KarXT for Schizophrenia
Final Policy Recommendations

March 11, 2024

Policy Recommendations

Introduction

The following policy recommendations reflect the main themes and points made during the Policy Roundtable discussion at the February 9th, 2024 New England CEPAC public meeting on the use of KarXT for the treatment of Schizophrenia. At the meeting, ICER presented the findings of its revised report on these treatments and the New England CEPAC voting council deliberated on key questions related to their comparative clinical effectiveness, potential other benefits and contextual considerations, and long-term value for money at current prices. Following the votes, ICER convened a Policy Roundtable of 2 patients, 2 clinical experts, 2 payers, and 1 representative 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, (part one) and here (part 2), 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 Pearson, MD, MSc, President of ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

All Stakeholders

Recommendation 1

All stakeholders have a responsibility and an important role to play in ensuring that effective new treatment options for people living with schizophrenia are introduced in a way that will help improve comprehensive care for people with schizophrenia and reduce health inequities, particularly for Black Americans.

Safe, and effective comprehensive treatment for schizophrenia remains a significant unmet health care need for all Americans, and Black Americans suffer disproportionately, since they are diagnosed with schizophrenia at twice the rate of other races, and they have worse clinical outcomes once diagnosed. Efforts are needed, therefore, to ensure that new treatments like KarXT serve as a stimulus to improve all aspects of care for people living with schizophrenia.

Clinical experts and patients at the ICER public meeting highlighted numerous factors leading to health inequities and poor care for many individuals. The failure of broader societal safety nets for

individuals, families and other caregivers affected by this condition is pervasive. High costs for medications can also create significant barriers to access and adherence. Funding should target an expansion of inpatient beds and allow lengths of stay that ensure that patients have sufficient time to be stabilized on a therapy that works for them prior to discharge. Too many patients are discharged with limited support and instead need access to humane, supervised housing to ensure a smooth transition. Outpatient care should not be limited to medical management but should instead include increased combination approaches using non-pharmacological interventions including cognitive remediation therapy, compliance therapy, social skills training, social group therapy, and supported employment therapy.

To address these significant and numerous concerns, individual stakeholders should take the following actions:

Manufacturers:

- Set the price for KarXT in fair alignment with added benefits for patients.

Private payers:

- Ensure that benefit designs developed in conjunction with employers and other plan sponsors do not create requirements for out-of-pocket spending that create major barriers to appropriate access, especially for lower income people and families.

- Improve outcomes by allowing for longer inpatient stays and by assuring that case managers are available to help people find appropriate housing and support following hospitalization.

- Expand the options for collaborative care to provide high quality care by facilitating telehealth and other methods for primary care clinicians and non-physician mental health providers to collaborate with psychiatrists and Board-certified psychiatric pharmacists.

Medicaid and Medicare:

- Improve payment and resources for clinicians caring for people with schizophrenia.

- Ensure that patients being discharged from inpatient care have adequate case management and support for housing and care in the community.

State and Federal Policymakers:

- Create policies that require greater attention to the needs of people with schizophrenia who are in prison.

- Require collaboration among providers and insurers at the state or regional level to develop dashboards for tracking access and outcomes of people living with schizophrenia. Measurement with public scrutiny will be important for driving improvement across the wide range of services needed to help people living with schizophrenia.

Clinical specialty societies should take the following actions:

- Develop and disseminate educational materials and create measurable goals to ensure that Black Americans receive care consistent with current best practices.

Payers

Recommendation 1

If KarXT receives FDA approval, payers should use the FDA label as the guide to coverage policy and engage clinical experts and diverse patient representatives in considering how to address coverage issues for which there is limited or no evidence at the current time.

Given the significant uncertainty that remains about the long-term effectiveness of KarXT, and its presumed high cost in relation to available generic treatment options, it is reasonable for payers to use limited prior authorization as a component of coverage. Prior authorization criteria should be based on the FDA label, clinical evidence, specialty society guidelines, and input from clinical experts and patient groups. The process for authorization should also be clear, accessible, efficient, and timely for providers. It should be fully compliant with the January 17, 2024 Centers for Medicare and Medicaid Services (CMS) Interoperability and Prior Authorization Final Rule.

We heard that prior authorization serves as a deterrent for patients in rural areas who often travel long distances to visit a pharmacy. If they are unable to pick up their prescription due to prior authorization delays, they may be less likely to come in to pick up prescriptions in the future.

Coverage Criteria: General

ICER has previously described general criteria for fair coverage policies that should be considered as cornerstones of any drug coverage policy: Cornerstones of 'fair' drug coverage: appropriate cost sharing and utilization management policies for pharmaceuticals.

Coverage Criteria: General

Drug-Specific Coverage Criteria: KarXT

Many people living with schizophrenia have suboptimal control of their symptoms with current therapies and / or experience intolerable side effects. KarXT, with its novel mechanism of action offers hope to these patients. However, lack of long-term data, the potential for side effects, and the expected high annual price for KarXT compared to current generic antipsychotic therapies, will likely lead many payers to develop prior authorization criteria or step therapy criteria for KarXT.

