022 to 2023 costs, to source prices for various aspects of the model such as consultant, nurse and dietitian appointments. The EAG considered the most recent PSSRU (2022) prices should be used. The company noted that it was not able to use the most recent PSSRU (2022) in its submission because it did not have the correct codes at the time, but agreed it was appropriate to use the most recent source of information for these costs. The committee concluded that the most recent source of cost information, PSSRU (2022), was most appropriate.

Other factors

Equality

3.16 The company noted that vadadustat could reduce inequality in access given the severity and multi-comorbid nature of dialysis-dependent CKD, for which people may have difficulty accessing outpatient care for intravenous ESAs. It also noted that vadadustat would be an important option for people whose disease is resistant to ESAs and in whom blood transfusions are more likely to be done, which can reduce suitability of a transplant. While the committee acknowledged that some people may have difficulty accessing treatment, the clinical experts had noted that most people would be specifically having outpatient care for haemodialysis, and that ESAs would be given alongside this (see section 3.2). The clinical experts said that the proportion of people having peritoneal dialysis who need help to administer ESAs is small (see section 3.3), and that some of these people would be able to do this at home. It noted that ESA resistance was not likely to be classified under any of the protected characteristics in the Equality Act 2010.

Kidney disease disproportionally affects people from deprived communities and from certain ethnic minority groups who may be more likely to develop kidney disease, progress faster to renal failure and need dialysis or a transplant. The committee acknowledged that people from deprived communities and ethnic minorities may be more likely to have kidney disease and have poorer outcomes. Race is a protected characteristic under the Equality Act 2010. But because its recommendation does not restrict access to treatment for some people over others, the committee agreed this was not a potential equality issue.

Uncaptured benefits

3.17 The committee considered whether there were any uncaptured benefits of vadadustat. The company and clinical experts noted that there may be an environmental benefit of vadadustat over ESAs because it does not need cold storage and there would be less need for special disposal of needles. The company also suggested that there may be an environmental benefit of fewer

people attending kidney care centres. But the EAG's clinical expert noted that the main reason for attending kidney care centres would be related to a person's confidence in dialysis equipment, so the use of vadadustat was unlikely to affect clinic attendance on its own. The clinical experts noted that there would be fewer training requirements for self-administration or healthcare professional administration. The committee noted that an oral treatment could particularly benefit the likely small proportion of people having peritoneal dialysis who need help with ESA injections (see section 3.3). It concluded that there were some potential benefits of vadadustat as an oral treatment that had not been captured in the model, and it took these into account in its decision making.

Cost-effectiveness estimates

Committee-preferred assumptions

3.18 The committee's preferred assumptions included:

- using the EAG's model structure incorporating haemoglobin (see section 3.7)
- adjusting time on dialysis for the UKRR population as the EAG did (see section 3.7)
- using the EAG's approach to applying the stopping rule at 6 months in cycle 2 (see section 3.9)
- not accepting the company's assumption that people do not stop treatment after week 52 and instead using the EAG's approach of using parametric models to extrapolate treatment discontinuation, but using a competing risk approach to transplant or death to govern all transitions in the model (see section 3.8)
- pooling results from the INNO$_2$VATE-incident and INNO$_2$VATE-prevalent trials and adjusting for differences between trials (see section 3.6)
- using the most recent sources for utilities and costs (see section 3.13 and section 3.15)
- using the narrow rescue therapy definition (see section 3.11)

- using parametric models to extrapolate survival (see section 3.12).

