TONMYA®/TNX-102 SL (CYCLOBENZAPRINE HCL SUBLINGUAL TABLETS)

TNX-CY-P306

A 40 TO 52-WEEK OPEN-LABEL EXTENSION STUDY TO EVALUATE TNX-102 SL 5.6 MG TAKEN DAILY AT BEDTIME IN PATIENTS WITH PTSD

(PROTOCOL NO. TNX-CY-P306)

Original Protocol Release Date: 16 March 2018

Date of Amendment 01: 19 September 2018

Date of Amendment 02: 09 November 2018

Date of Amendment 03: 25 April 2019

Date of Amendment 04: 05 June 2019

US IND No. 115936

Sponsor:
Tonix Pharmaceuticals, Inc. (Tonix)

[redacted]

INVESTIGATOR'S AGREEMENT

I have read the TNX-CY-P306 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

2. SYNOPSIS

Name of Sponsor/Company:
Tonix Pharmaceuticals, Inc.

Name of Investigational Product:
Tonmya®/TNX-102 SL (Cyclobenzaprine HCl Sublingual Tablets)

Name of Active Ingredient:
Cyclobenzaprine HCl

Title of Study:
A 40 to 52-Week Open-Label Extension Study to Evaluate TNX-102 SL Taken Daily at Bedtime in Patients with PTSD

Study period (months): 18	**Phase of development: 3**
Estimated date first patient enrolled: April 2018 Estimated date last patient completed: September 2019	

Objectives

Primary:

The primary objective of the study is to evaluate the long-term safety of TNX-102 SL 5.6 mg taken daily at bedtime over an additional 40 to 52 weeks in patients with PTSD who have participated in a double-blind lead-in P301 or HONOR study. Some patients will have also participated in an initial 12-week open-label extension study (TNX-CY-P303). This will provide at least 52 weeks of TNX-102 SL 5.6 mg exposure data for at least 50 patients.

Methodology:

This is an open-label, extension trial designed to evaluate safety of additional 40 to 52 weeks of TNX-102 SL 5.6 mg taken daily at bedtime for the treatment of PTSD. There are two possible "tracks" patients can use to enroll into this study:

Track A: patients that complete the double-blind lead-in HONOR study and complete ***or are active (at the time of study discontinuation) in the*** 12-week open-label extension study, P303, and received active drug in the 12-week double-blind lead-in study, P301/HONOR.

Track B: patients that are currently enrolled in the double-blind lead-in P301/HONOR study that has been discontinued due to results of an interim analysis ***or are active (at the time of study discontinuation) in the*** 12-week open-label extension study, P303, and received placebo in the 12-week double-blind lead-in study, P301/HONOR.

The study will consist of 5 or 6 in-clinic study visits, including Baseline Visit 1 (Day 0, which is anticipated to be the same visit as the last visit of the 12-week open-label extension study P303 for Track A patients), followed by in-clinic visits after 7, 16, 28 and 40 weeks of open-label treatment. Patients who are active in the 12-week double-blind lead-in study (P301/HONOR) at the time of enrollment to P306 will also have a 2-week phone check-in visit. All Track B patients will have 52 weeks of open-label treatment and a Visit 7. For patients enrolled from the discontinued double-blind lead-in study, P301/HONOR, the P306 Baseline Visit will occur in lieu of an early termination visit.

Patient safety parameters recorded at the final visit in the double-blind lead-in HONOR study (which is the baseline visit in the 12-week open-label extension study P303) can also be used as the baseline safety values for the P306 extension study for Track A patients. Patients will attend clinic visits at 7-, 9-, and 12-week intervals as indicated in the study visit schedule. Eligible patients who provide written informed consent will be provided with a supply of TNX-102 SL 2.8 mg tablets sufficient for

dosing until their next scheduled in-clinic study visit. At each clinic visit, patients will return their TNX-102 SL medication and will receive sufficient supplies to last them until the next scheduled visit. Patients will also have the option to have blood drawn for pharmacogenomic testing.

Number of patients (planned):
The study will enroll up to 200 patients.

Inclusion/Exclusion Criteria:

Inclusion criteria:

1. The patient has either a) completed a double-blind lead-in HONOR study and completed or is active (at the time of study discontinuation) in the 12-week open-label extension study, P303, or b) is currently enrolled in the double-blind lead-in HONOR study that has been discontinued due to results of an interim analysis, and is judged by the investigator as reasonably compliant, with at least 60% compliance with study medication usage (based on drug accountability).
2. The patient has provided written informed consent to participate in this extension study. *Note:* Separate written, signed informed consent will be required if the patient is to participate in the optional pharmacogenomic assessment. A decision not to participate in the optional pharmacogenomic testing will not affect the patient's eligibility for the main study.
3. The patient met all prior inclusion and exclusion requirements for the double-blind lead-in HONOR study, or the site received medical monitor approval for the patient to remain in the lead-in study after the retrospective discovery of an entry violation that did not pose any threat to the patient's safety or well-being.
4. During the course of the lead-in HONOR study or 12-week open-label extension P303 study, the patient has had no intervening medical conditions including pregnancy, clinically significant increase in suicidal ideation (plan or intent) or significant worsening of depression, newly arising clinically significant abnormal laboratory tests, or any clinically significant, uncontrolled, or unstable medical or surgical condition that could affect the patient's ability to participate in the study or potentially compromise the patient's well-being during the study.
5. The patient does not require treatment with a potent (strong) cytochrome P450 subtype 3A4 (CYP3A4) inhibitor, or St. John's wort.
6. The patient is willing to refrain from use of all other formulations of cyclobenzaprine for the duration of the study.
7. The patient is willing to refrain from use of monoamine oxidase inhibitors for the duration of the study.
8. Female patients of childbearing potential continue to agree to practice one of the medically acceptable methods of birth control detailed in the lead-in study.

Exclusion Criteria:
There are no exclusion criteria for this study.

Investigational product, dosage and mode of administration:

Name: Tonmya®[1]/TNX-102 SL (cyclobenzaprine HCl sublingual tablets)

Dose, route, frequency: 2 tablets of TNX-102 SL 2.8 mg taken simultaneously and sublingually (under the tongue) each day at bedtime starting on Day 0 for 40 to 52 weeks.

Duration of treatment:

40 to 52 weeks

Reference therapy, dosage and mode of administration: None

Criteria for evaluation:

The primary objective of the study is to evaluate the safety of bedtime treatment with TNX-102 SL 5.6 mg for an additional 40 to 52 weeks in patients with PTSD who have either completed the double-blind lead-in HONOR study and completed or are active (at the time of study discontinuation) in the 12-week open-label extension study, P303, or were enrolled in the double-blind lead-in HONOR study that has been discontinued due to results of an interim analysis. Safety will be assessed by the monitoring and recording of AEs, clinical laboratory tests, vital signs, the monitoring of suicidality using the Columbia Suicide Rating Scale (C-SSRS) scale, and the monitoring of depressive symptoms using the Beck Depression Inventory (BDI-II). Safety as well as durability of response will also be assessed by the monitoring of PTSD symptoms using the PTSD Checklist-Specific Version (PCL-S) at Visit 5 (Week 28) and Visit 6 (Week 40) in order to monitor for any potential worsening of PTSD symptoms or its symptoms clusters during the final 12-weeks of the study. Patients enrolled under Track B will also have an additional PCL-S evaluated for safety at their Visit 7 (Week 52).

Limited efficacy assessments consisting of the CGI-I, SDS, PROMIS Sleep Disturbance and the BDI-II will be collected at each visit. The PCL-S will be used for efficacy assessments at Visits 5 and 6 only.

Statistics

Analysis Population:

The Safety Population will comprise all patients who have been exposed to TNX-102 SL.

Safety Analyses:

Safety data will be summarized as a single treatment group receiving 1 or more doses of TNX-102 SL 5.6 mg. Adverse events will be coded using the same version of the Medical Dictionary for Regulatory Activities (MedDRA) as used for the lead-in HONOR study and will be summarized overall and by preferred term and system organ class (SOC). Adverse events will also be summarized by severity and relationship to study drug. Serious AEs and AEs leading to discontinuation of study drug will also be summarized. Adverse events that are ongoing in the 12-week open-label extension study P303 or the lead-in double blind HONOR study will be transcribed into the eCRF. All other adverse events that are reported after starting TNX-102 SL in this extension study, or that worsen after entry into this extension study, will be considered newly emergent AEs (NEAEs), even if the type of event was previously reported (and resolved) during either the HONOR study or the 12-week open-label extension study.

Actual values and change from baseline for clinical laboratory test results, vital sign measurements, depression status via the BDI-II and PTSD symptom status via the PCL-S, will be summarized at endpoint using descriptive statistics (n, mean, SD, median, minimum, and maximum). The number of

[1] Tonmya is the FDA conditionally accepted proposed proprietary name for TNX-102 SL for the treatment of PTSD.

patients with baseline and treatment-emergent suicidal ideation and/or suicidal behavior or self-injurious behavior, based on the C-SSRS, will be summarized by treatment group.

