# Health Technology Briefing
# October 2025

# Xanomeline tartrate-trospium chloride for treating schizophrenia

| Company/Developer | Bristol Myers Squibb Pharmaceuticals Ltd. |
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☒ New Active Substance ☐ Significant Licence Extension (SLE)

| NIHRIO ID: 27099 | NICE ID: Not available | UKPS ID: 675153 |
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## Licensing and Market Availability Plans

Currently in phase III clinical development

## Summary

Xanomeline tartrate-trospium chloride is a fixed-dose combination in development for the treatment of schizophrenia. Schizophrenia is a long-term serious mental health condition where people may see, hear or believe things that are not real. This means that a person may not always be able to distinguish their own thoughts and ideas from reality. The symptoms of schizophrenia are divided into positive symptoms (such as hallucinations and delusions) and negative symptoms (such as lack of emotion, lack of drive, poor speech, social withdrawal and self-neglect). Schizophrenia is usually treated with a combination of medicine and other kinds of support tailored to each individual. Most medicines used today treat positive symptoms like hearing voices or seeing things that aren't there. Whilst these medicines can help, they can cause serious side effects and don't improve negative symptoms. Some people experience movement issues, tiredness, restlessness, or weight gain, which can raise the risk of diabetes or heart disease.

Xanomeline tartrate-trospium chloride is a combination of two medicine given orally as a single capsule. Xanomeline tartrate reduces schizophrenia symptoms and trospium chloride helps counter side effects caused by xanomeline. It works in a way that can improve both negative and positive symptoms, as well as improve memory or concentration problems. If approved xanomeline tartrate-trospium chloride will provide a novel treatment option for patients with schizophrenia.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.
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## Proposed Indication

For treatment of adult patients with schizophrenia.[1,2]

## Technology

### Description

Xanomeline tartrate-trospium chloride (Cobenfy, KarXT) is a fixed-dose combination that combines xanomeline tartrate, a muscarinic receptor subtypes M1 and M4 agonist, with trospium chloride, a nonselective antimuscarinic antagonist that targets M2 and M3 muscarinic receptor subtypes.[3] Xanomeline does not directly affect dopamine receptors, but primarily stimulates M1 and M4 muscarinic cholinergic receptors.[4] Trospium chloride is unable to cross the blood-brain barrier and works by antagonising muscarinic receptors primarily in peripheral tissues, which helps to reduce cholinergic adverse effects associated with xanomeline that may limit tolerability.[5,6]

In phase III trial (NCT04659161) participants received oral xanomeline 50 mg-trospium chloride 20 mg BID (twice a day) for the first 2 days followed by xanomeline 100 mg-trospium 20 mg BID for the remainder of week 1 . At day 8, dosing was to be titrated upwards to xanomeline 125 mg-trospium 30 mg BID, unless the subject was continuing to experience adverse events from the previous dose of 100mg/20mg BID.[2]

### Key Innovation

Xanomeline-trospium is a potent agonist of muscarinic $M_1/M_4$ receptors and exhibits no direct dopamine $D_2$ receptor activity.[7] Standard schizophrenia treatment involves antipsychotic medications that target $D_2$ dopamine receptors. However, these drugs have limitations in addressing all symptoms and can lead to adverse effects such as motor impairments, metabolic effects, sedation, sexual dysfunction, cognitive impairment, and tardive dyskinesia.[3] Xanomeline alone is poorly tolerated because of severe cholinergic side-effects. However, the combination of xanomeline and trospium, that does not cross the blood–brain barrier, appears to reduce antipsychotic symptoms and have better tolerability.[8] Coadministration of trospium and xanomeline is believed to block the unwanted peripheral cholinergic side effects of xanomeline. Indeed, the combination appears to be associated with a 50% reduction of cholinergic side effects in healthy volunteers.[9-11] Xanomeline can readily cross blood–brain barrier and, thus, enters the brain, thereby stimulating muscarinic receptors (M1 and M4). By doing so, xanomeline has been shown to target negative symptoms and potentially improve positive symptoms.[3] If licensed, xanomeline-trospium chloride will provide a novel treatment option for patients with schizophrenia.

### Regulatory & Development Status

Xanomeline tartrate-trospium chloride does not currently have a Marketing Authorisation in the UK.

