PERSPECTIVE ON THE RXPIPELINE

Understanding changes in the medication market and their impact on cost and care.

EnvisionRx continuously monitors the drug pipeline. As treatment options change, we evaluate and share our perspective on the clinical benefits, cost-effectiveness and overall impact to payers and patients. Our Perspective on the Rx Pipeline report provides ongoing actionable insights from our team of clinical experts and the steps we are taking to protect and improve plan performance.

Included in this Edition

- Taking the Sting Out of Treatment for Anemia of Chronic Kidney Disease: Oral Medication Alternatives on the Horizon

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ANEMIA OF CKD

Taking the Sting Out of Treatment for Anemia of Chronic Kidney Disease: Oral Medication Alternatives on the Horizon

PIPELINE STAGE

TIMING

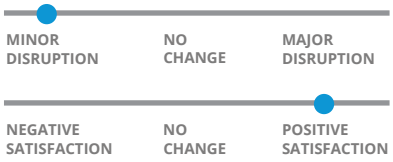
When will payers be impacted?

CLINICAL EFFECTIVENESS

Compared to available options, is this drug better for treatment?

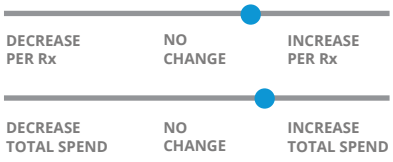
PATIENT EXPERIENCE

Will this positively or negatively impact members?



PAYER IMPACT

How will this influence Rx spend?



Situation Summary

The primary function of the kidneys is to filter blood, turning the waste into urine and balancing needed minerals and salts into blood circulation.[1] Kidneys also create and maintain hormones necessary for bodily function, such as renin, erythropoietin, vitamin D activation, insulin clearance, and more.[2] In chronic kidney disease (CKD), which effects anywhere from 10 to 30 million U.S. adults, the kidneys do not function efficiently.[1,3] Over a long period of time, this can cause waste to build up in the body.

Risk factors for kidney disease primarily include diabetes and high blood pressure, as well as HIV, exposure to toxins and heavy metals, and a family history of kidney failure. It can eventually lead to end-stage renal disease (ESRD) and is a risk factor for cardiovascular disease.[4] Although not often considered a top cause of mortality, deaths from CKD exceeded tuberculosis and HIV in 2017. Fortunately, ESRD morbidity and mortality rates have decreased since the 1960s due to transplants, however, not all patients qualify for a transplant, as they are reserved primarily for those with stage 5 CKD (eGFR< 15 mL/min/1.73m^2) or those who are dialysis dependent/ESRD.[3]

CKD Increases Risk of Anemia: Anemia of CKD is a common complication and accounts for increased mortality and hospitalizations. Anemia is a deficiency in hemoglobin (Hb) or red blood cells. Healthy kidneys produce erythropoietin, which stimulates erythropoiesis, formulating red blood cells. In CKD, kidneys may not properly produce erythropoietin, which may contribute to anemia. Nutritional deficiencies, decreased red blood cell survival, uremic-induced inhibitors of erythropoiesis, and decreased iron homeostasis (which most often is due to diet or blood loss) have also been hypothesized to contribute to CKD-driven anemia.[5]

In data extracted from the National Health and Nutrition Examination Survey (NHANES), anemia was twice as prevalent in CKD patients as compared to the general population (15.4% vs. 7.6%). It can occur in patients who are both non-dialysis dependent (NDD) and dialysis

