National Institute for Health and Care Excellence

Health Technology Evaluation

Vadadustat for treating symptomatic anaemia in adults having dialysis for chronic kidney disease [3821]
Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	MEDICE Arzneimittel Pütter	MEDICE suggest an evidence submission for vadadustat via a cost-comparison route and would like to discuss this approach with NICE during the current scoping consultation stage and prior to the decision problem meeting. The submission and evidence base for this appraisal will be aligned with the Medical and Healthcare Products Regulatory Agency (MHRA) marketing authorisation which approves vadadustat for the treatment of symptomatic anaemia associated with chronic kidney disease (CKD) in adults on chronic maintenance dialysis. The rationale for a cost-comparison approach is supported by the trial design and associated results of the pivotal INNO2VATE trials for vadadustat in dialysis dependent (DD) CKD for the hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) class. It is further supported by the recent appraisal of roxadustat in non-dialysis dependent (NDD) CKD (1). MEDICE believe that the results of the relevant pivotal trials satisfy the criteria of “similar or greater benefits” vs. current standard of care, i.e.,	Comments noted. Vadadustat for treating symptomatic anaemia in adults having dialysis for chronic kidney disease does not meet the criteria for the cost-comparison route because there is not a NICE approved comparator. For technologies evaluated using cost-comparison analysis in the technology appraisal programme, relevant comparators are those

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		erythropoiesis-stimulating agents (ESAs), as required for a cost-comparison approach. Furthermore, MEDICE believe the cost-comparison framework is the most efficient way to explore relevant meaningful differences between vadadustat and ESAs, and the vadadustat value proposition. The rationale is briefly outlined as follows: 1. ESAs are the only current standard of care option in the target population and vadadustat would be an alternative option for these patients. 2. The pivotal trials supporting this appraisal (INNO2VATE for patients in DD-CKD) established non-inferiority vs. darbepoetin alfa on all outcomes related to haemoglobin (Hb) and MACE (death and cardiovascular events) based on pre-specified non-inferiority (NI) margins, which can be assumed to reflect the comparative effectiveness of vadadustat versus ESAs based on the acknowledged class effect (described below in more detail) (2, 3, 4). Furthermore, the NI margins were aligned with those used in pivotal trials for other investigated HIFs, including roxadustat which was recommended by NICE in NDD-CKD in 2022 (1). 3. The risk of adverse events and treatment management for vadadustat is expected to be similar to ESAs. Both HIF-PHIs and ESAs target Hb to the same fixed range. The pivotal trials of HIF-PHIs and ESAs (including INNO2VATE for vadadustat in DD-CKD) dose adjust to target the same Hb level (i.e., primary efficacy endpoints) in the HIF-PHI and ESA arms of the available clinical trials. a. Resource use specific to anaemia management (e.g., ESA rescue, blood transfusions, iron supplementation) is expected to be either similar or reduced with the use of vadadustat versus ESAs. The use of vadadustat could enable cost savings through reduced administration costs with oral administration,	recommended in published NICE guidance for the same population. Please see section 4.2.13 of the NICE health technology evaluations: the manual

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		reduced costs of medical supplies (i.e., syringes, which are not required with oral administration), reduced logistics and storage costs (cold storage not required), reduced drug wastage due to logistics and cold storage (cold storage not required), reduced costs associated with clinical waste disposal (e.g., sharps bins, needles), and the potential for reduced nursing time through more patients choosing home dialysis over in-centre dialysis. The use of vadadustat would also reduce the need for cold-chain handling in the home dialysis setting (e.g., storage for several seeks in narrow temperature range of 2 to 8oC, especially transport during periods of travel), which can be difficult for the patient and risks wastage/quality degradation of ESA products. b. Risk of adverse events is also expected to be similar as no signals for statistically significant differences in adverse events was observed in the INNO2VATE trials. c. The above is also consistent with expected use in clinical practice based on consultation of clinical expert opinion. 4. The health-related quality of life impact of anaemia management is expected to be maintained with vadadustat versus ESAs on account of: a. Similar safety profile as observed in the INNO2VATE trials; b. Literature sources that support improvement in health-related quality of life with improved anaemia management via oral administration of HIF-PHIs as measured by EQ-5D (5). 5. Given the above, MEDICE anticipates the impact of introducing vadadustat as an alternative treatment option for the management of anaemia in DD-CKD patients will have negligible economic impact for	