Xanomeline tartrate-trospium chloride is also currently in phase III development for the treatment of psychosis associated with Alzheimer's disease.[12]

## Patient Group

### Disease Area and Clinical Need

Schizophrenia is a severe mental disorder characterised by positive (delusions, hallucinations, thought disorganisation) and negative (alogia, social withdrawal, blunted affect) symptoms, which are associated

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with severe functional impairment.[13] The exact cause of schizophrenia is unknown. But most experts believe the condition is caused by a combination of genetic and environmental factors.[14] People with schizophrenia are more likely to be unemployed, homeless, living in poverty, having difficulties keeping up with household and self-care tasks, and relying on ongoing support from family carers and available mental health services.[15] Schizophrenia usually starts in late adolescence and early adulthood but can begin in early adolescence, although rarely before the age of 10.[16]

The estimated prevalence across all ages and populations in the UK is 0.7%. In the UK the lifetime prevalence of schizophrenia and schizophrenia-related disorders is approximately 14.5 per 1000 people, although there is considerable variation between estimates.[16] Patients with schizophrenia have a higher mortality than the general population due to physical illness (including cardiovascular diseases and cancers), accidents, and suicide.[17] In England (2023-24) there were 8,360 finished consultant episodes (FCEs) and 4,889 admissions for schizophrenia (ICD-10 code F20), which resulted in 584,127 FCE bed days and 42 FCE day cases.[18]

| Recommended Treatment Options |
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| The National Institute for Health and Care Excellence (NICE) recommends the use of antipsychotic medication (e.g. clozapine, aripiprazole) as pharmacological treatment options for adults with schizophrenia.[19] |

## Clinical Trial Information

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| Trial | NCT04820309; **EMERGENT-5;** An open-label study to assess the long-term safety, tolerability, and efficacy of KarXT in De Novo subjects with DSM-5 schizophrenia<br>**Phase III:** Completed<br>**Locations:** USA<br>**Primary completion date:** May 2024 |
| Trial Design | Non-randomised, open label, single group assignment |
| Population | N=568 (actual); adult participants with schizophrenia |
| Intervention(s) | Xanomeline-trospium chloride capsules |
| Comparator(s) | None |
| Outcome(s) | Primary outcome measure:<br>• Incidence of treatment-emergent adverse events (TEAEs) from initial dose through 7 days after the final dose (up to 53 weeks)<br>See trial record for other outcomes |
| Results (efficacy) | Treatment with xanomeline-trospium chloride led to improvements in symptoms of schizophrenia across all efficacy measures, including Positive and Negative Syndrome Scale (PANSS) total, Clinical Global Impression-Severity (CGI-S), PANSS positive subscale and PANSS negative subscale scores at 52 weeks. At week 52, 30% of participants had a ≥30% reduction from baseline in the PANSS total score, with an average reduction of -5.5 points from baseline.[20] |
| Results (safety) | Long-term treatment with xanomeline-trospium chloride was generally well tolerated, with no new safety or tolerability issues emerging. The most common |

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| | treatment-emergent adverse events (TEAEs) were nausea, vomiting, constipation, dry mouth, diarrhoea, dyspepsia, dizziness, hypertension and somnolence.[20] |

| Clinical Trial Information | |
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| Trial | NCT04659174; **EMERGENT-4**; An Open-label extension study to assess the long-term safety, tolerability, and efficacy of KarXT in subjects with DSM-5 schizophrenia<br>**Phase III:** Completed<br>**Locations:** USA and Ukraine<br>**Primary completion date:** October 2023 |
| Trial Design | Non-randomised, open label, single group assignment |
| Population | N=152 (actual); adult participants with schizophrenia |
| Intervention(s) | Xanomeline-trospium chloride capsules |
| Comparator(s) | None |
| Outcome(s) | Primary outcome measure:<br>• Number of participants with TEAEs from first dose to end of study (up to approximately 53 weeks)<br>See trial record for other outcomes |
| Results (efficacy) | Treatment with xanomeline-trospium chloride led to continued improvements in symptoms of schizophrenia across all efficacy measures, including the PANSS total, CGI-S, PANSS positive subscale and PANSS negative subscale scores over 52 weeks.[20] |
| Results (safety) | Long-term treatment with xanomeline-trospium chloride was generally well-tolerated, with no new safety or tolerability issues identified. The most common TEAEs were nausea, vomiting, dyspepsia, dry mouth and hypertension.[20] |

| Clinical Trial Information | |
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| Trial | NCT04738123; **EMERGENT-3**; A Phase 3, randomized, double-blind, parallel-group, placebo-controlled, multicentre study to evaluate the efficacy and safety of KarXT in acutely psychotic hospitalised adults with DSM-5 schizophrenia<br>**Phase III:** Completed<br>**Locations:** USA and Ukraine<br>**Primary completion date**: December 2022 |
| Trial Design | Randomised, placebo-controlled, triple masked, parallel assignment |
| Population | N=256 (actual); adult participants with schizophrenia |
| Intervention(s) | Xanomeline-trospium chloride capsules |
| Comparator(s) | Matched placebo |
| Outcome(s) | Primary outcome measure: |