Efficacy Analyses:

Descriptive statistics by study visit will be displayed for:

- Proportion of patients with a CGI-I score of "very much improved" or "much improved" from baseline
- Change from baseline in the SDS
- Change from baseline in patients' quality of sleep score using the PROMIS Sleep Disturbance scale
- Change from baseline in BDI-II total score
- Change from Visit 5 to Visit 6 in PCL-S total score

Pharmacogenomic Analyses:

Potential genetic determinants of treatment response will be examined by the assessment of genetic variants in relation to treatment outcome. A blood sample will be obtained from patients who have signed a separate informed consent form for the pharmacogenomic analyses. The blood sample can be obtained as soon as the patient has agreed to be tested and has signed the separate informed consent form; i.e., the blood draw is not tied to any specific study visit, hence it can be obtained at any time.

The first step of the pharmacogenomic analyses will involve exome sequencing and analysis for allelic polymorphisms related to treatment response to TNX-102 SL. It is presumed that unused sample will be stored up to fifteen years, and potentially utilized to develop a pharmacogenomic test for determining likelihood of treatment response to TNX-102 SL.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation or Specialist Term	**Explanation**
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BDI-II	Beck Depression Inventory–II
BMI	Body Mass Index
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression- Improvement from Initiation of Treatment
CK	Creatinine Kinase
CoC	Certificate of Confidentiality
CRF	Case Report Form
CRO	Contract Research Organization
C-SSRS	Columbia Suicide Severity Rating Scale
CYP3A4	Cytochrome P450 subtype 3A4
e.g.	*Exempli gratia* (for example)
EC	Ethics Committee
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HCl	Hydrochloride
HIPAA	Health Insurance Portability and Accountability Act
i.e.	*id est* (that is)
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IND	Investigational New Drug
IRB	Institutional Review Board
MCH	Mean corpuscular hemoglobin

Abbreviation or Specialist Term	Explanation
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	*Medical Dictionary for Regulatory Activities*
Mg	Milligram(s)
N, n	Number (of patients)
NA	Not applicable
NEAE	Newly Emergent Adverse Event
PCL-S	PTSD Checklist-Specific Version
PROMIS	Patient-Reported Outcome Measurement Information System
PTSD	Posttraumatic Stress Disorder
RBC	Red blood cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard deviation
SDS	Sheehan Disability Scale
SL	Sublingual
SNRIs	Serotonin–norepinephrine reuptake inhibitors
SOC	System Organ Class
SOP	Standard Operating Procedures
SPI	Safety Planning Intervention
SSRIs	Selective serotonin reuptake inhibitors
TNX-102 SL	Cyclobenzaprine HCl sublingual tablets
Tonmya	FDA conditionally accepted proposed proprietary name for TNX-102 SL for the treatment of PTSD
US	United States
VA	Veteran's Administration
WBC	White blood cell
WHO	World Health Organization

4. INTRODUCTION

The background information provided in the lead-in study protocol and the most current TNX-102 SL Investigator's Brochure is relevant to this extension study. [redacted]

5. TRIAL OBJECTIVES AND PURPOSE

5.1. Primary Objective

The primary objective of the study is to evaluate the long-term safety of TNX-102 SL taken daily at bedtime over an additional 40 to 52 weeks in patients with PTSD who have participated in a double-blind lead-in HONOR study and possibly a 12-week open-label extension study P303.

5.2. Secondary Objectives

The secondary objective of the study is to evaluate the long-term effect of TNX-102 SL taken daily at bedtime over an additional 40 to 52 weeks in patients with PTSD who have participated in a double-blind lead-in HONOR study and possibly a 12-week open-label extension study P303.

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This is a 40 to 52-week, multicenter, open-label extension study designed to establish long-term safety exposure and to examine the long-term effect with daily bedtime dosing of TNX-102 SL 5.6 mg (2 x 2.8mg tablets) in patients with PTSD. This study will be conducted at approximately 35 sites in the United States (US).

Patients who have either: (a) completed the double-blind lead-in study and complete, ***or are active (at the time of study discontinuation)*** in the 12-week open-label extension study, P303; or (b) are currently enrolled in the double-blind lead-in study (HONOR study) that has been discontinued due to results of an interim analysis , will be eligible. For Track A patients, this extension study consists of 5 in-clinic visits, including the Screening/Baseline visit and visits after 7, 16, 28 and 40 weeks of treatment (Visits 3-6). There will also be a telephone visit after two weeks of treatment (Visit 2) for patients enrolling from the double-blind lead-in study, P301/HONOR. The total treatment duration of this study will be 40 weeks for patients enrolled under Track A criteria, and 52 weeks for patients enrolled under Track B criteria. Therefore, the maximum total duration of continuous treatment with TNX-102 SL could be approximately 64 weeks for those patients assigned to TNX-102 SL in the lead-in HONOR study who then also completed the 12-week open-label extension study P303.

For patients enrolling from the open-label extension study, P303, there is no need to repeat assessments at Visit 1 for this study, if the patient enrolls and initiates study treatment within fourteen days of completing the 12-week open-label extension study P303. For patients who are active in the double-blind lead-in study, P301/HONOR, all Baseline procedures and assessments will be completed at Visit 1.

After the patient has participated in the lead-in HONOR study or the open-label extension study, P303, and has consented to participate in this open-label extension study, patients will be dispensed a 7-week supply of open-label TNX-102 SL tablets (3 bottles) and will be instructed to take 2 tablets of study drug sublingually daily at bedtime, starting on the evening of Visit 1. A phone visit will be completed after 2 weeks of treatment for patients enrolling from the double-blind lead-in study, P301/HONOR. All patients will return to the study center for safety and efficacy assessments at Weeks 7, 16, 28, and 40 (or early termination). Patients enrolled under Track B criteria will continue to dose for an additional 12 weeks and have the last study visit at Week 52. Patients will return their TNX-102 SL medication (including empty bottles) at these visits. Patients will also receive a 9-week supply of TNX-102 SL (4 bottles) at the Week 7 visit, and a 12-week supply (5 bottles) at the Week 16, 28 and 40 (Week 40 for Track B patients only) visits. Patients will be allowed to take other medications deemed appropriate by their health care providers to manage their PTSD and other conditions, including currently approved PTSD therapies. See Section 8.5 for a discussion of allowed concomitant treatments.

The study timeline and events schedule is provided in Appendix 1.

6.2. Number of Patients and Treatment Assignment

Up to 200 patients will enroll into this study. Eligible patients will either have completed a double-blind lead-in HONOR study and participated in a 12-week open-label study P303 or will

have been currently enrolled in a double-blind lead-in HONOR study when that study was discontinued due to results of an interim analysis.

All patients will be assigned to TNX-102 SL, 5.6 mg regardless of which treatment arm they were randomized to in the lead-in HONOR study.

6.3. Study Endpoints

6.3.1. Safety

Safety will be assessed by:

- Adverse events (AEs) and serious AEs (SAEs) throughout the entire duration of the study, including assessment of AEs involving the oral cavity
- Change from baseline in clinical laboratory test results
- Changes from baseline indicative of increased suicidal ideation or behavior as assessed by the Columbia Suicide Severity Rating Scale (C-SSRS)
- Change from baseline in Beck Depression Inventory-II (BDI-II)
- Changes from baseline in vital signs and weight
- Track A patients only: Change from Visit 5 to Visit 6 in PTSD Checklist-Specific Version (PCL-S)
- Track B patients only: Change from Visit 5 to Visit 7 in PTSD Checklist-Specific Version (PCL-S)

6.3.2. Efficacy

Descriptive statistics by treatment and study visit will be displayed for a number of efficacy endpoints including:

- Proportion of patients with a Clinical Global Impression-Improvement from Initiation of Treatment (CGI-I) score of "very much improved" or "much improved" from baseline
- Change from baseline in the Sheehan Disability Scale (SDS)
- Change from baseline in patients' quality of sleep using the Patient-Reported Outcome Measurement Information System (PROMIS) Sleep Disturbance scale
- Change from baseline in BDI-II score
- Change from Visit 5 to Visit 6 in PTSD Checklist-Specific Version (PCL-S)

7. SELECTION AND WITHDRAWAL OF PATIENTS

7.1. Informed Consent

A potential patient may be screened for eligibility only after the nature of the study, its purpose, and any other information relevant to the patient's decision to participate have been explained to him or her and the patient has voluntarily confirmed his or her willingness to participate. The investigator will determine the potential patient's suitability for the study by interviewing the

patient and by reviewing the patient's experience in the double-blind lead-in HONOR study and/or 12-week open-label extension study P303.

Informed consent is documented by means of a written, signed, and dated informed consent form (ICF). Separate written, signed informed consent must be obtained if the patient is to participate in the optional pharmacogenomic assessment. Additional information is provided in Section 14.3.