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		the NHS, with potential for cost savings due to the convenience of home-based anaemia management (i.e., reduced administration costs, reduced costs of medical supplies, reduced logistics and storage costs, reduced drug wastage and reduced nursing time). MEDICE also believe that the evidence base supporting a cost comparison is sufficiently robust, leaving decision making uncertainty to be low.	
Timing issues	MEDICE Arzneimittel Pütter	MEDICE believes NHS patient access to vadadustat is of reasonable urgency as it will offer benefits to both patients and the NHS that are tangible in nature in terms of convenience and cost-savings via averted resource use. For example, avoiding the dependence on cold chains with high energy requirements and a lower drug wastage contributes to the sustainability and are in line with the goals of the NHS to reduce the CO2 footprint in the medium and long term (15). In addition, vadadustat may be an important treatment option for individuals with inadequate response (i.e., hyporesponders) to ESAs, which has an incidence of 12.5–30% for CKD patients, depending on the definition (10). Current treatment for these patients is a continual increase in ESA dose, which increases their risk of adverse events and is associated with higher cost (e.g., cost of higher doses of ESAs, increase cost of adverse event management). In principle, hyporesponders remain suitable for ESA therapy. However, when ESAs are administered at very high doses, as in the case of a lack of haematological response, ESA treatment would be stopped, and blood transfusions typically performed; blood transfusions are also associated with significant cost.	Comment noted. NICE aims to appraise vadadustat for treating symptomatic anaemia in adults having dialysis for chronic kidney disease as timely as possible in relation to the technology receiving its UK marketing authorisation.

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Wording	MEDICE Arzneimittel Pütter	MEDICE agree that the current wording of the decision problem remit reflects the EMA/MHRA marketing authorisation for vadadustat which states 'Vafseo is indicated for the treatment of symptomatic anaemia associated with chronic kidney disease (CKD) in adults on chronic maintenance dialysis'.	Comment noted. No action required.
Additional comments on the draft remit	MEDICE Arzneimittel Pütter	MEDICE are open to a workshop for this scope consultation, in particular to explore the appropriateness of a cost-comparison route.	Comments noted. Please see comments above on why this evaluation does not meet the criteria for the cost-comparison route.

Comment 2: the draft scope

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Background information	MEDICE Arzneimittel Pütter	Wording of the background information regarding anaemia and CKD is aligned with the final scopes for roxadustat (6) and daprodustat NICE assessments (7). MEDICE suggest inclusion of the following paragraph at the start of the technology description: 'Vadadustat (Vafseo, MEDICE Arzneimittel Pütter GmbH & Co. KG) is a hypoxia-inducible factor prolyl-hydroxylase inhibitor which leads to increased cellular levels of hypoxia-inducible factor thereby stimulating endogenous erythropoietin (EPO) production, increasing iron mobilization and RBC production, resulting in a gradual rate of rise in Hb.' In addition, the sponsor listed as 'Akebia Therapeutics' should be changed to 'MEDICE Arzneimittel Pütter GmbH & Co. KG ' throughout the document, including in the description of the technology on page 2 of Appendix B.	Comments noted. The aim of the background section is to provide a very brief summary of the disease area. Further details can be included in all submissions for this appraisal. Company name updated to MEDICE Arzneimittel Pütter

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			GmbH & Co. KG throughout the scope.
Population	MEDICE Arzneimittel Pütter	Population description aligns with the MHRA label; no change is needed.	Comment noted. No action required.
Subgroups	MEDICE Arzneimittel Pütter	Draft scope suggests subgroups analysis according to previous exposure to ESAs, should evidence allow. MEDICE would like to clarify that the INNO2VATE trials were designed as two separate non-inferiority open-label RCTs to support the broader target population approved in its label for dialysis dependent patients requiring correction and maintenance of Hb levels (limited exposure to ESAs) as well as maintenance of Hb levels (already receiving ESAs). In principle, MEDICE do not disagree with the suggested subgroup analyses, should clinical trial data allow; however, based on data available from the INNO2VATE trials, no clinically meaningful differences between ESA and vadadustat are anticipated and do not expect the available evidence to substantiate subgroup analyses.	Comment noted. No action required.
Comparators	MEDICE Arzneimittel Pütter	As established in the roxadustat appraisal (1), it is anticipated that the HIF class will displace some proportion of the well-established ESA class as an additional oral option for the target patient population (based on local clinician discretion). Based on this, MEDICE agree all relevant comparators have been included in the draft scope. MEDICE believe the INNO2VATE trials comparing vadadustat to a single ESA (i.e., darbepoetin alfa) serves as sufficient evidence to establish similar benefits of vadadustat compared to the entire class of ESAs administered as standard of care to DD-CKD patients in the NHS. A class effect for ESAs is well established and acknowledged within the clinical and research community. For example, a 2014 Cochrane review comparing the efficacy and safety of ESAs in the CKD setting concluded insufficient evidence to suggest the superiority of any ESA formulation (4). Palmer et al. 2014	Comment noted. No action required.

