NDA 216158

NDA APPROVAL

Bristol-Myers Squibb Company
Attention: Jonalyn Ongos
Associate Director, Regulatory Affairs
99 High Street, Fl 26
Boston, MA 02110

Dear Jonalyn Ongos:

Please refer to your new drug application (NDA) dated September 26, 2023, received September 26, 2023, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Cobenfy (xanomeline and trospium chloride) capsules.

This NDA provides for the use of Cobenfy (xanomeline and trospium chloride) capsules for the treatment of schizophrenia in adults.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Patient Package Insert) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 216158**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Cobenfy (xanomeline tartrate and trospium chloride) capsules shall be 36 months from the date of manufacture when stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

ADVISORY COMMITTEE

Your application for Cobenfy was not referred to an FDA advisory committee because the clinical trial design is similar to previously approved products in the class and the evaluation of the safety data [when used in the treatment of schizophrenia] did not raise significant safety or efficacy issues that were unexpected for a drug of this class or in the intended population. The application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

We are waiving the pediatric studies requirement for ages 12 years and under because necessary studies are impossible or highly impracticable.

We are deferring submission of your pediatric studies for ages 13 to 17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not yet been initiated.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. These required studies are listed below.

4640-5 Conduct a randomized, double-blind, placebo-controlled study to assess the efficacy and safety (with sparse PK) of Cobenfy for the treatment of schizophrenia in pediatric patients aged 13 to 17 years. We recommend that you use population pharmacokinetic modeling and simulation approach to select appropriate dose levels of Cobenfy in adolescents (13 to 17 years). As part of an efficacy and safety study in adolescents, please plan to collect PK blood samples at steady-state to characterize the PK of Cobenfy in pediatric patients with schizophrenia aged 13 to 17 years.

Final Protocol Submission:	06/2025
Study Completion:	12/2029
Final Report Submission:	06/2030

4640-6 Conduct an open-label, long-term safety study (minimum of 52 weeks) of Cobenfy in pediatric subjects aged 13 to 17 years with schizophrenia.

Final Protocol Submission:	06/2025
Study Completion:	12/2030
Final Report Submission:	06/2031

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocol(s) to your IND 127471, with a cross-reference letter to this NDA. Reports of these required pediatric postmarketing studies must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess these serious risks.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

4640-1 Perform a lactation study (milk only or mother-infant pair study) in lactating women (healthy subjects or patients) who have received therapeutic doses of COBENFY (xanomeline and trospium chloride) using a validated assay to assess concentrations of xanomeline and trospium chloride in breast milk and the effects on the breastfed infant if available, based on study population.

The timetable you submitted on September 25, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/2025
Final Protocol Submission:	12/2025
Study/Trial Completion:	12/2027
Final Report Submission:	06/2028

4640-2 Collect data from a prospective pregnancy exposure registry, preferably a disease-based multiproduct pregnancy registry, using a cohort analysis that compares the maternal, fetal, and infant outcomes of women with schizophrenia exposed to Cobenfy (xanomeline and trospium chloride) during pregnancy with unexposed comparator population of women with schizophrenia in a timely manner. Align the study protocol with protocol(s) outside the US to reach the target sample size. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortion, stillbirths, elective terminations,

preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes described in the protocol will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

The timetable you submitted on September 25, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	03/2025
Final Protocol Submission:	03/2026
Annual Progress Reports:	03/2027
	03/2028
	03/2029
	03/2030
	03/2032
	03/2033
	03/2034
	03/2035
Interim Analysis Report:	03/2031
Study/Trial Completion:	03/2036
Final Study Report:	03/2037

4640-3 Conduct a retrospective pregnancy cohort study using claims or electronic health record data with medical chart validation that is adequately powered to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in women with schizophrenia exposed to Cobenfy (xanomeline and trospium chloride) during pregnancy compared to appropriate comparator population(s).

The timetable you submitted on September 25, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	03/2025
Final Protocol Submission:	03/2026
Interim Analysis Report:	03/2027
	03/2028
	03/2029
	03/2030
	03/2031
	03/2032
	03/2033
	03/2034

	03/2035
Study/Trial Completion:	03/2036
Final Study Report:	03/2037

4640-4 To evaluate the potential adverse effects of COBENFY on voiding dynamics, especially urinary retention, conduct a non-invasive, 1-year, urological safety study. Assess specific urological safety parameters, such as maximum urinary flow rate (Qmax), post-void residual urine volume (PVR), validated symptom questionnaires, and urinalysis, at periodic intervals.