7.2. Inclusion Criteria

1. The patient has either a) completed the double-blind lead-in study and completed or is active (at the time of study discontinuation) in the 12-week open-label extension study (P303), or b) is currently enrolled in the double-blind lead-in study that was discontinued due to results of an interim analysis, and is judged by the investigator as reasonably compliant, with at least 60% compliance with study medication usage (based on drug accountability).
2. The patient has provided written informed consent to participate in this extension study. *Note:* Separate written, signed informed consent will be required if the patient is to participate in the optional pharmacogenomic assessment. A decision not to participate in the optional pharmacogenomic testing will not affect the patient's eligibility for the main study.
3. The patient met all prior inclusion and exclusion requirements for the double-blind lead-in study, or the site received medical monitor approval for the patient to remain in the lead-in study after the retrospective discovery of an entry violation that did not pose any threat to the patient's safety or well-being.
4. During the course of the lead-in study or 12-week open-label extension study, the patient has had no intervening medical conditions including pregnancy, clinically significant increase in suicidal ideation (plan or intent) or significant worsening of depression, newly arising clinically significant abnormal laboratory tests, or any clinically significant, uncontrolled, or unstable medical or surgical condition that could affect the patient's ability to participate in the study or potentially compromise the patient's well-being during the study.
5. The patient does not require treatment with a potent (strong) cytochrome P450 subtype 3A4 (CYP3A4) inhibitor, or St. John's wort.
6. The patient is willing to refrain from use of all other formulations of cyclobenzaprine for the duration of the study.
7. The patient is willing to refrain from use of monoamine oxidase inhibitors for the duration of the study.
8. Female patients of childbearing potential continue to agree to practice one of the medically acceptable methods of birth control detailed in the lead-in study.

7.3. Patient Exclusion Criteria

There are no exclusion criteria for this study.

7.4. Withdrawal Criteria

There are no pre-specified withdrawal criteria for this study. In accordance with the Declaration of Helsinki, human patients have the right to withdraw from the study at any time for any reason. The investigator and Tonix also have the right to remove patients from the study. Additional information regarding withdrawal or discontinuation of patients is described in detail in Section 9.6.

8. STUDY DRUG MATERIALS AND MANAGEMENT

8.1. Study Drug Packaging, and Labeling and Storage

The study medication bottles will be labeled minimally with the following information: study number TNX-CY-P306 (P306), sponsor name and address, bottle number, drug name, quantity, storage conditions, usage instructions, and caution statements for investigational new drug, i.e., Caution: New Drug Limited by United States Law to Investigational Use, and Keep Out of Reach of Children and Pets.

Each study medication bottle will contain 40 tablets. Since the patient will dose with two tablets sublingually each night, three bottles will be dispensed to each patient at Visit 1/Baseline. Four bottles will be dispensed at Week 7 and five bottles at Weeks 16, 28 and 40 (Week 40 for Track B patients only); this will provide the patient with enough study drug between visits, plus additional tablets to cover loss and/or visit window variability. The patient should be instructed to take all the tablets in one bottle before opening another bottle. The patient should be instructed to keep this study medication in a safe location out of extreme environmental conditions and out of the reach of children and pets, and that this medication is not to be taken by any individual other than the study patient. Each patient will also be instructed that they will be expected to return all bottles and all unused study medication at each clinic visit; unused medication will be counted to assess compliance with study drug treatment.

Storage of the study drug at the investigational site should be under locked and secure conditions with limited staff access. Study drug should be stored at 20-25°C/68-77°F in a temperature/ humidity-monitored room; however, brief excursion (15-30°C/59-86°F) as defined in the Study's Reference Manual (IP Receipt and Storage) is permitted without sponsor's approval.

8.2. Dosing Instructions

Patients will be instructed to take two **(2)** TNX-102 SL 2.8 mg tablets sublingually, placed simultaneously under the tongue, each evening at bedtime starting on evening of Day 0 and continuing without interruption for 40 to 52 weeks. The study drug should be taken at bedtime after teeth brushing and other oral care has been completed. The mouth/sublingual area should be moist at the time of dosing, so the patient should drink a few sips of water prior to dosing, especially if prone to dry mouth. Patients will be instructed to place the two TNX-102 SL 2.8 mg tablets under their tongue and keep them there until they have dissolved. They should not swallow, crush or chew the tablets. Patients should not eat or drink (or chew gum) for at least 15 minutes after dosing, and preferably not until morning. Patients will be reminded that only two (2) tablets are allowed per day. Note: In the event that the patient misses a dose, instruct the patient to continue dosing with two (2) tablets the next evening; i.e., they should not take more to make up for the missed dose.

Patients should also be reminded to keep the desiccant in the bottle after opening and to screw the cap on tightly after dosing.

8.3. Dispensing Instructions

Each enrolled patient will be assigned 3, 4 or 5 bottles of TNX-102 SL at each dispensing visit. Bottles of TNX-102 SL tablets are numbered and will be supplied to sites as open stock. Patients are reminded to open and use one bottle of TNX-102 SL tablets at a time.

8.4. Release of Clinical Study Supplies to the Investigator

Tonix or Tonix's designee's standard operating procedures (SOP) for releasing clinical trial supplies to the site will be followed.

8.5. Concomitant Medications

Many of the restrictions in the lead-in study related to concomitant medications and trauma-focused psychotherapy will be relaxed. Therefore, patients may utilize antidepressants, mood stabilizers, anticonvulsants, benzodiazepines, stimulants, and opioids, if needed, unless specifically excluded as outlined below. Patients may take medications to help them sleep, per the judgment of the investigator.

Any concomitant medications or other treatments, including dietary supplements, must be recorded in the patient's medical record and case report form along with the indication, dose and dates of treatment.

The following medications are specifically excluded during the study and patients must agree to refrain from use of these medications during the study:

- Any other forms of cyclobenzaprine (FLEXERIL®, AMRIX®, FEXMID®, or generic equivalents) continue to be specifically excluded during the study and patients must agree to refrain from use of these medications during the study.
- Monoamine oxidase inhibitors (tranylcypromine, phenelzine, isocarboxazid, and selegiline)
- Cytochrome P450 3A4 inhibitors (strong ones only) (refer to Appendix 2 for a list).
- St. John's wort

NOTE: Patients initiating treatment with antidepressants, tramadol or other opioids, triptans, or any other serotonergic medication should be cautioned about the possibility of serotonin syndrome which has been reported in patients receiving cyclobenzaprine with selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs) and other serotoninergic agents. (See Appendix 3, AMRIX® Package Insert, Warnings Section). The patient should be instructed to call the clinic immediately in the event of any of the warning signs or symptoms of serotonin syndrome, as outlined in the informed consent. The investigator should carefully review the patient's complete list of medications when considering new treatments and the site should ask the patient to call the site (or return for an unscheduled clinic visit) within one week after adding a new serotonergic therapy (or increasing the dose of a prior treatment).

8.6. Study Drug Accountability and Reconciliation

All patients will be expected to bring their bottles of study medication with them to study visits. The site staff will inspect the medication bottles and perform a count of the tablets remaining in the bottles and the number of tablets that the patient should have returned (based on the number of days since the previous visit). The number of tablets dispensed, the number returned, and the number expected to be returned will be recorded in the patient's record. An assessment of medication adherence should be done by the study staff to ensure that the patient understands all dosing instructions and is taking the medication as prescribed. If it is found that the patient is not taking the study medication as prescribed, the patient will be re-counseled on correct administration, and this should be noted in the patients' record, and discussed with the medical monitor, if necessary.

If the patient fails to return all unused study drug as expected, the patient should be questioned regarding the reason for the lower than expected tablet number and about potential misuse, abuse or diversion. In situations where more than 2 tablets per week cannot be accounted for, the investigator will be asked to evaluate the situation, and a written summary should be added to the source and entered onto the case report form (CRF). In addition, the medical monitor should be contacted any time a patient requests replacement medication for any reason (e.g., loss of bottles or damage to study drug). Situations where replacement drug is requested, or when more than 2 tablets per week cannot be accounted for, should be recorded as deviations.

All study medication, including partial and empty bottles, must be maintained at the study site until Tonix or its designee verifies drug accountability and provides instruction for the destruction or the return of the investigational product to the Sponsor's drug distribution depot.

Tonix or their designee will perform drug accountability which entails reconciliation between the amount of drug shipped to the study site, study drug assigned and dispensed to the patient (including returned unused assigned study drug), and study supplies that were never dispensed and/or assigned to patients.

9. STUDY VISITS AND PROCEDURES

The overall and detailed schedule for study procedures and visits is provided in Appendix 1.

9.1. Visit 1 – Screening/Baseline (Week 0, Day 1)

9.1.1. Informed Consent

Before the potential patient has undergone any study-related screening procedures, the nature of the study and the potential risks associated with it will be explained to the patient, and the patient will be given an opportunity to ask questions to his or her satisfaction. After all questions are answered, but before proceeding further, the patient must read and sign a written informed consent form. This signed informed consent form will be retained in the Investigator's study file, and the date the patient signed the form will be entered into the CRF. The patient will be provided with a copy of his or her signed and dated informed consent form. The patient will be required to sign all updated informed consents.

Separate written, signed informed consent must be obtained if the patient is to participate in the optional pharmacogenomic assessment.

9.1.2. Screening Overview

The first study visit, Visit 1, will be where the study is explained to the prospective study patient, where written informed consent will be obtained and documented, and where protocol-specified study procedures and assessments will be completed.

For patients enrolling into this study from the 12-week open label extension study, P303, the P306 Baseline Visit (Visit 1) date is intended to be the same date as the final visit of the 12-week open label extension study, P303. However, if there are extenuating circumstances, Visit 1 of P306 may occur within fourteen days of their final visit in P303 without repeating baseline assessments. If more than fourteen days elapse between the final visit of P303 and start of the P306 study, medical monitor approval will be required and baseline assessments will need to be repeated.

