KEY FINDINGS

Intervention	Evidence Rating	Annual WAC	Health-Benefit Price Benchmark	Change from Annual Price to Reach Threshold Price
Xanomeline-trospium chloride (KarXT, Karuna Therapeutics)	When compared to no antipsychotic therapy, olanzapine, or risperidone: Promising, but inconclusive (P/I) When compared to aripiprazole: Insufficient (I)	Placeholder price: $20,000	$16,000 to $20,000 per year	N/A

"Schizophrenia is a serious mental illness that affects how a person thinks, feels, and behaves. Among the important side effects of current treatments is weight gain leading to metabolic syndrome. This, in turn, places patients at risk for cardiovascular events and death. KarXT has a novel mechanism of action and, at least in the short run, does not seem to cause weight gain. This may lead to major health benefits compared with existing treatments, however current evidence on benefits and harms is limited."

– ICER's Chief Medical Officer David Rind, MD

THEMES AND RECOMMENDATIONS

- 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.
- 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.
- 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.

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Clinical Analyses

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

Schizophrenia is a serious mental illness that affects how a person thinks, feels, and behaves. The symptoms are typically separated into three general categories: positive symptoms (delusions, hallucinations, disorganized speech, thought and behavior); negative symptoms (poor motivation, lack of pleasure and enjoyment, lack of speech, lack of social interaction), and cognitive (impaired executive function, attention, and memory). The underlying cause of schizophrenia is unknown, but it is thought to be a neurodevelopmental brain disorder influenced by genetic and environmental factors.

Researchers estimate that schizophrenia affects about 3.9 million people in the United States (US) and 24 million people worldwide. Black Americans are diagnosed with schizophrenia at about twice the rate of White Americans and have worse outcomes. The annual economic burden is estimated to be approximately $343 billion in the United States alone. The majority of these costs are societal, not medical.

Most pharmacological therapies for patients with schizophrenia (first and second generation antipsychotics) block the dopamine D2 receptor thought to target positive symptoms. In addition, the newer atypical antipsychotic medications also modulate serotonin levels. Current guidelines recommend psychosocial interventions in addition to pharmacological therapy in order to target negative and cognitive symptoms. These may include cognitive behavioral therapy, supported employment services, self-management skills training, cognitive remediation, and others.

KarXT (Karuna Therapeutics) is an oral therapy taken twice daily. It combines one drug (xanomeline) that targets central nervous system (CNS) muscarinic receptors (M1 and M4 receptor agonists) with a second drug (trospium) that reduces the peripheral side effects of muscarinic receptor activation. Karuna Therapeutics submitted a new drug application (NDA) for KarXT on September 28, 2023.

In meta-analyses of the three placebo-controlled randomized trials, KarXT significantly improved the total Positive and Negative Syndrome Scale (PANSS) score and the proportion of patients with at least a 30% improvement in the PANSS score over five weeks in patients hospitalized for schizophrenia. There were no differences in weight gain or discontinuation rates between KarXT and placebo.

As there were no head-to-head trials with other antipsychotic medications, we performed network meta-analyses with acute, short-term trials of three commonly used second-generation antipsychotic medications (aripiprazole, olanzapine, risperidone). There were no significant differences between KarXT and the three antipsychotics in change from baseline PANSS score or the percentage of patients with at least a 30% improvement in PANSS score. There was less weight gain for KarXT compared to olanzapine and risperidone, but not with aripiprazole. Similarly, KarXT was significantly more likely to be discontinued in the acute setting compared with olanzapine and risperidone, but not with aripiprazole.

The major source of uncertainty is the lack of data on the efficacy of KarXT for longer than five weeks. In addition, KarXT has a new mechanism of action, which may lead to unanticipated adverse events over the long run. The initial data suggest that weight gain may not be an important side effect of KarXT, but this needs to be confirmed over time. Similarly, we have no data on the incidence of tardive dyskinesia and other long-term movement disorder side effects. The hope is that KarXT will represent a safer and effective

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Clinical Analyses

therapy for long-term maintenance of patients living with schizophrenia, but we have no data yet on the prevention of relapse, return to work and school, or improvements in relationships with friends and family.

For the evidence ratings, we assumed that KarXT will be used for maintenance therapy in patients who respond to KarXT in the acute setting. The patients in the EMERGENT trials were not considered to have treatment-resistant schizophrenia, so patients will have additional therapeutic options available.

