Treatments for Anemia in Chronic Kidney Disease: Final Policy Recommendations

March 5, 2021

Policy Recommendations

Introduction

The following policy recommendations reflect the main themes and points made during the Policy Roundtable discussion at the February 11, 2021 CTAF Public Meeting on the use of roxadustat for the treatment of chronic kidney disease (CKD). At the meeting, ICER presented the findings of its revised report on these treatments and the CTAF voting council deliberated on key questions related to their comparative clinical effectiveness, and potential other benefits and contextual considerations. Following the votes, ICER convened a Policy Roundtable of two patients, two clinical experts, two payers, and two representatives from a pharmaceutical manufacturer to discuss how best to apply the evidence and votes to real-world practice and policy. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants.

A recording of the conversation can be accessed here, and a recording of the voting portion of the meeting can be accessed here. More information on Policy Roundtable participants, including conflict of interest disclosures, can be found in the appendix of this document. ICER's report on these treatments, which includes the same policy recommendations, can be found here.

The roundtable discussion was facilitated by Dr. Steven D. Pearson, MD, MSc, President of ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

All Stakeholders

All stakeholders have a responsibility and an important role to play in ensuring that effective new treatment options for patients with CKD are introduced in a way that will help reduce health inequities.

People from diverse racial and ethnic backgrounds are at a higher risk of developing CKD.[1] Unfortunately, patients from these communities are also at a higher risk of not receiving adequate education on anemia or on treatment options for this condition. All stakeholders should accept and act upon their responsibility to address these disparities.

- ***Manufacturers should engage with people from diverse communities to help inform the design and implementation of clinical trials, ensure that patients enrolled in pivotal trials are fully representative of people of color and those from less advantaged backgrounds, and should commit to designing trials that capture the comprehensive set of patient outcomes that matter most to patients.***

- ***Payers should engage with people from diverse CKD patient groups and with clinical experts in order to infuse coverage policies with sensitivity to the way that different treatments may offer distinct advantages or disadvantages for people based on their social background and living situation.***
- ***Patient advocacy groups for people with CKD should seek to represent diverse perspectives, requiring outreach to patients who are often not engaged by academic health systems, manufacturers, or other policymakers. Patient groups should consider collaborating with organizations and people in diverse communities to help build the trust needed to empower all patients. Among other important goals, educational outreach about anemia is lacking for many patients and their families.***
- ***Clinicians should follow the principle of shared decision-making to ensure that the values of patients with diverse needs and perspectives on risks and benefits of different treatments are at the heart of all treatment decisions.***

Regulators

Given the level of uncertainty about the benefits versus harms and the long-term effect of using roxadustat compared to erythropoiesis-stimulating agents (ESAs), we strongly suggest a mandate for a registry or other rapid and comprehensive post-marketing assessment

At the time of this report, the Food and Drug Administration (FDA) has not yet rendered a decision on regulatory approval for roxadustat. However, CTAF voted unanimously that the evidence was not currently adequate to demonstrate its superiority to usual care. The history of using ESAs to treat anemia in patients with CKD taught the medical community an important lesson about the risks of treating to blood test levels without fully understanding the true clinical outcomes for patients. Much harm was done until multiple randomized controlled trials (RCTs) emerged to show that correction of anemia and maintenance of hemoglobin (Hb) to near normal levels with ESAs increased mortality and cardiovascular events without consistently improving quality of life.[2-5] Despite its clear ability to raise Hb levels, roxadustat lacks adequate evidence at this time to demonstrate convincingly that at doses and targets used in clinical trials, it does not have an adverse effect on mortality.[6,7] Therefore, if roxadustat is approved by the FDA, the regulator should require a substantial post-marketing program of evidence generation to establish with more certainty the effects of treatment on mortality and cardiovascular outcomes.

