Xanomeline-Trospium Chloride (COBENFY)
National Drug Monograph
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VA Pharmacy Benefits Management Services and VA National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Xanomeline-trospium (KarXT) combines xanomeline, a dual muscarinic (M1) and (M4) receptor agonist, with a peripherally restricted muscarinic receptor antagonist, trospium, that reduces the peripheral side effects of muscarinic receptor activation.

Indication(s) Under Review in This Document

- Xanomeline-trospium is indicated for the treatment of schizophrenia

Dosage Form(s) Under Review

- Capsules: 50mg/20mg, 100mg/20mg, 125mg/30mg

Clinical Evidence Summary

Efficacy Considerations [1-5]

- The efficacy of KarXT, supporting its FDA approval, was evaluated from industry-sponsored studies, including a double-blind phase 2 trial (Brannan et al 2021, NCT 03697252, EMERGENT-1), and two randomized, double-blind, placebo-controlled, 5-week, inpatient, phase 3 trials in people with schizophrenia (Study 1, Kaul et al 2024, NCT04659161, EMERGENT-2 and Study 2, Kaul et al 2024, NCT04738123, EMERGENT-3).
- Participants were adults aged 18–65 years with a diagnosis of schizophrenia who had a recent worsening of psychosis warranting hospital admission, a Positive and Negative Syndrome Scale (PANSS) score of 80 or higher, and a Clinical Global Impression-Severity score of 4 or higher.
- Participants were randomly assigned (1:1) to KarXT or placebo twice per day. Participants randomly assigned to KarXT received 50 mg xanomeline and 20 mg trospium twice per day for the first 2 days and then 100 mg xanomeline and 20 mg trospium twice per day for days 3–7. Beginning on day 8, KarXT dosing was flexible with an optional increase to 125 mg xanomeline and 30 mg trospium twice per day and the option to return to 100 mg xanomeline and 20 mg trospium based on tolerability.
- The primary endpoint was the change from baseline to week 5 in the PANSS total score.

- Study participants had a mean age of approximately 44 years, were primarily male and had a mean baseline PANSS total score of approximately 98 (markedly ill). (Table 1)
- The PANSS is a clinician administered 30 item, gold standard rating scale used for measuring symptom severity of patients with schizophrenia. Single items of the PANSS are rated on a 7-point scale (1=absent, and 7=extreme). Thus, the range of possible PANSS total scores is from 30 to 210. The minimum clinically important difference (MCID) for the PANSS is approximately 15 points.[6]
- The mean change from baseline to week 5 in EMERGENT-2 and EMERGENT-3 PANSS total score favored KarXT with least squares mean difference of -9.6 and -8.4 respectively, primarily driven by reduction in positive symptoms. Subjects receiving KarXT were also more likely to be PANSS responders (Table 2).
- KarXT was not associated with weight gain compared with placebo and the incidence of extrapyramidal symptoms were low and similar between treatment groups. KarXT was associated with an increase from baseline in supine heart rate compared to placebo.

Table 1. Baseline Characteristics of Study Participants [3,4]

Study		**EMERGENT-2**		**EMERGENT-3**	
Duration (weeks)		5		5	
Arms		KarXT	Placebo	KarXT	Placebo
N		126	126	125	131
Age, mean (SD)		45.6 (10.4)	46.2 (10.8)	43.6 (11.4)	42.6 (12.2)
Sex, n (%)	**Male**	95 (75)	95 (75)	87 (70)	104 (79)
	Female	31 (25)	31 (25)	38 (30)	27 (21)
Race, n (%)	**Asian**	2 (2)	1 (1)	1 (1)	0
	Black	97 (77)	92 (73)	79 (63)	77 (59)
	White	26 (21)	35 (25)	45 (36)	53 (40)
	Other	1 (1)	2 (2)	0	1 (1)
Baseline PANSS, mean (SD)		98.3 (8.9)	97.9 (9.7)	97.3 (8.9)	96.7 (8.9)

n: number, N: total number, PANSS: positive and negative syndrome scale, SD: standard deviation

Table 2. Primary Endpoint – Change from baseline to week 5 in PANSS [3,4]

EMERGENT-2	**KarXT (n=117)**	**Placebo (n=119)**
Baseline PANSS total score, mean (SD)	98.3 (8.9)	97.9 (9.7)
LS Mean change from Baseline (SE)	- 21.2 (1.7)	- 11.6 (1.6)
Adjusted mean difference vs placebo (95% CI)	**- 9.6 (-13.9 to -5.2)**	-
p-value vs. placebo	<0.0001	-
Cohen's d	0.61	-