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		suggest that given similar comparative effectiveness, other considerations should be made when determining choice of ESA, such as drug cost, availability, and dosing frequency preferences. Furthermore, a 2023 update to the original Cochrane review, which included 62 additional studies, reported findings consistent with the 2014 review (2). Finally, an independent 2018 systematic review and meta-analysis similarly found no differences in efficacy and safety between ESAs (3). The current appraisal is the first to allow NICE to assess the evidence for a HIF-PHI vs. ESAs in the DD-CKD group; therefore, no precedent for a committee accepting an ESA class effect in the target population exists. However, the 2022 NICE appraisal for roxadustat in a NDD-CKD population (1) further supports the assumption of a class effect for ESAs. While acknowledging some differences in the frequency of administration, the committee concluded that the effectiveness of ESAs is similar, supporting a class effect.	
Outcomes	MEDICE Arzneimittel Pütter	Yes	Comment noted. No action required.
Equality	MEDICE Arzneimittel Pütter	If recommended by NICE, vadadustat will be the only recommended HIF-PHI for anaemia in DD-CKD patients. MEDICE believe that access to an oral option at home could reduce inequalities in access to care for DD-CKD patients given the severity and multi-comorbid nature of their disease, which may limit their ability to access outpatient anaemia care required for ESA administration.	Comment noted. The committee will consider equalities issues during the appraisal.
Other considerations	MEDICE Arzneimittel Pütter	N/A	No action required.

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Questions for consultation	MEDICE Arzneimittel Pütter	**Where do you consider vadadustat will fit into the existing care pathway for anaemia in chronic kidney disease?** Vadadustat has a marketing authorisation for the treatment of symptomatic anaemia associated with CKD in adults on chronic maintenance dialysis. MEDICE believes the appropriate positioning of vadadustat within the NHS is as an alternative to ESAs for the maintenance treatment of symptomatic anaemia after the correction of Hb or conversion from current ESA therapy, in subjects who have recently initiated dialysis treatment for DD-CKD. It is anticipated vadadustat will be offered to people who are receiving either peritoneal or haemodialysis, in both the in-centre and home settings. **Which ESAs are considered to be established clinical practice in the NHS for treating anaemia in people with CKD?** There are three licensed forms of ESA currently available in England and Wales, two short-acting (epoetin alfa and epoetin beta) and one long-acting (darbepoetin alfa) (8). The NICE guidelines for anaemia management indicate that available evidence on efficacy suggest no difference between darbepoetin alfa and epoetin alfa, or between darbepoetin alfa and epoetin beta. There were no studies comparing epoetin alfa and epoetin beta. ESAs are made available to NHS trusts through a system of tendering for local supply contracts, with costs varying between locations and over time. Therefore, it is recommended to agree on a first choice ESA rather than specifying a particular agent for all patients (8). The NICE guidelines for managing CKD highlight the lack of evidence comparing the efficacy of ESAs, and that the choice of ESA should consider the patient's dialysis status, ESA route of administration, and local availability of ESAs (9). Regarding the most frequently used ESA, NHS digital data (prescription cost analysis) indicate that darbepoetin alfa is the predominant ESA used in NHS clinical practice for treating anaemia in individuals with CKD. For example, for	Comments noted. No action required.

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		the year 2022 darbepoetin alfa prescriptions were six-fold greater than those for epoetin alfa, which was the next most used ESA (16). **Is there a group of people who could be treated with vadadustat for whom ESA therapy is not suitable? If so, what treatments do these people currently have?** Vadadustat may be an important treatment option for individuals with inadequate response (i.e., hyporesponders) to ESAs, which has an incidence of 12.5–30% for CKD patients, depending on the definition (10). Current treatment for these patients is a continual increase in ESA dose, which increases their risk of adverse events. In principle, hyporesponders remain suitable for ESA therapy. However, when ESAs are administered at very high doses, as in the case of a lack of haematological response, ESA treatment would be stopped, and blood transfusions would probably be performed. According to the SmPCs (11, 12, 13), ESAs are also contraindicated in the following patients: • Patients who develop pure red cell aplasia (PRCA) following treatment with any ESA should not receive any other ESA. However, PRCA is very rare: average annual incidence was calculated at 1.06 (95% confidence interval [CI], 0.83-1.28) per million (14). • Uncontrolled (or poorly controlled; epoetin beta) hypertension. **Would vadadustat be a candidate for managed access?** MEDICE do not consider vadadustat a candidate for managed access because the evidence available to support the clinical and economic benefits is sufficiently robust for decision making. MEDICE are also not aware of any additional clinical data that would be available to inform a management	

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		access reassessment. Therefore, MEDICE do not expect data collection in NHS practice would be required to reduce decision making uncertainty. **Do you consider that the use of vadadustat can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** MEDICE believe the health-related benefits of vadadustat to be similar to ESAs in the target population based on the non-inferiority efficacy and safety results of the INNO2VATE trial program. For this reason, a cost comparison approach is justified. Should MEDICE be required to submit a full cost-utility analysis (CUA), it is anticipated that the QALY calculation in a CUA will capture all health-related benefits relevant to vadadustat. Although data directly collected from the trial does not exist, it is also reasonable to expect that higher health-related benefits to patients treated with vadadustat versus ESAs could be gained on account of vadadustat's oral administration route and convenience in home administration allowing for minimal disruption of anaemia management on their daily routine, as was accepted for roxadustat (1, 5).	
Additional comments on the draft scope	MEDICE Arzneimittel Pütter	None	No action required.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

Kidney Care UK