Manufacturer

The manufacturer should not hold data in confidence from RCTs completed more than one to two years ago. The company has a responsibility to patients and clinicians to move these data into the public domain, to submit data rapidly for peer review in advance of regulatory approval, and to share these data in a transparent manner with groups seeking to assess the evidence to inform clinical practice and policy.

Several pivotal studies for roxadustat have been completed for over the past one to two years, yet the data have not all been submitted for peer reviewed publication. This by itself raises questions about the commitment of the manufacturer to transparency and suggests that the company may be trying to hold the data in-confidence in order to manage the narrative about results. Similarly, the practice followed by this manufacturer of reporting pooled data from different trials undermines the ability of clinicians, patients, and other stakeholders to perform an adequate analysis of the risks and benefits of treatment. The manufacturer should adopt the best practices of other companies in making clinical trial evidence more accessible in a timely fashion.

If roxadustat gains regulatory approval, the manufacturer should price the drug in alignment with its demonstrated value, which at the current time is highly uncertain given the lack of clarity about overall mortality and cardiovascular outcomes. In this setting, with significant uncertainty of this magnitude, the manufacturer should set the price lower than treatments with more established evidence and wait until further evidence addresses the uncertainties before seeking a higher price.

Manufacturer and Researchers

The manufacturer and researchers should avoid focusing primarily on Hb levels and the need for transfusion. Future research should expand outcomes measured to include patient-relevant outcomes such as quality of life, functional status, fatigue, overall cardiovascular events, and mortality in addition to the need for transfusion.

Researchers should conduct real-world comparative studies of roxadustat versus ESAs that evaluate a broad set of patient subgroups including ethnic and racially diverse populations and those who are hyporesponsive to ESAs.

Clinicians highlighted that using roxadustat would be of interest especially in the patients who are hyporesponsive to ESA, which is a group that has not been explicitly assessed in the current trials.

Clinicians

Clinicians should have decision support tools and invest the time needed for shared decision-making given the uncertainty and potential variability in patients' values about an oral treatment option for anemia in CKD.

We heard that an oral option will likely be more important for dialysis-independent CKD (DI-CKD) and home dialysis patients, especially for patients receiving peritoneal dialysis where an oral treatment could reduce the need for injections.

We also learned that particularly for patients receiving in-center hemodialysis, an infused option included in dialysis is likely easier than taking an additional oral medication. Patients stressed the need to explore values among different groups including ethnic and racial minorities and that it will be beneficial to engage with representatives from these communities.

Given the mechanism of action for roxadustat, patients were excluded from clinical trials if they had acute coronary syndrome, acute stroke, acute seizure, or thrombotic event within the last 12 weeks.[6,8] Until further data are gathered, clinicians should consider delaying treatment with roxadustat for patients with this clinical scenario.

Chronic anemia treatment in most patients is not an emergent situation. Postponing treatment with roxadustat should be considered in these patient subgroups to reduce the risk of harm.

Patient Organizations

Patients and advocacy groups should continue their efforts to encourage innovation while pushing manufacturers to generate better evidence to guide patient and clinician decision-making.

Patients have the most to gain from better evidence on the comparative safety and effectiveness of new treatments.

Patients and advocacy groups should emphasize the need for education and developing educational materials, which will facilitate shared decision making by summarizing potential benefits, harms, and evidence gaps about roxadustat compared to ESAs.

There is a need for an organized effort from educators, families, patients, advocacy groups, and clinicians to provide information about different treatment options in lay language that will facilitate shared decision-making. This effort should involve organizations on the ground, existing partnership with patients advocates, local faith-based organizations, and clinics. In order for shared decision-making to be feasible and effective, the knowledge gaps about anemia should be highlighted and dealt with. This is especially important for ethnic and racially diverse groups and for all underserved and vulnerable populations.

Payers

If approved by the FDA, roxadustat will present a novel mechanism of action and an oral treatment option for patients.[9] There is no current evidence demonstrating that roxadustat is superior to ESAs. As a treatment that would be indicated for patients prior to end-stage renal disease and those with end-stage renal disease, the coverage and treatment issues will be very different for private payers as opposed to patients with Medicare.