PANSS responders (≥30% reduction from baseline in PANSS total score	51/93 (55%)	28/99 (28%)
Adjusted mean difference vs placebo (95% CI)	27% (13 to 39)	-
p-value	<0.0001	-
EMERGENT-3	**KarXT (n=114)**	**Placebo (n=120)**
Baseline PANSS total score, mean (SD)	97.3 (8.9)	96.7 (8.9)
LS Mean change from Baseline (SE)	- 20.6 (1.6)	-12.2 (1.6)
Adjusted mean difference vs placebo (95% CI)	**-8.4 (-12.4 to -4.3)**	-
p-value vs. placebo	<0.001	
Cohen's d	0.60	-
PANSS responders (≥30% reduction from baseline in PANSS total score	40/79 (51%)	23/91 (25%)
Adjusted mean difference vs placebo (95% CI)	25% (10.8 to 38.6)	
p-value	P=0.006	
Minimal clinically important difference for PANSS change	**15 points**	

CI: confidence interval; LS: least squares; n: number; N: total number; PANSS: positive and negative syndrome scale; SD: standard deviation; SE: standard error

Safety Considerations[1]

Contraindications:

- Urinary retention
- Moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment
- Gastric retention
- History or hypersensitivity to KarXT or trospium
- Untreated narrow-angle glaucoma

Table 3. Adverse Reactions in >2% of participants (EMERGENT-2)[3]

	KarXT N=126 (%)	Placebo N=125 (%)
Constipation	21	10
Dyspepsia	19	8
Headache	14	12
Nausea	19	6
Vomiting	14	1
Hypertension	10	1
Dizziness	9	3
GERD	6	0
Diarrhea	6	3

Table 4. Adverse Reactions with >2% of participants (EMERGENT-3)[4]

	KarXT N=125 (%)	Placebo N=128 (%)
Nausea	19	2
Dyspepsia	16	2
Vomiting	16	1
Constipation	13	4
Headache	11	12
Hypertension	6	2
Insomnia	6	8
Diarrhea	6	1

Other warnings and precautions[1]

- Risk of urinary retention
- Risk of use in patients with hepatic impairment **(not recommended in patients with mild hepatic impairment, Child-Pugh Class A)**
- Risk of use in patients with biliary disease
- Decreased gastrointestinal motility
- Risk of angioedema
- Risk of use in patients with narrow-angle glaucoma
- Increases in heart rate
- Anticholinergic adverse reaction in patients with renal impairment (**not recommended for use in patients with moderate and severe renal impairment, eGFR <60ml/min)**
- Central nervous system effects

Required pre-prescribing assessment[1]

- Assess liver enzymes and bilirubin prior to initiation
- Assess heart rate at baseline

Other Therapeutic Options

Table 5.

Drug	Formulary status	Clinical Guidance/ Indication	Other Considerations
Xanomeline-trospium	NF/TBD	Schizophrenia	GI side effects, hypertension/increased heart rate
Aripiprazole	F	Autism, Bipolar d/o, Tourette's, MDD, Schizophrenia	Akathisia
Olanzapine	F	Agitation, Bipolar d/o, MDD, Schizophrenia	Sedation, weight gain
Quetiapine	F	Bipolar d/o, MDD, Schizophrenia	Sedation, weight gain
Risperidone	F	Autism, Bipolar d/o, Schizophrenia	Extrapyramidal symptoms (EPS)
Ziprasidone	F	Bipolar d/o, Schizophrenia	Akathisia

Projected Place in Therapy

- Schizophrenia is a neurodevelopmental disorder producing deficits in perceptual, motor, cognitive and emotional functioning. The prevalence of schizophrenia is estimated at 1% of the U.S. population.
- Xanomeline-trospium possesses a unique mechanism of action. It combines xanomeline, a dual muscarinic (M1) and (M4) receptor agonist with a peripherally restricted muscarinic receptor antagonist, trospium, that reduces the peripheral side effects of muscarinic receptor activation. This mechanism appears to minimize the risk of neurologic (extrapyramidal) and metabolic (weight gain) adverse effects associated with other antipsychotics while increasing the risk of GI (N,V, constipation) adverse effects. However, extrapyramidal side effects (e.g., tardive dyskinesia) and weight gain may appear outside of a controlled inpatient setting with continued use beyond the 5-week study duration.
- Evidence from EMERGENT-2 and EMERGENT-3 suggest that individuals with schizophrenia may benefit from xanomeline-trospium. However, the trials were short (5 weeks), limiting knowledge of long-term efficacy and safety. Two ongoing 52-week trails of KarXT (EMERGENT-4 and EMERGENT-5) will better characterize its long-term safety and tolerability profile in individuals with schizophrenia when published.
- There were no head-to-head trials with other antipsychotics. The Institute for Clinical and Economic Review (ICER) performed a network meta-analysis with acute trials of aripiprazole, olanzapine, and risperidone. They found 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. ICER rated the net health benefit of KarXT as promising, but inclusive compared to placebo.

- Antipsychotics are the primary class of medications used in the management of schizophrenia, the choice of which is based on an individualized evaluation that considers patient characteristics and side effect profiles of the different antipsychotic medications.[7]

References

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