For patients enrolling directly from the double-blind lead-in study, P301, all Visit 1 assessments will be performed. These patients are also expected to enter the P306 study at the same time as their final P301 visit; however, if there are extenuating circumstances, then Visit 1 of P306 may occur within fourteen days of their final P301 visit.

Once the patient has provided written informed consent to participate and has met all relevant inclusion criteria, this patient is eligible to begin the open-label treatment period, starting at bedtime on the day of enrollment. The patient should be dispensed three bottles of TNX-102 SL tablets, along with dosing and storage instructions. The end-of-study information collected at the final visit of the 12-week open label extension study P303, or the Visit 1 assessments completed as part of this protocol, will be considered the baseline values for Study P306.

9.1.3. Patient Numbering

All patients who participated in the double-blind lead-in HONOR study will retain their original concatenated 6-digit site-patient number, i.e., all patients entering P306.

9.1.4. Pharmacogenomic Assessment

Patients should be offered the opportunity to participate in the pharmacogenomic assessment as soon as Protocol Amendment 01 has been approved and implemented at the clinical site. The blood draw for this assessment is not tied to any specific visit; instead, it should be obtained after the patient has reviewed and signed the separate pharmacogenomic testing informed consent form, irrespective of the visit at which the consent is signed.

9.1.5. Visit 1 Baseline Assessments/Procedures (Week 0)

The following assessments/procedures will be completed at Visit 1.

For all patients:

- Obtain written informed consent to participate
- Inclusion criteria
- Review and transcribe new concomitant medications as well as those which are to be continued from the double-blind lead-in HONOR study or the 12-week open-label extension study P303
- Review and transcribe new AEs as well as those which are ongoing from the double-blind lead-in HONOR study or the 12-week open-label extension study P303

For patients enrolling from the double-blind lead-in study, P301/HONOR only (or patients rolling over to study P306 more than 14 days after the final visit of the 12-week open-label extension study P303):

- Obtain vital signs, including weight. The height collected at baseline from the lead-in study will be utilized for body mass index (BMI) calculations in this study.
- Perform a visual exam of the oral cavity
- Have the patient complete the PROMIS-Sleep Disturbance scale and the SDS. Review each scale for completeness once done.
- Have the patient complete the BDI-II
- Conduct the C-SSRS after reviewing the results of the BDI-II
- Draw blood for clinical laboratory testing
- Review patient's lifetime psychiatric treatment history, demographic information and medical history to ensure the information recorded during the double-blind lead-in study is accurate and complete, as it will also be included in the extension study's database.

Only those patients meeting all of the inclusion criteria will be eligible to continue.

For all patients:

After all study requirements for Visit 1 of P306 have been fulfilled, the patient will:

- Be dispensed 3 bottles of TNX-102 SL tablets and be instructed to begin dosing with study medication at bedtime, starting the evening of Visit 1;
- Receive instruction regarding proper sublingual dosing technique and the time of expected dosing; and
- Schedule the telephone Visit 2 (for patients enrolled from the double-blind lead-in study, P301/HONOR, only) and receive an appointment to return to the clinic for Visit 3.

9.2. Visit 2 (Telephone Visit: Week 2)

For patients enrolled from the double-blind lead-in study, P301/HONOR only: Visit 2 will be done as a telephone call to the patient and should be conducted after 2 weeks of treatment, on Day 14 ± 3 days.

The following steps should be completed:

- Assess changes in concomitant medications
- Assess study drug compliance based on patient verbal report
- Assess occurrence of AEs, including any oral AEs and whether an unscheduled visit is indicated for an examination of the oral cavity
- Review patient instructions regarding drug dosing and storage
- Administer the 'Since Last Visit' C-SSRS telephonically

9.3. Visits 3, 4, and 5 (Weeks 7, 16, and 28)

These visits are conducted after 7, 16, and 28 weeks (± 7 days) of treatment respectively. The following assessments and procedures are to be conducted at each of these visits in the following general order:

- Collect returned study medication from patient and perform drug accountability
- Assess study drug compliance
- Assess for changes in concomitant medications
- Assess for occurrence of AEs

  if any oral AEs have been reported (other than numbness, tingling or bitter taste), perform and document an examination of the oral cavity
- Have the patient complete the "baseline" PCL-S (Visit 5 only)
- Have the patient complete the PROMIS-Sleep Disturbance Scale and the SDS. Review each scale for completeness once done.
- Have the patient complete the BDI-II
- Conduct the C-SSRS after reviewing the results of the BDI-II
- Vital signs and weight

- Draw blood for clinical laboratory tests (Visit 5 only)
- Urine pregnancy test (for women of child-bearing potential)
- Inspect the oral cavity and document findings, if any (Visit 5 only)
- Conduct the CGI-I, using the P306 baseline visit as comparison
- Dispense 4 new bottles of TNX-102 SL tablets at Week 7 (Visit 3). At Weeks 16 (Visit 4) and 28 (Visit 5), dispense 5 new bottles.

Review patient instructions regarding drug dosing and storage, and schedule appointment for next clinic visit.

9.4. Visit 6 (Week 40)

Visit 6 is to be conducted after 40 weeks (±7 days) of treatment in the extension study. At this visit, the patient (Track A only) will return all remaining study drug and the following assessments and procedures are to be completed in the following general order:

- Collect returned study medication from patient and perform drug accountability
- Assess study drug compliance
- Assess for occurrence of AEs
- Assess for changes in concomitant medications
- Obtain vital signs including weight
- Track A patients only: Draw blood for clinical laboratory tests
- For women of child-bearing potential, conduct urine pregnancy test
- Track A patients only: Inspect the oral cavity and document findings, if any
- Have the patient complete the PCL-S
- Have the patient complete the PROMIS-Sleep Disturbance Scale and SDS
- Have the patient complete the BDI-II
- Conduct the C-SSRS after reviewing the results of the BDI-II
- Conduct CGI-I comparing to the P306 baseline
- Track B patients only: Dispense 5 new bottles of TNX-102 SL tablets

9.5. Visit 7 (Week 52)

Track B patients only: Visit 7 is to be conducted after 52 weeks (±7 days) of treatment in the extension study. At this visit, the patient will return all remaining study drug and the following assessments and procedures are to be completed in the following general order:

- Collect returned study medication from patient and perform drug accountability

- Assess study drug compliance
- Assess for occurrence of AEs
- Assess for changes in concomitant medications
- Obtain vital signs including weight
- Draw blood for clinical laboratory tests
- For women of child-bearing potential, conduct urine pregnancy test
- Inspect the oral cavity and document findings, if any
- Have the patient complete the PCL-S
- Have the patient complete the PROMIS-Sleep Disturbance Scale and SDS
- Have the patient complete the BDI-II
- Conduct the C-SSRS after reviewing the results of the BDI-II
- Conduct CGI-I comparing to the P306 baseline

9.6. Early Termination (ET)

In accordance with the Declaration of Helsinki, patients have the right to withdraw from the study at any time for any reason, and they will be advised of this right. The investigator and Tonix also have the right to remove patients from the study. Specific reasons for removal of a patient from the study could include, but are not limited to:

- An AE
- An illness that, in the judgment of the investigator or Tonix, might invalidate the study results or place the patient at risk
- The request of the patient, investigator, or Tonix, whether for administrative or other reasons
- Pregnancy

Patients who wish to terminate their participation in the study should be instructed to come to the clinic for an Early Termination Visit. The purpose of the Early Termination visit is to obtain critical information about the patient's participation, and should be scheduled preferably before there has been a substantial lapse in study medication usage. However, even if there has been a medication lapse, the patient should be encouraged to return to the clinic for this visit, and should be instructed to return all remaining study medication.

The following assessments and procedures are completed at this visit in the following general order:

- Collect returned study medication from patient and perform drug accountability
- Assess study drug compliance
- Assess for occurrence of AEs

- Assess for changes in concomitant medications
- Obtain vital signs including weight
- Draw blood for clinical laboratory tests
- For women of child-bearing potential, conduct urine pregnancy test
- Inspect the oral cavity and document findings, if any
- Have the patient complete the PROMIS-Sleep Disturbance Scale and SDS
- Have the patient complete the BDI-II
- Conduct the C-SSRS after reviewing the results of the BDI-II
- Conduct CGI-I comparing to the P306 baseline

Once these assessments have been completed, the patient may be discharged from the study, provided there is no need for additional follow-up to continue to monitor an AE or other condition.

9.7. Unscheduled Visits

Patients may need to be seen at other times than the scheduled study visits for additional safety assessments or to follow-up, as medically necessary, on clinical laboratory, physical examination, or other findings. In addition, if a patient calls between scheduled visits to report a visible lesion in the oral cavity or other concerning oral cavity AE, the patient should be asked to return to the clinic as soon as possible for an unscheduled oral cavity examination. Unscheduled examinations are NOT required for reports of oral numbness, tingling, bitter taste, or for other mild or transient AEs that are not concerning to the patient. If an additional study visit occurs, the date and nature of the visit will be documented in the CRF and in the source documents. The patient should be advised to bring study medication with them to the unscheduled visit.