Reimbursement Considerations for Private Payers (Primarily DI-CKD Patients)

Given the lack of evidence to differentiate the clinical effectiveness, private payers may consider whether their formularies require both roxadustat and one or more ESAs. However, the different delivery mechanism may have important advantages or disadvantages for different patients, suggesting that both options should be covered.

It is possible that private payers may consider negotiating lower prices with manufacturers of ESAs and roxadustat by offering not only preferred formulary tiering but exclusive formulary placement. The lack of robust evidence on the cardiovascular and overall mortality outcomes for roxadustat may also lead some private payers to consider not adding this treatment to their formulary. We heard from patient advocates and clinical experts that the distinctive oral delivery mechanism for roxadustat will create important potential benefits for some patients, whereas for others the ESAs will remain a preferred option, suggesting that payers fully engage with all stakeholders if they wish to consider a narrow formulary.

Given the significant uncertainty that remains about the effectiveness of roxadustat, it is reasonable for payers to use prior authorization as a component of coverage.

Prior authorization criteria for roxadustat should be based on clinical evidence and input from clinical experts and patient groups. The process for authorization should be clear and efficient for providers. It is possible that the numbers of DI-CKD patients who could be started on roxadustat exceeds the current number on ESAs. Options for specific elements of coverage criteria within insurance coverage policy are discussed below.

Coverage Clinical Criteria Considerations:

A. ***Patient Eligibility Criteria***: The patient eligibility criteria are likely to mirror those in the clinical trials, which were very similar to existing coverage criteria for ESAs. One common set of criteria are: adult patients with DI-CKD (stages III-V) with an eGFR <60 ml/min/m^2 or adult patients with dialysis-dependent CKD (DD-CKD) who have anemia with a Hb <10-10.5 g/dl.[10] Some payers cover ESAs not for treatment of anemia-related symptoms such as fatigue, but only when the "therapeutic goal is reducing the risk of alloimmunization and/or other red blood cell transfusion related risks."[11] However, this therapeutic goal criteria would seem to be difficult to operationalize further and may not prove useful.

B. ***Exclusion Criteria***: Trials of roxadustat excluded patients with multiple conditions, which payers may consider when determining eligibility criteria for treatment.[7,9,12-18] The exclusion criteria include:

- Active infection
- Known history of any of the following conditions: myelodysplastic syndrome or multiple myeloma, thalassemia, sickle cell anemia, pure red cell aplasia, hemochromatosis or coagulation disorder, gastrointestinal bleeding, chronic liver disease, New York Heart Association Class III or IV congestive heart failure, myocardial infarction, acute coronary syndrome, acute stroke, acute seizure, or recent thrombotic event (within the last 12 weeks), malignancy that has not been in remission for at least five years, HIV, hepatitis B or C, untreated proliferative diabetic retinopathy, diabetic macular edema, macular degeneration, or retinal vein occlusion
- Prior organ transplant
- Pregnant or breastfeeding

Step Therapy:

Given that the evidence is not adequate to distinguish clinical benefit and that there are more data and years of clinical experience with ESAs, some payers may wish to consider stepping through ESAs if they are substantially lower-priced than roxadustat before obtaining coverage for a more expensive option.

Given the uncertainty about the clinical benefits and harms and lack of long-term safety data, stepping through roxadustat first is not advisable, however, step therapy through ESAs may be an approach some payers will consider, especially if ESAs offer a lower overall cost of care. However, as noted earlier, patient advocates and clinical experts highlighted the potential distinctive living situations and other factors that might make an oral option not just preferred by the patient but the option that would have the best chance of achieving the intended clinical outcome. This situation might arise for patients who are house bound or are challenged with transportation to clinics and infusion centers. Therefore, if step therapy is to be considered, rapid, transparent exception mechanisms should be in place.