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| | • Change from baseline in PANSS Total Score at week 5<br>See trial record for other outcomes |
| Results (efficacy) | Xanomeline-trospium chloride was associated with significantly greater improvement from baseline to week 5 in PANSS-EC scores compared with placebo across all 3 EMERGENT trials, along with significantly greater improvement in the PANSS total scores in all 3 trials.[21] |
| Results (safety) | Xanomeline-trospium chloride was generally well tolerated. In the pooled analyses, a total of 51.8% and 29.4% of participants in the xanomeline-trospium and placebo arms, respectively, experienced ≥1 treatment-related adverse event.[21] |

| Clinical Trial Information | |
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| Trial | NCT04659161; **EMERGENT-2;** A Phase 3, randomised, double-blind, parallel-group, placebo-controlled, multicentre study to evaluate the efficacy and safety of KarXT in acutely psychotic hospitalised adults with DSM-5 schizophrenia<br>**Phase III:** Completed<br>**Locations:** USA<br>**Primary completion date:** May 2022 |
| Trial Design | Randomised, placebo-controlled, triple masked, parallel assignment |
| Population | N=252 (actual); adult participants with schizophrenia |
| Intervention(s) | Xanomeline-trospium chloride capsules |
| Comparator(s) | Matched placebo |
| Outcome(s) | Primary outcome measure:<br>• Change from baseline in PANSS Total Score at week 5<br><br>See trial record for other outcomes |
| Results (efficacy) | Xanomeline-trospium chloride was effective in reducing positive and negative symptoms and was generally well tolerated. The trial met the primary endpoint with a mean change from baseline to week 5 in PANSS total score that favoured KarXT (−21·2 points, SE 1·7) versus placebo (−11·6 points, 1·6; least squares mean difference −9·6; 95% CI −13·9 to −5·2; p<0·0001, Cohen's *d* effect size=0·61).[22] |
| Results (safety) | Xanomeline-trospium showed a distinctive safety and tolerability profile and was not associated with many of the adverse events typically observed with currently approved antipsychotic drugs.[22] |

| Clinical Trial Information | |
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| Trial | NCT03697252: **EMERGENT-1;** A Phase 2, randomised, double-blinded study to assess the safety, tolerability, and efficacy of KarXT in hospitalised adults with DSM-5 schizophrenia |

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| | **Phase II:** Completed<br>**Locations:** USA<br>**Primary completion date:** September 2019 |
| Trial Design | Randomised, placebo-controlled, triple masked, parallel assignment |
| Population | N=182 (actual); aged 18 to 60 years; adult participants with schizophrenia |
| Intervention(s) | xanomeline-trospium chloride capsules |
| Comparator(s) | Matched placebo |
| Outcome(s) | Primary outcome measure:<br>• Change From Baseline in PANSS Total Score at week 5<br>See trial record for list of other outcomes |
| Results (efficacy) | In a 5-week trial, xanomeline–trospium chloride resulted in a greater decrease in the PANSS total score than placebo. The change in the PANSS total score from baseline to week 5 was −17.4 points in the xanomeline–trospium group and −5.9 points in the placebo group (least-squares mean difference, −11.6 points; 95% confidence interval [CI], −16.1 to −7.1; P<0.001).[23] |
| Results (safety) | The most common adverse events in the xanomeline–trospium chloride group were constipation (17%), nausea (17%), dry mouth (9%), dyspepsia (9%), and vomiting (9%). None of these adverse events resulted in the discontinuation of xanomeline-trospium chloride, and all were rated by site investigators as mild or moderate in severity.[23] |

## Estimated Cost

The cost of xanomeline-trospium chloride is not yet known.

## Relevant Guidance

### NICE Guidance

- NICE guideline. Rehabilitation for adults with complex psychosis. [NG181]. August 2020.
- NICE clinical guideline. Psychosis and schizophrenia in adults: prevention and management (CG178). March 2014.
- NICE Evidence summary. Schizophrenia: lurasidone. [ESNM48]. September 2014.
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- NICE Quality standard. Psychosis and schizophrenia in adults. [QS80]. February 2015.

### NHS England (Policy/Commissioning) Guidance

- NHS England. Improving the physical health of people living with severe mental illness: Guidance for integrated care systems. Publishing reference: B1955. January 2024.
- NHS England. Implementing the early intervention in psychosis access and waiting time standard. Version 3. Publication reference: PR1954. February 2023.
- NHS England. Mental Health Implementation Plan 2019/20 - 2023/24. Publishing approval reference: 000830. July 2019.

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- NHS England. Treatment of psychosis and schizophrenia algorithm. Version 2. Guideline number:
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Other Guidance

- The American Psychiatric Association. Practice guideline for the treatment of patients with schizophrenia.[24]
- Scottish Intercollegiate Guidelines Network. Management of schizophrenia. 2013.[25]

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***NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.***

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