10. STUDY ASSESSMENTS

10.1. Screening Assessments

The results of the screening assessments should be reviewed to ensure that the patient continues to satisfy all entry criteria and otherwise remains a satisfactory patient for the extension study. Laboratory assessments obtained at the final visit of the double-blind lead-in HONOR study or the 12-week open-label extension study P303 will not be available prior to the patient's entry into the extension study, but should be reviewed within 7 days when they become available, to ensure the patient's ongoing well-being.

10.2. Efficacy Assessments

A secondary objective of this study is to evaluate the long-term effect of TNX-102 SL and these endpoints are derived from both clinician-administered and subjective patient-completed assessments. The clinician-administered assessments must be administered by qualified and trained individuals at each clinical site. Study specific training will be required before new staff that were not trained for the lead-in study are allowed to administer these scales. In an attempt to minimize variability in responses of a given patient over time, it is important that the same rater administer the scales to a given patient throughout the study as much as possible. It is also important that the assessments, including those that are patient-completed, be conducted in the specified order, according to specific instructions, and in a setting where the patient has minimal distractions and sufficient time to complete them. After completion of these assessments, the study coordinator should review the responses for completeness with the patient.

10.2.1. Clinical Global Impression of Improvement (CGI-I)

The CGI-I is a commonly used clinician-rated scale designed to assess overall clinical improvement (change) since baseline. The CGI-I will be completed at each in-clinic visit after baseline. It will be the responsibility of the Principal Investigator or his qualified designee to assess change in the subject's overall status.

10.2.2. Sheehan Disability Scale (SDS)

The SDS scale is a self-report questionnaire that was designed to assess the subject's view of the degree to which symptoms have disrupted work, social life/ leisure activities, and family life/ home responsibilities during the past week. In addition, the SDS asks the subject to provide the number of days or work lost as well as unproductive days. The SDS will be administered at each in-clinic visit.

10.2.3. PROMIS Sleep Disturbance Scale

PROMIS refers to the Patient-Reported Outcome Measurement Information System (www.nihpromis.org), an NIH-funded initiative to develop instruments to be used across chronic conditions. The PROMIS scale for sleep disturbance (form 8a) will be administered at all in-clinic visits.

10.2.4. Beck Depression Index (BDI-II)

BDI-II refers to the patient-rated assessments of depressive symptomology. The BDI-II will be administered at all in-clinic visits. Each patient's response to the BDI suicidality question (item 9) should be reviewed and compared to the C-SSRS responses to ensure careful assessment of any suicidal ideation and resolution of any discrepancies between the self-reported BDI-II and the C-SSRS interview.

10.2.5. PTSD Checklist-Specific Version (PCL-S)

Developed by the National Center for Posttraumatic Stress Disorder, the PCL-S is a 17-item self-report measure reflecting DSM-IV symptoms of PTSD. The PCL-S aims to link symptom endorsements to a specified event or stressful experience, which for P306 has been identified by the subject as their Index Trauma during the lead-in double blind study (TNX-CY-P301). Respondents rate each item from 1 ("not at all") to 5 ("extremely") to indicate the degree to which they have been bothered by that particular symptom over the past month.

In addition, the long-term safety of TNX-102 SL on PTSD based on PCL-S completed by patients in Visit 5 (Week 28) and Visit 6 (Week 40) and Visit 7 (Week 52 for patients enrolled under Track B), is assessed with this scale. The mean change in PCL-S total score and PCL-S clusters scores from Visit 5 (Week 28) to Visit 6 (Week 40), or to Visit 7 for Track B patients will detect any potential worsening in total PTSD score or symptoms clusters in the final 12-weeks, or 24-weeks for Track B patients, of the study. Since PCL-S is added to the study when a significant number of patients have passed the Visit 4 (Week 16 time point, Visit 5 (Week 28) is chosen as the "baseline" for PCL-S in order to capture the vast majority of the patients who enrolled in the study from its beginning.

10.3. Pharmacogenomics Testing

For pharmacogenomic analysis, a single blood draw collected in two PAXgene DNA tubes will be obtained from each patient after they have provided separate written, signed informed consent for pharmacogenomic analysis. The purpose of this testing is to allow exome sequencing and analysis for genetic variants related to treatment response to TNX-102 SL. It is presumed that unused sample will be stored up to fifteen years, and potentially utilized to develop a pharmacogenomic test for determining likelihood of treatment response to TNX-102 SL. A decision not to participate in optional pharmacogenomic testing will not affect the patient's eligibility for the main study. Patients have the right to stop participating at any time during the study or during the time of sample storage, and, if a patient decides to withdraw from the pharmacogenomics portion of this study, any remaining sample will be destroyed and not used for further research. Data collected before a patient's withdrawal from the pharmacogenomics portion of this study will remain in the research database.

10.4. Safety Parameters

Safety will be assessed by evaluation of adverse events, responses on the C-SSRS, clinical laboratory tests, examinations of the oral cavity, vital signs, weight, patient-rated assessments of depressive symptomology (BDI-II) and PTSD symptomology (PCL-S).

10.4.1. Adverse Events (AEs)

Patients will be monitored for AEs throughout the study, from the time the patient signs an informed consent onward. AEs that are spontaneously reported, elicited or observed are to be recorded on the CRF with the date, time of onset, date and time of resolution, severity, seriousness, causality (relationship to study medication), actions required, and outcome.

To elicit AEs, non-leading, simple questions with minimal connotations should be used as the initial questions at all evaluation points during the study. Examples of these questions can be:

- How have you felt since your last visit?
- Have you had any health problems since your last visit?

If an AE occurs, the investigator will institute support and/or treatment as deemed appropriate. If a non-serious AE is unresolved on the last day of the study, an effort should be made to follow up until the AE is resolved or stabilized, the patient is lost to follow-up, or there is some other resolution of the event.

There are many symptoms associated with PTSD that can vary in intensity and frequency over time. Only symptoms that significantly worsen or become more frequent, and in the opinion of the patient are outside of their normal experience, should be reported as adverse events.

If a patient reports an oral adverse event other than numbness, tingling or bitter taste, the Investigator should examine the oral cavity to confirm presence or absence of any lesion or other abnormality, and document the exam. Additional details related to onset, duration, severity and reversibility of the oral event will also be documented.

10.4.1.1. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a clinician-administered interview developed by researchers at Columbia University to assess suicide risk and to track suicidal ideation and behavior during clinical trials. This scale is intended to be administered by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

The "since last visit" version of the C-SSRS will be completed at all study visits. Note that if there has been a significant change in responses to this scale indicative of increased suicide risk, appropriate intervention should be prescribed Section 10.4.1.2 and an AE should be recorded. The patient's response to BDI-II item 9 (suicidal ideation) should be reviewed prior to conducting the C-SSRS at the in-clinic visits to ensure the patient's responses are consistent between the BDI and the C-SSRS (and/or the reason for any inconsistency documented in the patient's chart).

10.4.1.2. Safety Planning Intervention (SPI)

The C-SSRS is completed at every visit in order to assess for changes in suicidality during the study. If a patient scores a 4 or 5 on the Suicidal Ideation section of the C-SSRS at a clinic visit following enrollment, the patient should be withdrawn from the study and referred for appropriate emergency care. A score of 4 or 5 should also result in the reporting of a SAE.

If a patient scores a 2 or 3 on the Suicidal Ideation section of the C-SSRS at any visit, the investigator should consider the implementation of a Safety Planning Intervention (SPI). The recommended SPI for this study is the plan developed by Barbara Stanley, PhD and Gregory Brown, PhD which has been adopted by the US Veteran's Administration (VA) (Stanley & Brown, 2012). The VA SPI is a brief clinical intervention aimed at mitigating suicide risk. It consists of a written, prioritized list of coping strategies and sources of support that patients can use to alleviate a suicidal crisis. Sites may use an internally-developed SPI if similar in scope and purpose to the VA SPI.

10.4.1.3. Visual Examination of Oral Cavity

A visual examination of the oral cavity should be done at Baseline/Visit 1 (or the Week 12 Visit of the 12-week open label study) and after 28 weeks (Visit 5) and 40 weeks (Visit 6) for Track A patients, or after 52 weeks of treatment (Visit 7) for Track B patients, and/or at ET. In addition to these regularly scheduled examinations, a visual inspection of the oral cavity (including the sublingual area) should be done any time a patient reports a lesion or other finding in the oral cavity other than numbness, tingling or bitter taste, in order to document the presence or absence of any visible abnormalities. Additional details related to onset, duration, severity and reversibility of oral events will also be documented in the CRF.

10.4.1.4. Vital Signs

Vital signs (sitting blood pressure and heart rate, respiratory rate, oral temperature, and weight) will be assessed at Visits 1, 3, 4, 5, 6 and 7 (Visit 7 for Track B patients only). Height will be transferred from the lead-in study database for BMI calculations (done at Baseline and Visit 6 for Track A patients or Visit 7 for Track B patients).

10.4.1.5. Clinical Laboratory Assessments

The clinical laboratory evaluations to be performed in this study are listed in Table 2. All tests will be performed at Baseline/Visit 1 (or the Week 12 Visit of the 12-week open label HONOR study), after 28 weeks (Visit 5) and after 40 weeks of treatment (Visit 6) for Track A patients, or after 52 weeks of treatment (Visit 7) for Track B patients, or ET.