Concomitant Use with ESAs:

All key clinical trials have allowed rescue therapy using ESAs in addition to roxadustat as part of the protocol. However, data on the safety and efficacy of concomitant use of these agents has not been presented.

Provider Qualifications:

Giving the tenuous risk and benefit tradeoffs and the need for close follow-up, payers may wish to require that management of roxadustat be done by or in consultation with a specialist.

Management of anemia in CKD is complex and requires regular follow up to adjust dosing of treatments and iron supplementation. One of the main concerns with roxadustat is the fact that high-risk patients were not included in trials. Clinical expertise is essential in determining how to manage these patients in practice.

Reimbursement Considerations for Medicare (Primarily DD-CKD Patients)

The selection of treatments for patients at dialysis centers is already heavily constrained and driven by financial considerations. If roxadustat is approved by the FDA, Medicare should seek to reimburse for its use in a way that creates more choice for patients and clinicians.

If roxadustat is covered outside of the end-stage renal disease bundle, Medicare should consider carving out the treatment of anemia from the end-stage renal disease bundle so that selection of treatment can be on a competitive basis related to effectiveness and cost.

If roxadustat is covered inside the end-stage renal disease bundle, Medicare should select reimbursement with a TDAPA (Transitional Drug Add-on Payment Adjustment) only under a new structure of linking the additional reimbursement amount to demonstrated value, which would provide incentives for the manufacturer to generate better evidence of effectiveness. Reimbursement within the existing end-stage renal disease bundle base rate presents lower risk of creating perverse incentives that would overpay for treatment while limiting patient choice.

If roxadustat is to be covered within the end-stage renal disease bundle, Medicare has two options to consider for reimbursement. One is to pay a TDAPA equal to its average sales price. The second option is to include roxadustat within the end-stage renal disease bundle with no change to the base rate.

- ***Reimbursement with TDAPA***:
    - If Medicare takes this approach, it may reward "innovation" in an existing functional category but roxadustat does not have evidence of superior performance to existing ESA options and, therefore, its claim to a TDAPA seems limited. In addition, providing any additional payment on top of the existing bundle would provide a perverse incentive for dialysis centers to favor the use of roxadustat solely for financial reasons.

If Medicare chooses reimbursement with TDAPA, it should not use average sales price as the basis for the payment. Instead, it should consider a demonstration project in which TDAPA is based on the relative added value of the new treatment. In this case, that would mean a $0 additional

payment until further evidence is generated to demonstrate an added clinical value for roxadustat over ESAs.

- ***Reimbursement without change to the end-stage renal disease base rate:***
    - This option allows for greater competitive market forces to favor the more effective and/or lower cost agent. In addition, concern about lack of market opportunity for roxadustat is mitigated by its likely greater use in the private market for DI-CKD patients.
    - If evidence confirm that roxadustat is better than ESA, the bundle should be adjusted to accommodate a higher price based on incremental value to ESA. TDAPA should be reserved to treatments that demonstrate improvement over the existing treatments in the bundle.

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Appendix

Appendix Tables 1 through 3 contain conflict of interest (COI) disclosures for all participants at the February 11, 2021 Public Meeting of CTAF.

Appendix Table 1. ICER Staff and Consultants

ICER Staff and Consultants	
Foluso Agboola, MBBS, MPH,* Vice President of Research, ICER	**Grace Fox, PhD,*** Research Lead, ICER
Lisa Bloudek, PharmD, MS,* Senior Research Scientist, University of Washington	**Reem Mustafa, MD, MPH, PhD,*** Associate Professor of Medicine; Director, Outcomes and Implementation Research, University of Kansas Medical Center
Jonathan D. Campbell, PhD, MS,* Senior Vice President for Health Economics, ICER	**Steven D. Pearson, MD, MSc,*** President, ICER
Josh J. Carlson, PhD, MPH,* Associate Professor, Department of Pharmacy, University of Washington	**David M. Rind, MD, MSc,*** Chief Medical Officer, ICER
Laura Cianciolo,* Program Manager, ICER	**Azanta Thakur,*** Program and Event Coordinator, ICER
Noemi Fluetsch, MPH,* Research Assistant, Health Economics and Outcomes Research, ICER	

*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.

