NDA 219428

NDA APPROVAL

Tonix Pharmaceuticals, Inc.
26 Main Street, Suite 101
Chatham, NJ 07928

Attention: Regina Kiu, MS, RAC
Sr. Director, Regulatory Affairs

Dear Regina Kiu:

Please refer to your new drug application (NDA) received October 15, 2024, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tonmya (cyclobenzaprine hydrochloride sublingual tablets), 2.8 mg.

This NDA provides for the use of Tonmya (cyclobenzaprine hydrochloride sublingual tablets) for the treatment of fibromyalgia 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.

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 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.

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

Submit final printed container labeling that are identical to the enclosed 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 219428**." 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 Tonmya (cyclobenzaprine hydrochloride sublingual tablets) shall be 48 months from the date of manufacture when stored at 20°C to 25°C [68°F to 77°F]).

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.

We are waiving the pediatric study requirement for ages birth to less than 13 years due to the low prevalence of fibromyalgia in this age group, which makes the necessary studies impossible or highly impracticable because of an insufficient number of patients available for randomization in clinical trials.

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

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.

4872-1 Conduct a juvenile animal study in the rat model to characterize the impact of Tonmya (cyclobenzaprine) on the developing brain and reproductive tissues to support clinical studies in pediatric patients from 13 years of age to less than 17 years of age.

The timetable you submitted on August 11, 2025, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12/2025
Study Completion:	07/2026
Final Report Submission:	10/2026

4872-2 Conduct a randomized controlled study evaluating the pharmacokinetics, safety, and efficacy of Tonmya (cyclobenzaprine) in pediatric patients 13 years of age to less than 17 years of age.

The timetable you submitted on August 11, 2025, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	01/2027
Final Protocol Submission:	05/2027
Study Completion:	11/2029
Final Report Submission:	05/2030

4872-3 Conduct a clinical open-label extension safety study of Tonmya (cyclobenzaprine) in pediatric patients 13 years of age to less than 17 years of age.

The timetable you submitted on August 11, 2025, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	01/2027
Final Protocol Submission:	05/2027
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 clinical protocols to your IND 112512, 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 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.

[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.

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 signals of a serious risk of adverse maternal, fetal, or infant outcomes due to exposure to Tonmya (cyclobenzaprine) during pregnancy nor to identify an unexpected serious risk of the potential presence of cyclobenzaprine in human milk resulting in effects on the breastfed infant.

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:

4872-4 Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to Tonmya (cyclobenzaprine) during pregnancy to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant.

The timetable you submitted on August 11, 2025, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	02/2026
Final Protocol Submission:	08/2026
Interim Study Report #1:	08/2029
Interim Study Report #2:	08/2032
Interim Study Report #3:	08/2035
Study Completion:	08/2036
Final Report Submission:	02/2037

4872-5 Perform a milk-only lactation study in lactating women who have received Tonmya (cyclobenzaprine) to measure concentrations of cyclobenzaprine in breast milk using a validated assay. Assess the effects on the breastfed infant based on study population.

The timetable you submitted on August 11, 2025, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	02/2026
Final Protocol Submission:	08/2026
Study Completion:	08/2028
Final Report Submission:	02/2029

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 protocols to your IND 112512 with a cross-reference letter to this NDA. Submit nonclinical protocols and all final reportsto 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).**

Submission of the protocols for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312.

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).

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].

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

If you have any questions, contact Sandy Truong, Senior Regulatory Project Manager, at sandy.truong@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Michelle Horner, DO, DFAACAP
Acting Deputy Director
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURES:

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

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/

MICHELLE S HORNER
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