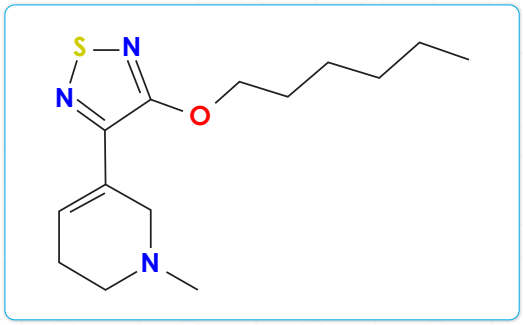
METROCHEM



XANOMELINE

3-hexoxy-4-(1-methyl-3,6-dihydro- 2H-pyridin-5-yl)-1,2,5-thiadiazole

Xanomeline-Trospium Combination: A Breakthrough in Schizophrenia Treatment

On September 26, 2024, the USFDA granted approval to the novel Xanomeline-Trospium chloride combination, branded as COBENFY, for the treatment of schizophrenia. Developed by Bristol Myers Squibb (BMS), this innovative therapy combines Xanomeline, a muscarinic agonist, with Trospium chloride, a non-CNS-penetrant muscarinic antagonist, to minimize peripheral side effects commonly associated with muscarinic activation. This document explores the pharmacological properties, development journey, regulatory milestones, and the significant market potential of this promising therapeutic option.

Epidemiology of Schizophrenia

According to estimates from the WHO, schizophrenia affects approximately 24 million people globally, equating to 1 in 300 individuals (0.32%). Among adults, this rate rises to 1 in 222 individuals (0.45%).

Mechanism of Action

Xanomeline functions as an agonist at muscarinic acetylcholine receptors (mAChR) M1 and M4. Its interaction with these receptors elevates acetylcholine levels in the striatum, resulting in decreased psychosis and enhanced cognition. However, Xanomeline's binding to peripheral muscarinic receptors, particularly M2 and M3, has been associated with several side effects. Trospium chloride addresses this challenge by binding to M2 and M3 receptors, preventing Xanomeline from binding to these peripheral receptors and thereby mitigating associated side effects.

Dosage Information

Xanomeline/Trospium chloride combination capsules are available in the following dosages:

- 50 mg/20 mg
- 100 mg/20 mg
- 125 mg/30 mg

Advancing Xanomeline: Metrochem's R&D Milestones

- Metrochem's Polymorphic Form: Xanomeline tartarate Crystalline form
- Current Status: Xanomeline feasibility completed and we have 100 gm API sample is in hand with ICH quality.
- PV & DMF timelines: PV timeline – 10th Jan'26 and DMF timeline- 15th Mar'26

Impurity Profile

Metrochem's Xanomeline API adheres to stringent regulatory standards for impurity levels

Nitrosamine Impurities

Extensive analysis confirms the absence of nitrosamine impurities in Xanomeline API

NITROSAMINE IMPURITIES RISK ASSESSMENT OF XANOMELINE TARTRATE

Primary possible source of the Nitrosamine impurities formation:

Impurity	Nitrosating reagent presence	2°/3° Amine presence	Possibility of formation	Conclusion
NDMA (N-Nitroso dimethylamine)	There is no presence or use of nitrite or any other nitroso derivatives in the manufacturing process of the key starting materials and drug substance.	DMA (Dimethyl amine) is not directly used during the synthesis of key starting material and drug substance. DMF (Dimethylformamide) is not directly used in the synthesis of key starting material and drug substance.	NDMA impurity formation in the manufacturing process of the drug substance is not possible, due to absence of nitrite or any other nitroso derivatives	No risk
NDEA (N-Nitroso diethylamine)		DEA (Diethyl amine) is not directly used or indirectly possible during the synthesis of key starting materials and drug substance. TEA (Triethyl amine) is not directly used in the synthesis of key starting material and drug substance.	NDEA impurity formation in the manufacturing process of the drug substance is not possible.	No risk
NMBA (Nitroso-N-methyl-4-amino butyric acid)		N-methylpyrrolidone is not directly used in the synthesis of drug substance.	NMBA impurity formation in the manufacturing process of the drug substance is not possible.	No risk
NDBA (N-Nitroso dibutylamine)		DBA (Dibutylamine) is not directly used or indirectly possible during the synthesis of key starting materials and drug substance.	NDBA impurity formation in the manufacturing process of the drug substance is not possible.	No risk
NDIPA (N,N-nitroso diisopropylamine) NEIPA (N-Nitroso ethyl isopropylamine)		DIPA (Diisopropylethylamine) is not directly used or indirectly possible during the synthesis of key starting material and drug substance. EIPA (Ethyl isopropylamine) is not directly used or indirectly possible during the synthesis of key starting material and drug substance.	NDIPA impurity formation in the manufacturing process of the drug substance is not possible. NEIPA formation in the manufacturing process of the drug substance is not possible.	No risk
NMPA (N-Nitroso-N-methylaniline)		Dimethylaniline is not directly used or indirectly possible during the synthesis of key starting material and drug substance.	NMPA impurity formation in the manufacturing process of the drug substance is not possible.	No risk
Product related Nitrosamine impurity	There is no presence or use of nitrite or any other nitroso derivatives in the manufacturing process of the key starting materials and drug substance.	Xanomeline is having 3^0 amine	N-Nitroso N-Desmethyl xanomeline impurity formation in the manufacturing process of the drug substance is not possible, due to absence of nitrite or any other nitroso derivatives	No risk

Conclusion:

Based on the above risk assessment it is concluded that there is no possibility for formation of nitrosamines in drug substance "Xanomeline Tartrate" in conformance with Assessment report by European Medicines Agency, EMA/409815/2020 Rev.21; Referral under Article 31 of Directive 2001/83/EC angiotensin-II-receptor antagonists (sartans) containing a tetrazole group

Patent Landscape

Xanomeline as a compound claimed in US5043345A (assigned to Novo Nordisk). US '345 and its equivalents already expired.

US5834495A (assigned to Eli Lilly/Novo Nordisk) claims Crystalline Xanomeline tartrate. US '495 and its equivalents already expired.

Xanomeline in combination with Trospium Chloride approved on Sep 26, 2024 and NCE exclusivity exists up to Sep 26, 2029.

Market Opportunities

The rising prevalence of schizophrenia is driving significant growth in the global therapeutics market, which is anticipated to surpass $12.5 billion by 2031, as highlighted in a recent Allied Market Research report.

Manufacturing and Quality Assurance

Manufacturing takes place at our state-of-the-art Unit IV Vizag API facility, ensuring compliance with stringent GMP standards. Our commitment to quality includes:

- Thoroughly eliminating any genotoxic impurities.
- Fully complying with specific regulatory standards for target markets.
- Utilizing advanced backward integration to ensure consistent global supply of premium-quality APIs.
- Employing streamlined, robust processes to deliver tailored PSD solutions efficiently.
- Aligning batch sizes with market demand projections post-validation

Conclusion

Xanomeline represents a promising therapeutic option for addressing unmet needs in the treatment of Schizophrenia. Its selective mechanism of action, favorable safety profile, and significant market potential make it an attractive candidate for continued development and commercialization.

Disclaimer

This whitepaper is intended for educational and informational purposes only. The final responsibility for ensuring compliance with applicable regulations lies with the end user.

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