Appendix Table 2. Policy Roundtable Participants and COI Disclosures

Policy Roundtable Participant	Conflicts of Interest
Jeffrey S. Berns, MD, Professor of Medicine; Associate Chief, Renal Electrolyte and Hypertension, University of Pennsylvania	No conflicts of interest to disclose.
Kerry Cooper, PharmD, Vice President of US Renal Medical Affairs, AstraZeneca	Full-time employee of AstraZeneca.
Leslie Fish, RPh, PharmD, Vice President, IPD Analytics	Full-time employee of IPD Analytics.
Yola Gawlik, MHA, Executive Director, US Government Affairs and Policy, Amgen	Full-time employee of Amgen.
Patrick O. Gee, Sr., PhD, JLC, Founder and CEO, iAdvocate, Inc.	No conflicts of interest to disclose.
Pinelopi Kapitsinou, MD, Associate Professor of Medicine, Division of Nephrology and Hypertension, Northwestern University, Feinberg School of Medicine	Dr. Kapitsinou owns stock in excess of $10,000 in Biogen, Merck, and Pfizer.
Rosalie Patel, PharmD, Principal Pharmacist, Formulary Strategy and Management	Rosalie Patel is a full-time employee of Blue Shield of California.
Troy Zimmerman, Vice President, Government Relations, National Kidney Foundation	NKF receives more than 25% of its revenue from health care and life sciences companies.

Appendix Table 3. CTAF Panel Member Participants and COI Disclosures

Participating Members of CTAF	
Ralph G. Brindis, MD, MPH, MACC, FSCAI, FAHA,* Clinical Professor of Medicine, UCSF	**Elizabeth J. Murphy, MD, DPhil,*** Professor of Clinical Medicine, UCSF; Chief, Division of Endocrinology and Metabolism, Zuckerberg San Francisco General Hospital
Robert Collyar,* Patient Advocate; Board Member, Breast Cancer Action; Co-Founder, Clinical Trials Information Project	**Kathryn A. Phillips, PhD,*** Professor of Health Economics and Health Services Research; Director and Founder, UCSF Center for Translational and Policy Research on Personalized Medicine; Department of Clinical Pharmacy/School of Pharmacy, UCSF Institute for Health Policy Studies, and UCSF Comprehensive Cancer Center
Rena K. Fox, MD,* (Chair) Professor of Medicine, UCSF	**Ann Raldow, MD, MPH,*** Assistant Professor, Department of Radiation Oncology, UCLA David Geffen School of Medicine
Kimberly Gregory, MD, MPH,* Women's Healthcare Quality and Performance Improvement, Department of Obstetrics and Gynecology; Director, Division of Maternal Fetal Medicine, Cedars-Sinai Medical Center	**Richard Seiden, JD,*** Patient Advocate, Retired Partner, Foley & Lardner LLP
Paul Heidenreich, MD, MS,* Professor and Vice-Chair for Quality, Clinical Affairs, and Analytics, Stanford University	**Alexander Smith, MD, MPH,*** Associate Professor of Medicine, UCSF
Jeffrey Hoch, PhD,* Associate Director, Center for Healthcare Policy and Research, UC Davis	**Joanna Smith, LCSW, MPH, CHA,*** Chief Executive Officer, Healthcare Liaison, Inc.
Sei Lee, MD,* Associate Professor of Medicine, Division of Geriatrics, UCSF	**Anthony Sowry,*** Patient Advocate and Lead Volunteer, California, National Patient Advocate Foundation; Senior Vice President, Maritime Container Shipping (Retired)
Joy Melnikow, MD, MPH,* Director, Center for Healthcare Policy and Research; Professor, Family and Community Medicine, University of California, Davis	

*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.