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GLOSSARY OF TERMS

- **Estimated Glomerular Filtration Rate (eGFR)**
  A calculation used to determine the stage of kidney disease. It measures the filtration rate of the kidneys.
- **Kidney Failure**
  Defined as an eGFR below 15 mL/min/1.73 m^2, or patient requiring dialysis.
- **Dialysis Dependent Chronic Kidney Disease (DD-CKD)**
  Chronic kidney disease requiring dialysis treatment, a process to help purify and filter the blood when the kidneys can no longer do so.
- **Non-Dialysis Dependent Chronic Kidney Disease (NDD-CKD)**
  Chronic kidney disease not requiring dialysis treatment.
- **Hemoglobin (Hb)**
  A protein in red blood cells that carries oxygen to and carbon dioxide away from organs and tissue in the body.
- **Prescription Drug User Fee Act (PDUFA) Date**
  A deadline for the Food and Drug Administration (FDA) to review new drugs, usually 10 months after the New Drug Application (NDA) is accepted.

dependent (DD). Symptoms of anemia may include weakness, dizziness, easily bruised or pale or dry skin, fatigue, shortness of breath, feeling cold, and chest pain.[6, 7]

The World Health Organization defines anemia as an Hb concentration of <13.0 g/dL for adult males and postmenopausal women, and an Hb <12.0 g/dL for premenopausal women. For CKD patients, as the estimated glomerular filtration rate (eGFR) declines below 60 mL/min/1.73 m^2, rates of anemia increase.

To diagnose anemia, providers analyze a complete blood count and red blood cell distribution width (RDW). If patient history or preliminary laboratory data indicate possible blood loss, providers may evaluate plasma levels of iron, iron binding capacity (transferrin), transferrin saturation and ferritin to determine if there's an iron deficiency.

Frequent monitoring for anemia is needed for those with CKD and can range from annual monitoring for patients without current anemia and an eGFR ≥30 mL/min/1.73 m^2 to weekly if initiating certain treatments.[8]

Current Treatment Options for Anemia of CKD: Cornerstones of CKD-related anemia management in both DD and NDD patients include oral or intravenous iron therapy, injectable erythropoiesis-stimulating agents (ESAs), and in severe cases, red blood cell (RBC) transfusions. Iron therapy may be the first step prior to prescribing ESAs in order to maximize their effectiveness. ESAs are initiated when Hb < 10g/dL and patients have adequate iron storage.

While ESAs have changed the management of DD and NDD anemia of CKD, they are not benign. ESAs carry significant black box warnings from the Food and Drug Administration (FDA) for potential increased cardiovascular events, risk of tumor progression in cancer and increased need for the close monitoring of hemoglobin levels. The 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend "balancing the potential benefit of reducing blood transfusion and anemia-related symptoms against the risk of harm in individual patients" in using ESAs.[8]

Epogen® and Procrit® (epotein alfa), dosed three times a week, were the first ESAs approved by the FDA in 1989. In 2001, Aranesp® (darbopoetin alfa) was approved and allowed for an extended dosage schedule. Retacrit™ was approved as the first epotein alfa biosimilar in May 2018, however, all of these products are injectable and have significant monitoring needs.[9]

New Oral Treatment Option in the Drug Pipeline: Hypoxia inducible factor prolyl hydroxylase inhibitors (HIF-PHI) are a novel pipeline drug class for both DD and NDD CKD anemia and may

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offer some relief from the numerous injections and extensive lab monitoring that is needed for safe management of ESAs. HIF-PHIs are orally dosed three times per week and restore production of erythropoietin and improve iron regulation. HIF-PHIs have the potential to replace ESAs as the standard of care in the treatment of anemia of CKD and reduce the need for ongoing iron supplementation.[10]

FibroGen, AstraZeneca and Ascella have a first-in-class product, FG-4592 (roxadustat), with an FDA Prescription Drug User Fee Act (PDUFA) date of December 20, 2020.[9] Competition is not far behind with three competing products in phase III clinical trials, all with similar indications: BAY-85-3934 (molidustat), AKB-6548 (vadadustat) and daproudstat.[11]

Roxadustat is approved in China for treatment of DD and NDD CKD and in Japan for NDD CKD anemia.[11] Multiple clinical studies evaluating more than 10,000 patients worldwide have been done with roxadustat and currently, there are 38 trials investigating roxadustat listed on clinicaltrials.gov.[12] Promising clinical data, as follows, was presented at the American Society of Nephrology Kidney Week in November 2019 and will be part of the FDA new drug submission application:[13]