Cost-effectiveness estimates

3.19 The ICERs cannot be reported here because they incorporate confidential discounts for the intervention, comparators and other drugs in the model. The costs for ESAs used in the model were those negotiated by the Medicines Procurement and Supply Chain, formerly the Commercial Medicines Unit. Because the choice and costs of ESAs vary across the UK, the results differed by price of ESA used. So, the committee considered analyses based on both the lowest and highest available prices for ESAs in its decision making (see section 4.4.5 of NICE's manual on health technology evaluations). Also, because of the small incremental quality-adjusted life years (QALYs), small changes in cost caused the results to vary substantially. In the company's base case, where the incremental QALYs favoured vadadustat, the results varied from vadadustat being dominant (vadadustat was cheaper and more effective) to having an ICER that was above the range normally considered a cost-effective use of NHS resources. In the EAG's base case, the results ranged from vadadustat being dominated by ESAs (vadadustat was more expensive and less effective) to vadadustat being less effective and less costly (in the southwest quadrant of the cost-effectiveness plane). When the committee's preferred assumptions were applied (see section 3.18), the results ranged from vadadustat being dominated by ESAs to vadadustat being less effective and less costly than ESAs. But on average (using the midpoint Medicines Procurement and Supply Chain price for ESAs), vadadustat was less effective and less costly than ESAs, with an ICER over £30,000 per QALY in the southwest quadrant of the cost-effectiveness plane. The committee concluded that, because of the variable price of ESAs across the country and because of the small incremental QALY differences between treatments, the cost-effectiveness results varied. But on average, using its preferred assumptions, vadadustat was less effective and less costly than ESAs.

Acceptable ICER

3.20 The committee accepted that there was little evidence of a difference in

treatment effect between vadadustat and darbepoetin alfa (section 3.5), but that this was uncertain. It considered that there are some people for whom an additional treatment option would be beneficial, but this benefit was likely not captured in the model (see section 3.17). It concluded that despite the possibility that ESAs may be slightly more effective than vadadustat (as in the EAG and committee-preferred base cases), it could recommend vadadustat if it was considered cost effective in the southwest quadrant of the cost-effectiveness plane. When a technology is less effective and less costly than its comparator, the commonly used approach of accepting ICERs below a given threshold is reversed. So, the higher the ICER, the more cost effective a treatment becomes.

NICE's health technology evaluations manual notes that judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the high level of uncertainty, specifically:

- whether there were any differences in clinical effectiveness between vadadustat and ESAs
- how often people stop treatment beyond the clinical trial evidence and how this might differ in clinical practice.

So, the committee concluded that an acceptable ICER would be around the middle of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

Net health benefit

3.21 The committee also considered the net health benefit in its decision making. This was because, in the committee's preferred analyses, vadadustat had lower total costs and lower total QALYs than ESAs on average. Net health benefit can be more informative than ICERs in such cases. The incremental net health benefit of vadadustat was compared with ESAs at threshold values of £20,000 and £30,000 per QALY gained. This resulted in a positive incremental net health benefit, confirming that vadadustat was cost effective compared with ESAs at both

£20,000 and £30,000 per QALY gained.

Conclusion

Recommendation

3.22 Using the committee's preferred assumptions, vadadustat was less effective and less costly than ESAs (in the southwest quadrant of the cost-effectiveness plane). The committee had concluded that because there was uncertainty in the treatment effect between vadadustat and darbepoetin alfa, and there were likely other benefits not captured in the decision (see section 3.17), an ICER that was in the southwest quadrant was acceptable. It noted that its preferred ICER for vadadustat compared with ESAs (and using an average cost of ESAs) was higher than £30,000 per QALY gained. In the southwest quadrant of the cost-effectiveness plane, this meant that it was a cost-effective use of NHS resources. So, vadadustat is recommended.

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 integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation 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 guidance 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 draft guidance.

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 who is having dialysis for chronic kidney disease has symptomatic anaemia and the healthcare professional responsible for their care thinks that vadadustat is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation 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 vadadustat being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

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

Chair

Charles Crawley
Chair, technology appraisal committee B

NICE project team

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

Heather Stegenga
Technical lead

Rufaro Kausi
Technical adviser

Vonda Murray

Project manager

Richard Diaz
Associate director

ISBN: 978-1-4731-6791-9