With the exception of the urine pregnancy tests, all clinical laboratory evaluations will be analyzed via a central clinical laboratory, and information regarding appropriate sample volume, collection tubes, sample labeling and handling, and shipment will be provided in a study manual. Each clinically significant abnormal laboratory value or other clinically meaningful abnormality should be followed until the abnormality resolves or until a decision is made that it is not likely to resolve. If such abnormalities do not return to normal within a reasonable period, their etiology should be identified and Tonix or designee should be notified. Treatment-emergent clinically significant abnormalities in laboratory values will be recorded as AEs.

Table 2: Clinical Laboratory Assessments

Clinical chemistry	**Hematology**
Alanine aminotransferase (ALT)	Hematocrit

Alkaline phosphatase	Hemoglobin
Aspartate aminotransferase (AST)	MCH concentration (MCHC)
Bilirubin (total)	Mean corpuscular hemoglobin (MCH)
Blood urea nitrogen (BUN)	Mean corpuscular volume (MCV)
Calcium	Platelet count
Chloride	Red blood cell (RBC) count
Cholesterol (total)	White blood cell (WBC) count differential
Creatinine kinase (CK)	Neutrophil count (absolute and %)
Creatinine	Lymphocyte count (absolute and %)
Glucose	Monocyte count (absolute and %)
Phosphorus	Eosinophil count (absolute and %)
Potassium	Basophil count (absolute and %)
Protein (albumin and total)	WBC count
Sodium	
Urine Pregnancy Test (qualitative dipstick)[a]	
Pharmacogenomic testing (optional; can be obtained at any visit, including an early termination visit)	

[a] Pregnancy testing for females of child-bearing potential only. A positive pregnancy test mandates withdrawal from the study (all visits).

11. DEFINITIONS, RECORDING, AND REPORTING OF ADVERSE EVENTS AND PREGNANCY

11.1. Definition of Adverse Events

According to International Council on Harmonisation (ICH) guidance E2A, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, an AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which is not necessarily required to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

A newly-emergent adverse event (NEAE) is defined as any new AE that starts after the patient's baseline visit for P306, or any ongoing AE that was first reported during the lead-in study or 12-

week open-label extension study and which then exhibits an increase in severity, frequency or relationship after the patient's participation in P306 has begun. NEAEs and "All AEs" will be tallied by System Organ Class (SOC) and preferred terms. AEs that are ongoing at the time of the patient's baseline visit for P306 but which resolve, or persist without change in severity, frequency or relationship to study drug during the extension study, will be included in the tally of all AEs.

11.2. Adverse Event Recording

11.2.1. Coding the Adverse Event

Standard medical terminology should be used in describing AEs. Medical Dictionary for Regulatory Activities (MedDRA)® will be used as the standard coding dictionary for AEs and in describing the patient's medical history, and the World Health Organization (WHO) Drug Dictionary will be used to code concomitant medications. Informal descriptions should be avoided.

11.2.2. Severity of Adverse Event

AEs should be graded as mild, moderate, or severe using the following definitions.

- ***Mild:*** Awareness of signs or symptoms, but easily tolerated and of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.
- ***Moderate:*** Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning.
- ***Severe:*** Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.

To make sure there is no confusion or misunderstanding of the difference between the terms "serious "and "severe," which are not synonymous, the following note of clarification is provided. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, maybe of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

11.2.3. Relationship of Adverse Events to Study Drug

The investigator will assess the potential relationship of the AE to study drug using the following descriptions.

- ***Not Related:*** This category applies to an AE that is clearly not related to the investigational agent/procedure, beyond a reasonable doubt. That is, another cause of the event is most plausible; and/or a clinically plausible temporal sequence is

inconsistent with the onset of the event and the administration of study drug and/or a causal relationship is considered biologically implausible.

- ***Unlikely Related:*** This category applies to an AE that could reasonably be considered caused by something else, and where there is no known or expected response pattern to the suspected study drug.
- ***Possibly Related:*** This category applies to an AE that follows a reasonable temporal sequence from administration of the study drug and that follows a known or expected response pattern to the suspected study drug, but that could readily have been produced by a number of other factors.

11.3. Serious Adverse Events (SAEs) and Serious Adverse Drug Reactions

Any SAE that occurs at any time during the study, or within 28 days after the patient's last exposure to study drug, including a clinically significantly abnormal laboratory test result that is considered serious, must be reported to Tonix or its designee(s) so that Tonix may comply with regulatory obligations. If the SAE is life-threatening or fatal, it must be reported to Tonix or its designee(s) immediately, by email or telephone. For these and all other SAEs, an SAE report form must be completed and sent by facsimile or email to Tonix or its designee(s) within 24 hours of the site's initial awareness of the event. These requirements apply equally to all patients, regardless of the study phase or the at-risk patient's treatment assignment.

A serious adverse event (experience) or reaction is any untoward medical occurrence that, at any dose:

- Results in death,
- Is life-threatening,
- Requires in-patient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect, or
- Is an important medical event

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. *These should also usually be considered serious.* Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

A death occurring during the study or reported to the Investigator after study participation (no required post-study time limit) must be reported to Tonix or its designee(s) immediately, whether or not it is considered treatment-related. Initial SAE reports must be followed by detailed

descriptions. These should include copies of hospital case records and other documents when requested. The Contract Research Organization (CRO) will confirm via email or facsimile when it has received SAE documentation. If such confirmation is not received at the site in a timely manner, it is then the responsibility of the site to contact the CRO to ensure that the SAE documentation was indeed received by the CRO.

The Investigator or other study personnel must immediately inform one of the Tonix Medical Monitors by phone or email of any AE considered serious or otherwise significant, as described above. **In addition, a completed SAE report form must be submitted to [redacted] within 24 hours of the site's initial awareness of the event.**

[redacted]

Contact information for the Medical Monitors is provided below:

[redacted]

For questions pertaining to the reporting of SAEs or the completion of SAE documentation, site personnel should call the [redacted]

The investigator, or the sponsor or designee in the case of a central Institutional Review Board (IRB), also must notify the Ethics Committee (EC)/IRB of the occurrence of the SAE, in writing, as soon as is practicable and in accordance with local law. A copy of this notification must be provided to Tonix or its designee.

In the event of an SAE that meets the criteria for expedited reporting, an Investigational New Drug (IND) Safety Report will be prepared for submission to the FDA.

11.4. Pregnancy

The active pharmaceutical ingredient in TNX-102 SL 2.8 mg tablets is cyclobenzaprine HCl, which is in Pregnancy Category B (See Appendix 3 for AMRIX® Package Insert). All pregnancies occurring during the study (after exposure to study drug) or within 30 days after discontinuation of study drug must be followed until resolution (i.e., birth or voluntary or spontaneous termination of the pregnancy). Any patient found to be pregnant at any time during the study will be withdrawn from the study immediately. Any pregnancy outcome that meets the criteria for an SAE will be reported as an SAE.

12. STATISTICS

A description of any statistical analyses to be performed will be provided in a statistical analysis plan (SAP), which will be finalized prior to database lock.

12.1. Evaluation of Safety

Safety data will be summarized as a single treatment group receiving 1 or more doses of TNX-102 SL (patients that have taken only 1 tablet of TNX-102 SL will be included).

Safety will be assessed by the monitoring and recording of AEs, clinical laboratory tests, vital signs, visual examination of the oral cavity findings, the monitoring of suicidality using the Columbia C-SSRS scale, and patient-rated assessments of depressive symptomology (BDI-II) and PTSD symptomology (PCL-S).

AEs will be coded using the MedDRA and will be summarized overall and by preferred term and SOC. AEs will also be summarized by severity and relationship to study drug. SAEs and AEs leading to discontinuation of study drug will also be summarized.

Actual values and changes from the extension study baseline values for clinical laboratory test results and vital sign measurements will be summarized at endpoint using descriptive statistics (n, mean, standard deviation (SD), median, minimum, and maximum). Laboratory values will be displayed in the data listings along with corresponding normal ranges, and those that are outside the normal range will be flagged.

Based on the C-SSRS results, the frequency and severity of suicidal ideation and behavior will be tabulated at each time point. The number of patients with baseline and treatment-emergent suicidal ideation and/or suicidal behavior or self-injurious behavior, based on the C-SSRS, will be summarized by treatment group.

All data gathered will be listed by patient and parameter, and clinically significant abnormalities should be recorded as AEs. AEs of special interest indicating potential abuse and dependency will be evaluated and summarized as described in the Statistical Analysis Plan.

12.2. Evaluation of Efficacy

As this is a long-term safety study, minimal conclusions will be available concerning long-term efficacy. The efficacy analyses will focus on durability of the response achieved prior to entry into this extension study, based on the CGI-I for patients in Track A and for patients on active drug in the lead-in HONOR study or the P303-early-terminated patients (due to IA results) who were on placebo in P301 in Track B. In addition, durability of response for both Track A and B patients will be assessed by measuring the change in PCL-S scores from Visit 5 (Week 28) to Visit 6 (Week 40) in order to detect any potential worsening in PTSD symptoms as a result of longer term use of TNX-102 SL 5.6 mg. For Track B patients, an additional Visit 7 (Week 52) PCL-S assessment with be available for subset analysis of durability of response.

12.3. Estimate of Sample Size

No sample size calculations were made for this study as it is a follow-on, open-label study. The sample size for this study will depend upon the number of patients who participate in the lead-in

HONOR study, remain eligible for entry, and indicate willingness to participate in this extension study.