Study	Trial Design	Enrollment	Primary Endpoint	Finding
OLYMPUS[14]	Phase III, multicenter, randomized, double blind, placebo-controlled study of roxadustat vs. placebo in NDD patients	n= 2761	Mean Hb change from baseline to average levels from week 28 to week 52	Hb increase of 1.75g/dL over weeks 28 to 52, compared to 0.40g/dL with placebo Roxadustat was superior to placebo
ROCKIES[15]	Phase III, randomized, open-label, active controlled study of roxadustat vs. epoetin alpha in DD patients	n=2106	Mean Hb change from baseline to average levels from week 28 to week 52	Improvement in Hb levels from baseline with a mean increase of 0.77g/dL averaged over weeks 28 to 52, compared to 0.68g/dL with epoetin alfa Roxadustat was non-inferior to epoetin alfa

Safety data was consistent to adverse events experienced by the DD and NDD CKD population or those treated with epoetin alfa. In roxadustat treated patients, most common adverse drug reactions (ADRs) were diarrhea, hypertension, pneumonia, headache and arteriovenous fistula thrombosis (in DD population). Serious ADRs reported were sepsis and myocardial infarction, which are both seen in end stage renal patients. A pooled analyses of those patients exposed to roxadustat showed positive efficacy and no increased cardiovascular risk in patients with anemia from CKD.[13]

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PAYER ACTION PLAN

- **Treatment Billing for Commercial Payers**
  As HIF-PHI are oral medications for DD-CKD or NDD-CKD, billing under the medical or prescription benefit may occur.
- **Treatment Billing for Medicare Payers**
  ESAs and iron supplements are seen under the Medicare Part B benefit in the CMS End Stage Renal Disease (ESRD) Prospective Payment System, sometimes referred to as the "CKD bundle," when used for CKD.[16] Payers should watch to see if this CMS guidance will be updated to include or exclude HIF-PHI in the CKD bundle and plan accordingly.
- **Utilization Management and Formulary Strategies**
  All payers that implement management strategies for ESAs may want to take HIF-PHI inhibitors into consideration for 2021 formulary strategy.

Impact to the Pharmacy Care Experience

Pipeline Monitoring: EnvisionRx is closely monitoring the drug pipeline for the first probable HIF-PHI approval, expected near the end of 2020.

Pharmacy & Therapeutics Review: Our Pharmacy & Therapeutics (P&T) committee, which helps determine a drug's formulary placement, will conduct a robust clinical review of any HIF-PHI drugs that receive approval.

Utilization Management and Formulary Strategies: HIF-PHIs may primarily find their place initially with the NDD-CKD patient population or those experiencing significant side effects on ESA or non-responders to ESA treatment. As ESAs are often a managed drug class, HIF-PHIs may require management strategies as well. As an example, implementation of a prior authorization may be warranted to verify indication and laboratory requirements. Additionally, as multiple HIF-PHI drugs may get approved in the future, having a preferred HIF-PHI and step therapy may become an option. EnvisionRx will evaluate and implement appropriate utilization management and formulary strategies for HIF-PHIs after review by our P&T committee.

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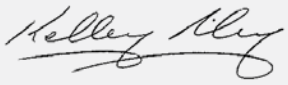
Our Clinical Steering Committee

The Envision Clinical Steering Committee brings together leaders from across our national pharmacy care company to monitor the drug landscape, provide recommendations on how to address changes, and to ensure our clients and patients are prepared—in advance.

With any new development, we partner with our Pharmacy & Therapeutics (P&T) Committee and consult with our best-in-class specialty pharmacy, to provide a balanced perspective on the clinical effectiveness of all available options, the cost impact to our plan sponsors and patients, and the impact on the overall patient experience.



Kel Riley, MD
Chief Medical Officer

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