KarXT significantly improved the total PANSS score and the proportion of patients with a response compared with placebo in the acute setting. KarXT side effects generally were those anticipated given the mechanisms of action of its two component medications. Importantly, we have no data on the efficacy and side effect profile of KarXT beyond five weeks. Given the lack of data on the long-term benefits and harms of KarXT, which has a novel mechanism of action and thus the possibility of unanticipated long term adverse events, we rate the net health benefit of KarXT as promising, but inconclusive (P/I) compared with no therapy.

Treatment with second-generation antipsychotics can result in serious long-term adverse effects including metabolic syndrome and tardive dyskinesia. A safer antipsychotic may be preferable to use initially even if it has lower efficacy; this is seen in practice where patients are frequently only treated with clozapine after they have not received benefit from other less effective antipsychotic medications. Our evidence ratings below take into account choices between KarXT and other antipsychotics where those same antipsychotics could be used as later line therapy if KarXT is insufficiently effective or causes significant side effects.

There are no trials directly comparing KarXT with aripiprazole. In our indirect comparisons in the acute setting, there were no significant differences between the two therapies in change in PANSS, PANSS response, weight gain, or discontinuation rates. However, we have no data on the efficacy and side effect profile of KarXT beyond five weeks in the hospital for the treatment of an acute exacerbation. Given no evidence for superiority in the acute setting and the lack of long-term data, we find the evidence to be insufficient (I) to judge the comparative clinical effectiveness of KarXT compared with aripiprazole.

There are no trials directly comparing KarXT with olanzapine or risperidone. In our indirect comparisons in the acute setting, there were no significant differences between KarXT and these two therapies in change in PANSS, PANSS response, or discontinuation rates. KarXT was associated with significantly lower weight gain, which may translate into fewer cases of metabolic syndrome, diabetes, and their cardiovascular complications over the longer term. However, we have no data on the efficacy and side effect profile of KarXT beyond five weeks in the hospital for the treatment of an acute exacerbation. Given the lack of long-term data, we rate the net health benefit of KarXT as promising, but inconclusive (P/I) compared with both olanzapine and risperidone.

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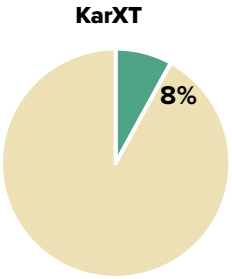
Economic Analyses

LONG-TERM COST EFFECTIVENESS

Making the highly favorable assumption that KarXT does not increase the risk of metabolic syndrome and associated consequences beyond that seen in the general population, our analyses suggest that treatment with KarXT results in less time with diabetes and in greater QALYs, greater life years, and greater evLYs. Under this assumption, the health benefit price benchmark (HBPB) range for KarXT is between $16,000 and $20,000 per year. The HBPB range for KarXT would be lower if KarXT is found to be associated with a risk of metabolic syndrome. In contrast, we assumed no reduction in the risk of tardive dyskinesia with KarXT compared with other second-generation antipsychotic medications. If KarXT does not cause tardive dyskinesia, its HBPB range would increase.

POTENTIAL BUDGET IMPACT

At the placeholder price of $20,000 per year, approximately 8% of adults living with schizophrenia who are eligible for treatment could be treated with KarXT without crossing the ICER potential budget impact threshold of $735 million per year.



Percent of eligible patients with schizophrenia that could be treated in a given year before crossing the ICER potential budget impact threshold

Public Meeting Deliberations

VOTING RESULTS

ICER assessed, and the independent appraisal committee voted on, the evidence of KarXT for adults with an established diagnosis of schizophrenia who are not considered to have treatment-resistant schizophrenia:

- A majority of panelists (10-2) found that current evidence is **not adequate** to demonstrate a net health benefit for KarXT when compared to aripiprazole.
- A slight majority of panelists (7-5) found that current evidence is **adequate** to demonstrate a net health benefit for KarXT when compared to olanzapine and/or risperidone.

Panel members also weighed potential benefits and disadvantages beyond the direct health effects and broader contextual considerations. Voting highlighted the following as particularly important for payers and other policymakers to note:

- Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability;
- Magnitude of the lifetime impact on individual patients of schizophrenia.

Consistent with ICER's process, because there is no firm estimate yet of a potential launch price for the treatment, the panel did not take separate votes on the treatment's long-term value for money.

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About ICER

The Institute for Clinical and Economic Review (ICER) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) and the New England Comparative Effectiveness Public Advisory Council (New England CEPAC). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care.

For more information about ICER, please visit ICER's website (www.icer.org).

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