12.4. Assessment of Demographic and Baseline Characteristics and Patient Disposition

For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (n, mean, median, SD, minimum, and maximum).

Demographic and baseline characteristic variables will be summarized based on the data obtained at the screening visit from the lead-in HONOR study. The number of patients who enroll in the study and the number and percentage of patients in each analysis population who complete the treatment period will be presented. The frequency and percentage of patients who withdraw from the study, along with the reason for withdrawal or discontinuation, will also be summarized.

13. PROCEDURES FOR MODIFYING THE PROTOCOL OR TERMINATING THE STUDY

13.1. Protocol Modifications and Deviations

The investigator will make all reasonable efforts to comply with the written protocol and protocol amendments. All protocol modifications must be reviewed and approved by the appropriate EC/IRB before the revised protocol can be implemented. Emergency revisions that eliminate an apparent hazard to patients do not require preapproval by the EC/IRB. However, the EC/IRB must be notified, in writing, as soon as possible after the modification has been made. A copy of this communication must be forwarded to Tonix.

13.2. Study Termination

The study may be prematurely terminated at any time at the discretion of Tonix, its designee, or the principal investigator. Should premature termination be considered necessary, written notification documenting the reason for study termination will be provided, and specific procedures for termination will be arranged. Circumstances that may warrant premature study termination include, but are not limited to, the following.

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to the requirements of the protocol
- Insufficient provision of complete and evaluable data
- Plans to modify, suspend, or discontinue development of the study drug

In the event that the study is terminated prematurely, all study materials must be returned to Tonix or its designee.

14. ETHICAL CONSIDERATIONS

14.1. Ethical Conduct of the Study

This protocol is written in accordance with the principles established by the 18th World Medical Assembly General Assembly (Helsinki, 1964CI) and amendments and clarifications adopted by subsequent General Assemblies. The investigator will make sure that the study described in this protocol is conducted in full conformance with those principles, the protocol, current FDA regulations, ICH GCP guidelines, Good Laboratory Practices (GLP) guidelines, local ethical and regulatory requirements, including the Federal Food, Drug and Cosmetic Act, US applicable Code of Federal Regulations (CFR) (title 21), any EC requirements relative to clinical studies. As required by the US FDA, the study drug may not be shipped to any participating investigator until the requisite study documentation has been submitted to the IND.

Should a conflict arise, the investigator will follow whichever law or guideline affords the greater protection to the individual patient. The investigator will also make sure he or she is thoroughly familiar with the appropriate administration and potential risks of administration of the study drug, as described in this protocol and the Investigator's Brochure, prior to the initiation of the study.

14.2. Ethics Committee/Institutional Review Board (EC/IRB) Review

The EC/IRB must be a properly constituted board or committee operating in accordance with 21 CFR Part 56, "Institutional Review Boards." This protocol, any protocol amendments, the associated informed consent forms, and the informed consent procedures must be submitted to the EC/IRB for review and approved before the enrollment of any patient into the trial.

All types of patient recruitment or advertising information must be submitted to Tonix or its designee and to the EC/IRB for review and approval prior to implementation. EC/IRB approval of any protocol amendments must be received before any of the changes outlined in the amendments are put into effect, except when the amendment has been enacted to eliminate a potential hazard to study patients. In such cases, the chair of the EC/IRB should be notified immediately and the amendment forwarded to the EC/IRB for review and approval.

14.3. Written Informed Consent

It is the responsibility of the investigator to obtain signed written informed consent from each potential study patient prior to the conduct of any screening or other study procedures. This written informed consent will be obtained after the methods, objectives, and potential risks of the study have been fully explained to the potential patient. The investigator must explain to each patient that he or she is completely free to refuse to enter the study or to withdraw from it at any time. NOTE: Patients on antidepressant therapy should be warned of a potential serious drug interaction and should be advised to contact their study site immediately if they experience any symptoms that might represent possible serotonin syndrome, including fever, confusion or agitation, hallucinations, sweating, high or low blood pressure, rapid heart rate, tremor, muscle rigidity or nausea, vomiting or diarrhea.

The method of obtaining and documenting informed consent and the contents of the ICF will comply with ICH GCP guidelines, the requirements of 21 CFR Part 50, "Protection of Human

Patients," the HIPAA regulations, and all other applicable regulatory requirements. A properly executed written ICF shall be read, signed, and dated by each patient prior to entering the trial or prior to performing any study procedure. The original signed and dated ICF will be kept on file at the study site. Patients will be given a copy of the signed ICF and will be informed of any new developments during the course of the study that might influence their continued participation in the study.

The investigator or a qualified designee will be available to answer each patient's questions throughout the study, and all questions must be answered to the patient's satisfaction. If the protocol is amended and a revised ICF is introduced during the study, each patient's further consent must be obtained. The new version of the ICF must be approved by the EC, prior to subsequently obtaining each patient's consent.

Receipt of written informed consent will be documented in each patient's or potential patient's CRF. The signed ICF must remain in each patient's study file and must be available for verification by study monitors at all times.

Separate written, signed informed consent must be obtained if the patient is to participate in the optional pharmacogenomic assessment.

15. DATA HANDLING AND RECORDKEEPING

15.1. Maintaining Privacy and Confidentiality

In order to maintain patient privacy, all CRFs, study drug accountability records, and other documents, including communications between the study site and Tonix, will identify patients only by their initials or their assigned study identification numbers. If required, the investigator will grant monitors and auditors from Tonix or its designee and/or regulatory authority's access to patients' original medical records for verification of the data gathered on the CRFs and to audit the data collection process. Patients' confidentiality will be maintained and will not be made publicly available.

Special Provisions for Confidentiality: A Certificate of Confidentiality (CoC) has been obtained from the FDA for the investigators to protect patients enrolled in the study. Investigators may use the Certificate to avoid being compelled to make "involuntary disclosure" (e.g., subpoenas, insurers, employers, or other third parties) of names and other identifying information about any individual who participates as a research patient (i.e., about whom the investigator maintains identifying information) during any time the Certificate is in effect.

15.2. Maintaining Essential Clinical Documents

Study site files for the retention of regulatory documents will be established at the beginning of the study, maintained for the duration of the study, and retained according to FDA and ICH/GCP guidelines and applicable regulatory requirements. The records maintained must be adequate to fully document appropriate protection of study patients/patients, the validity of the study, the integrity of the data, and the manner in which the study was conducted.

The investigator's site file, copies of protocols, CRFs, originals of test result reports, drug disposition logs, correspondence, records of written informed consent, and other documents pertaining to the conduct of the study must be kept on file by the investigator and in readily accessible order for at least 2 years after the last approval of a marketing application, until at least 2 years have elapsed after formal discontinuation of the clinical development of the investigational product, or according to local regulatory requirements. No study document may be destroyed without prior written consent from Tonix or its designee. Should the investigator wish to withdraw from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. Tonix must be notified in writing in advance if a custodial change is to occur. It is important that the investigator remain ready to provide background information from the archived study records on request.

The sponsor or designee will maintain adequate study records for at least 2 years after the last approval of a marketing application or for at least 2 years after clinical development of the study drug for the indication being studied has been discontinued. After that period, the sponsor will be contacted to determine whether the study records will be forwarded to the sponsor, destroyed, or kept at the location of the designee or another facility for a longer period of time.

15.3. Data Handling

Unless otherwise specified, procedures, data collection and evaluation will be conducted as per the SOPs of the CRO. The investigator will assume the responsibility of ensuring the completeness and accuracy of the clinical data.

All laboratory results will be analyzed by an accredited and licensed clinical laboratory facility. Clinical laboratory data will be transferred from the central laboratory to the clinical database maintained by the CRO using systems which are validated and Part 11-compliant.

The responsible clinical study monitor(s) will check data at the monitoring visits to the clinical study site. The investigator will ensure that the data collected are accurate, complete, and legible. Any changes made to the clinical data will be documented with a full audit trail.

Aspects of the clinical and statistical phases of the study, including all associated documentation may be reviewed by the Quality Assurance Unit of the contract research organization using a risk-assessment approach. The final clinical and statistical report will be audited to ensure that, as far as can be reasonably established, the methods described and the results reported accurately reflect the raw data generated during the study.

15.4. Case Report Forms (CRFs)

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study patient. Data must be recorded on CRFs approved by Tonix or its designee. Data (including AEs) will be recorded on raw data sheets and/or electronic or paper source documents.

If selected data is collected via paper (patient questionnaires, etc.), the data must be entered into the eCRF and verified that it has been transcribed correctly.

15.5. Screening Records

A record must be kept of all patients considered for the study who sign informed consent and who began any screening procedures. The information should include the patient' initials, unique patient identification numbers, whether they passed or failed screening, and, if they failed, the reason for screen failure.

15.6. Clinical Laboratory Certification

A central clinical laboratory will be used to analyze all samples in this study, with the exception of the urine pregnancy test and ad hoc urine drug screens. The investigator must maintain, on file, written evidence that the central clinical laboratory to be used is certified under the Clinical Laboratory Improvement Act or equivalent certification (depending on local regulations). Further, the investigator will maintain a copy of the certification, the range of normal values, the effective dates for the ranges, and the units of measurement for all laboratory tests requested in the protocol. If any of the laboratory measurements will be transformed and/or categorized in any way, a description of the procedures(s) used should be included. The investigator is expected to receive these documents before the shipment of clinical supplies.