None of these utilization management tools, however, should undermine the tenets of fair access to which all patients have a fundamental right. To explore the appropriate application of evidence to coverage policy, and to reflect the views of patient experts and clinicians on specific ways that payers might appropriately use coverage policy to manage resources prudently, we present the following perspectives on specific elements of cost sharing and coverage criteria for KarXT.

Coverage Criteria

- **Age:** The clinical trials of KarXT enrolled patients ages 18 to 65 years. There is no *a priori* reason to exclude patients over the age of 65 years, though they may be at higher risk for side effects from KarXT. However, it would be reasonable to restrict the use of KarXT to adults until studies have demonstrated the efficacy and safety of KarXT in adolescents.

- **Clinical eligibility**: Patients should have a documented diagnosis of schizophrenia. Although the clinical trials of KarXT were restricted to patients with a diagnosis of schizophrenia hospitalized for acute exacerbation of psychotic symptoms, clinicians will not stop therapy as patients transition back to the outpatient setting. Therefore, KarXT use should not be limited to the inpatient setting and will likely be initiated for many patients in the outpatient setting. Some payers may choose to include wording in clinical criteria that patients started on KarXT in the inpatient setting will be allowed to continue therapy.

  KarXT should not be used in combination with other antipsychotic medications at this time due to the risk for additive anti-cholinergic side effects and unknown efficacy. However, coverage criteria should be rapidly updated once data from the 4ARISE trial studying KarXT as an adjunct treatment are available.

- **Exclusion criteria**: Payers are likely to include many if not all the exclusion criteria from the clinical trials to ensure that patients are not at significant risk of serious side effects.

    - Patients who are pregnant or lactating or planning to become pregnant
    - Patients with significant liver disease
    - Patients at high risk for urinary retention, gastric retention, or acute angle glaucoma

- **Dose:** Dosing of KarXT is typically initiated at 50 mg xanomeline plus 20 mg trospium twice daily for two days and then increased to 100 mg xanomeline plus 20 mg trospium. If there is an inadequate clinical response after 7 days, the dose may be increased to 125 mg xanomeline and 30 mg trospium. Dose reductions may be required based on side effects.

- **Duration of coverage and renewal criteria**: No coverage limits or renewal criteria are needed.

- **Provider restrictions**: Schizophrenia is a serious illness and, in the ideal world, initial drug treatment should be managed by psychiatrists. KarXT can have significant side effects that require expertise in management. Specialty clinicians are better suited to identify patients

who are most likely to benefit, provide sufficient information for patients to make a well-informed decision, and monitor for response and side effects. However, given the current provider shortage of psychiatrists, payers should consider allowing all providers to prescribe KarXT if they indicate that they are in consultation with a psychiatrist or a Board-certified psychiatric pharmacist. In general, generalist physicians do not initiate new treatments for patients with schizophrenia, though they may assume the responsibility for routine refilling of prescriptions once a patient is on stable therapy.

Step Therapy for Initial Treatment

Payers should only require step therapy for KarXT when it provides adequate flexibility to meet the needs of diverse patients and when implementation can meet high standards of transparency and efficiency.

Clinical experts and patient representatives stated that delayed and restricted access to treatment due to step therapy requirements for patients with schizophrenia is common. While it is possible to tailor step therapy in a clinically responsible fashion, it is often administered with documentation burdens and inadequate procedures for exceptions that make step therapy a source of great frustration and the cause of poor outcomes for some patients, including poor adherence. That said, the studies of KarXT excluded patients who had never received treatment for schizophrenia, and there are more than 20 drugs with FDA approval for the treatment of schizophrenia, most of which are generic. These treatments have many years of safety data available, and their risks are well understood. Thus, clinical experts felt it would not be unreasonable for payers to require at least one therapeutic trial of a second generation antipsychotic drug at adequate dosing and duration prior to covering KarXT to treat patients living with schizophrenia. If patients do not receive adequate benefit, and/or if they experience significant weight gain or have other adverse effects from initial treatment, KarXT would be a reasonable second or third-line agent.

If long-term studies confirm that KarXT has equivalent efficacy to second generation antipsychotics without the weight gain and metabolic side effects common to existing treatments, payers should consider moving KarXT to a preferred position on their formulary if the drug is priced within reasonable cost-effectiveness ranges, even if that price is higher than the price for generic treatment options. In particular, patients with pre-existing diabetes or cardiovascular disease should be able to bypass any step therapy should long-term studies confirm the safety of KarXT.

Manufacturers

Recommendation

Manufacturers should set prices that will foster affordability and good access for all patients by aligning prices with the patient-centered therapeutic value of their treatments. In the setting of KarXT for people living with schizophrenia, while there is considerable hope associated with the promise of the drug, there also remains substantial uncertainty regarding its longer-term safety and effectiveness. Launch pricing should reflect these considerations.