The timetable you submitted on September 25, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	01/2025
Final Protocol Submission:	12/2025
Study/Trial Completion:	12/2027
Final Report Submission:	06/2028

4640-7 Conduct a dedicated drug interaction study to assess the effect of Cobenfy on the PK of a sensitive substrate of CYP3A4.

The timetable you submitted on September 25, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	03/2025
Final Protocol Submission:	09/2025
Study/Trial Completion:	09/2026
Final Report Submission:	03/2027

4640-8 Conduct a dedicated drug interaction study to assess the effect of Cobenfy on the PK of a substrate of P-gp.

The timetable you submitted on September 25, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	03/2025
Final Protocol Submission:	09/2025
Study/Trial Completion:	09/2026
Final Report Submission:	03/2027

4640-9 Perform a dedicated pharmacogenetic study to assess the effects of CYP2D6 phenotypes (i.e., normal, intermediate, poor, and ultrarapid metabolizers) on xanomeline pharmacokinetics.

The timetable you submitted on September 25, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	03/2025
Final Protocol Submission:	09/2025
Study/Trial Completion:	03/2027
Final Report Submission:	09/2027

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

Submit clinical protocol(s) to your IND 127471 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

[4] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[5]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

REQUESTED ENHANCED PHARMACOVIGILANCE (EPV)

We request that for Cobenfy you submit all serious and non-serious domestic and foreign cases of hepatoxicity, pancreatitis, or biliary adverse events including spasm of the sphincter of Oddi, choledocholithiasis, acute cholecystitis, and cholangitis as 15-day "Alert reports" (described under 21 CFR 314.80(c)(1)) until September 26, 2027.

We request that you provide a separate narrative summary including analysis of the cases that describe hepatotoxicity, pancreatitis, or biliary adverse events including spasm of the sphincter of Oddi, choledocholithiasis, acute cholecystitis, and cholangitis as part of your required periodic safety reports (e.g., periodic adverse drug experience report (PADER) required under 21 CFR 314.80(c)(2)), quarterly during the first 3 years through the 3rd year following initial U.S. approval date.

Your analysis of cases should include interval and cumulative data relative to the date of approval of Cobenfy. Your analysis of cases should provide an assessment of causality, with documentation of indication and dosage of Cobenfy, duration of therapy, temporal association (i.e., onset and resolution of symptoms and biochemical abnormalities), associated signs and symptoms (e.g., abdominal pain, back pain, nausea and vomiting, pruritis, fever, jaundice, fatigue, rash, dark urine), confounders, underlying risk factors, treatment given for the event, outcome, and

[5] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[7] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

dechallenge/rechallenge information. Your analysis of cases should provide the following additional information, if available:

- Age, sex, race/ethnicity, weight/BMI
- Hepatic enzymes and liver function tests (e.g., AST, ALT, alkaline phosphatase, bilirubin)
- Enzymes indicative of pancreatitis (e.g., lipase, amylase)
- Viral and auto-immune hepatitis serologies (e.g., HCV RNA, anti-HAV IgM, ANA, IgG level)
- Concomitant medications (including prescription and over-the-counter medications, herbal/dietary supplements, illicit substances, and their respective indications, dosages, and dates taken)
- Medical history (e.g., concurrent diagnosis of diabetes, history of cholecystectomy, alcohol intake, liver disorders, other drug reactions)
- Hospitalizations, testing (e.g., imaging and histology)

To identify reports of hepatotoxicity, pancreatitis, or biliary adverse events including spasm of the sphincter of Oddi, choledocholithiasis, acute cholecystitis, and cholangitis, we request that you include the following Standardised MedDRA Queries (SMQs) and Preferred Terms (PTs):

- SMQ Drug related hepatic disorder – comprehensive search (Broad search)
- SMQ Functional, inflammatory and gallstone related biliary disorders
- SMQ Acute pancreatitis
- PT Hepatic cyst
- PT Hepatobiliary cyst

POST APPROVAL FEEDBACK MEETING

New molecular entities qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with

compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website[8].

If you have any questions, contact Tiffanie Taylor, Regulatory Project Manager, at 301-796-4395 or Tiffanie.Taylor@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Teresa Buracchio, MD
Director
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
- Carton and Container Labeling

[8] https://www.uspnf.com/

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TERESA J BURACCHIO
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