Drug prices that are set well beyond the cost-effective range cause not only financial toxicity for patients and families using the treatments, but also contribute to general health care cost growth that pushes families out of the insurance pool, and that causes others to ration their own care in ways that can be harmful.

Manufacturers should therefore price novel treatments in accordance with the demonstrated benefits to patients. In settings of substantial uncertainty, initial pricing should err on the side of being more affordable. This would allow more patients access, generating additional data on the real-world effectiveness of novel treatments that could be used in future assessment updates. With accumulation of evidence of substantial patient benefit, manufacturers should be allowed to increase pricing in accordance with benefit. This is particularly true for KarXT, which has only been studied in five-week trials, but may be used by patients for decades.

Researchers/Regulators

Recommendation

Conduct research that directly compares real-world treatment options and engages patients at the beginning of the study design phase.

The FDA requirement of five-week placebo controlled trials for approval is inadequate. Multiple stakeholders expressed concerns about the lack of information directly comparing new treatments and the need for active comparator trials. Since manufacturers have little incentive to conduct head-to-head trials, federal agencies (PCORI, NIMH) should work with patients and clinical researchers to design and fund be head-to-head trials of drugs to treat schizophrenia, including KarXT. Patients and caregivers should be engaged at the earliest stages of research to ensure optimal study design in terms of target populations, comparators, and outcome measures that matter to patients. Appropriate head-to-head trials with follow-up of at least 12 months would help to inform decision making by patients and clinicians.

The NIH should increase funding for basic and translational research focused on schizophrenia.

NIH funding for schizophrenia has been steady since about 2008, while funding for other neurologic disorders has increased substantially. Given the tremendous economic costs to society from schizophrenia, more research dollars should be allocated to promising approaches to prevent, diagnose, and treat the disease.

Appendix

Appendix Tables 1-3 contain conflict of interest (COI) disclosures for all participants at the February 9th, 2024 Public meeting of KarXT for Schizophrenia.

Appendix Table 1: ICER Staff and Consultants and COI Disclosures

ICER Staff and Consultants*	
Sarah Emond, MPP, President and CEO, ICER	**Grace Ham, BS**, Program and Events Coordinator, ICER
Yamaya Jean, MA, Program Manager, ICER	**Avery McKenna, BS**, Research Lead, ICER
Becca Piltch, MPP, Program Manager, ICER	**Steven Pearson, MD, MSc**, Special Advisor, ICER
Finn Raymond, BS, Research Assistant, ICER	**David Rind, MD, MSc**, Chief Medical Officer, ICER
Jeff Tice, MD, Professor of Medicine, University of California, San Francisco	**Mel Whittington, PhD, MS**, Senior Fellow Center for the Evaluation of Value and Risk in Health (CEVR), Tufts Medical Center
Abigail Wright, PhD, MSc, Research Lead, 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. New England CEPAC Panel Member Participants and COI Disclosures

Participating Members of New England CEPAC*	
Rob Aseltine, PhD, Professor and Chair, UConn Health	**Marthe Gold, MD, MPH,** Senior Research Scholar, New York Academy of Medicine
Megan Golden, JD, CEO, Mission: Cure	**Rebecca Kirch, JD**, EVP Policy and Programs, National Patient Advocate Foundation
Stephen Kogut, PhD, MBA, RPh, Professor of Pharmacy Practice, University of Rhode Island College of Pharmacy	**Donald Kreis, MS, JD**, Patient Advocate, New Hampshire Office of the Consumer Advocate
Tara Lavelle, PhD, Assistant Professor, Tufts Medical Center	**Stephanie Nichols, PharmD, MPH, BCPP, FCCP**, Associate Professor, University of New England
Brian O'Sullivan, MD, Professor of Pediatrics, Geisel School of Medicine, Dartmouth	**Jeanne Ryer, MSc, EdD,** Director, NH Citizens Health Initiative
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*No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Appendix Table 3. Policy Roundtable Participants and COI Disclosures

Policy Roundtable Participant	**Conflict of Interest**
Kristin Khalaf Gillard, PharmD, PhD, Executive Director, Health economics and outcomes research, Karuna Therapeutics	*Dr. Gillard is a full-time employee of Karuna Therapeutics.*

Tony Grillo, PharmD, Vice President, Express Scripts	*Dr. Grillo is a full-time employee of Express Scripts.*
Steven Lamberti, MD, Professor of Psychiatry, University of Rochester Medical Center	*No conflicts to disclose.*
Arundati Nagendra, PhD, Director of Research and Scientific Affairs, Schizophrenia & Psychosis Action Alliance	*S&PAA receives <25% funding from healthcare companies, including from Karuna Therapeutics.*
Marc Pomper, Caregiver	*No conflicts to disclose.*
Marina Sehman, PharmD, CSP, Director, Clinical Pharmacy, IPD Analytics	*Dr. Sehman is a full-time employee of IPD Analytics.*
Vinod Srihari, MD, Professor of Psychiatry; Director, Specialized Treatment Early in Psychosis Program, Yale School of Medicine	*No conflicts to disclose.*