15.7. Site Monitoring and Tonix's Right to Review Records

Monitoring and auditing procedures developed by Tonix and/or its designee will be implemented to ensure compliance with FDA and ICH GCP and GLP guidelines.

Tonix's designated representative (the monitor or auditor) will contact the investigator and conduct regular visits to the clinical site. The monitor will be expected and allowed to verify the investigator's qualifications, to inspect clinical site facilities, and to inspect study records, including proof of EC/IRB review, with the stipulation that patient confidentiality will be maintained in accordance with local and federal regulations, including HIPAA requirements. The monitor will also be responsible for confirming adherence to the study protocol, inspecting CRFs and source documents, and ensuring the integrity of the data. CRFs will be checked for accuracy, completeness, and clarity and will be cross-checked for consistency with source documents, including laboratory test reports and other patient records. Instances of missing or uninterpretable data will be resolved in coordination with the investigator.

The monitor/auditor will also investigate any questions concerning adherence to regulatory requirements. Any administrative concerns will be clarified and followed. The monitor will maintain contact with the site through frequent direct communications with the study site by e-mail, telephone, facsimile, and mail. The investigator and all other site personnel agree to cooperate fully with the monitor and will work in good faith with the monitor to resolve any and all questions raised and difficulties detected by the monitor.

15.8. Audits and Inspections

The investigator understands that regulatory authorities, the EC/IRB, and/or Tonix or their designees have the right to access all CRFs, source documents, and other study documentation for on-site audit or inspection and will retain this right from the start of the study to at least 2 years after the last approval of a marketing application or for at least 2 years after clinical development of the study drug for the indication being studied has been discontinued. The investigator is required to guarantee access to these documents and to cooperate with and support such audits and inspections.

16. CONFIDENTIALITY

16.1. Protection of Patient Anonymity

The investigator must make sure that each patient's anonymity is maintained. On CRFs or other documents submitted to Tonix or its agent, patient should not be identified by their names, but rather by their initials and the assigned study identification numbers. The investigator should keep a separate record of the patient initials, randomization codes, patient names, address, and contact information. Documents that contain the names associated with these initials and codes are not for submission to Tonix or its agents (e.g., written informed consent forms). These records should be maintained by the investigator in strict confidence except to the extent necessary to allow auditing by regulatory authorities, Tonix, or its agents. These records should be kept in compliance with HIPAA regulations.

Special Provisions for Confidentiality: In addition, a Certificate of Confidentiality (CoC) has been obtained from the FDA for the investigators to protect patients enrolled in the study. Investigators can use the Certificate to avoid being compelled to make "involuntary disclosure" (e.g., subpoenas, insurers, employers, or other third parties) of names and other identifying information about any individual who participates as a research patient (i.e., about whom the investigator maintains identifying information) during any time the Certificate is in effect.

16.2. Confidentiality of Study Information

All information relevant to this study, whether supplied by Tonix or its agents to the investigator or collected by the investigator in support of this study, is privileged and confidential. The investigator agrees to use this information to carry out the study and will not use it for other purposes without written consent from Tonix. It is understood that the investigator is under obligation to provide Tonix with all data obtained during the study. The information obtained from this study will be used by Tonix towards the clinical development of the indicated investigational drug and may be disclosed by Tonix to regulatory authorities, other investigators, corporate partners, or consultants as required.

16.3. Publication of Data and Protection of Trade Secrets

No presentations, abstracts (including meeting abstracts), or other publications based on the conduct or results of this study will be permitted without the express written permission of Tonix or its designated agent. All such presentations or publications will proceed only as collaborations between Tonix and the investigators.

If the investigator wishes to publish the results of this study, a copy of the proposed manuscript or abstract (including meeting abstracts) will be provided to Tonix or its designee for review, revision, and approval at least sixty (60) days before the expected date of submission for publication, unless otherwise arranged with Tonix in writing. This will enable Tonix to protect its proprietary information and augment the publication with insights or information of which the investigator may not be aware.

Patient names and other identifiers, such as photographs or audio or video recordings, may not be disclosed in any publication or public forum without prior written authorization from the

patients involved or their legal guardians. Tonix retains authority to delete any of its confidential information from such disclosures.

17. LIST OF REFERENCES

Stanley B and Brown GK. Safety planning intervention: A brief intervention to mitigate suicide risk. Cognitive and Behavioral Practice 2012; 19:256-264.

18. APPENDICES

APPENDIX 1. STUDY DESIGN AND SCHEDULE OF ASSESSMENTS

Period	**Baseline**	**Phone[f]**	**Clinic Visits**				
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7[j]**
Study Week	**0**	**2**	**7**	**16**	**28**	**40**	**52**
Study Day	**0**	**14 ± 3**	**49 ± 7**	**112 ± 7**	**196 ± 7**	**280 ± 7**	**365 ± 7**
Informed Consent	X						
Inclusion Criteria	X						
Concomitant Medications[b]	X	X[f]	X	X	X	X	X
Vital Signs and weight	X[a]		X	X	X	X	X
Inspection of oral cavity[c]	X[a]				X	X [i]	X
Pregnancy Test[d]	X[a]		X	X	X	X	X
Clinical Laboratory Assessments	X[a]				X	X [i]	X
BDI-II	X[a]		X	X	X	X	X
C-SSRS	X[a]	X[f]	X	X	X	X	X
CGI-I (compared to P306 baseline only)[e]			X	X	X	X	X
PROMIS-Sleep (short form)	X[a]		X	X	X	X	X
SDS	X[a]		X	X	X	X	X
PCL-S					X[h]	X[h]	X
Pharmacogenomic blood draw (optional)[g]	*	*	*	*	*	*	*
Adverse Events	X	X[f]	X	X	X	X	X
Telephone Visit		X[f]					
Dispense Study Drug	X		X	X	X	X[j]	
Collect/ Count Study Drug Returned			X	X	X	X	X

Abbreviations: BDI-II = Beck Depression Inventory-II; C-SSRS = Columbia-Suicide Severity Rating Scales; CGI-I (Clinician Global Impression of Improvement); PROMIS = Patient Reported Outcomes Measurement Information System; SDS = Sheehan Disability Scale; PCL-S = PTSD Checklist-Specific Version

[a] These assessments are only to be conducted for patients entering the study from Track B, or Track A patients that roll over into P306 greater than 14 days after the final visit of the previous study.

[b] Medications that are ongoing at the end of the previous study will be recorded as such in this study.

[c] In addition to the regularly scheduled examination, a visual examination of the oral cavity should be done at any visit in which an oral adverse event has been reported.

[d] Women of child-bearing potential only.

[e] The CGI-I will be done only in comparison to the baseline visit of P306.

[f] Patients enrolled from the double-blind lead-in study, P301/HONOR, only will have the phone check-in.

*/[g]The blood draw for the pharmacogenomic assessment can be obtained at any study visit (including an early termination visit). It should only be obtained one time during the study. Separate written, signed informed consent will be required if the patient is to participate in the optional pharmacogenomic assessment.

[h] Visit 5(Week 28) will be the "baseline" for PCL-S because it will capture the vast majority of the patients who have enrolled from the start of P306. The mean change in PCL-S total score and PCL-S clusters scores from Visit 5 (Week 28) to Visit 6 (Week 40), and to Visit 7 for Track B patients, will detect any potential worsening in total PTSD score or symptoms clusters due to long-term treatment of TNX-102 SL in the final 12-weeks, and 24-weeks for Track B patients, of the study.

[i] Track A patients only.

[j] Track B patients only.

APPENDIX 2. LIST OF CYP3A INHIBITORS

Taken from Table 3, FDA Draft Guidance for Industry: Drug Interaction Studies—Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations; Feb 2012; updated Sept. 26, 2016). Excluded strong CYP3A4 inhibitors are listed in the far left column of the table.

	Strong Inhibitors **≥ 5-fold increase in AUC** **Or, > 80% decrease in CL**	**Moderate Inhibitors** ≥ 2 but < 5-fold increase in AUC Or 50-80% decrease in CL	**Weak Inhibitors** ≥ 1.25 but < 2-fold increase in AUC Or, 20-50% decrease in CL
CYP3A4	**Boceprevir**	amprenavir	alprazolam
	clarithromycin	aprepitant	amiodarone
	cobicistat	atazanavir	amlodipine
	conivaptan	cimetidine	atorvastatin
	danoprevir	ciprofloxacin	bicalutamide
	elvitegravir	clotrimazole	chlorzoxazone
	grapefruit juice	crizotinib	cilostazol
	indinavir	cyclosporine	fosaprepitant
	itraconazole	darunavir/ritonavir	fluoxetine
	ketoconazole	diltiazem	gingko
	lopinavir	dronedarone	goldenseal
	mibefradil	erythromycin	isoniazid
	nefazodone	fluconazole	istradefylline
	nelfinavir	fluvoxamine	ivacaftor
	paritaprevir	fosamprenavir	lapatinib
	posaconazole	imatinib	lomitapide
	ritonavir	tofisopam	nilotinib
	saquinavir	verapamil	oral contraceptives
	telaprevir		pazopanib
	telithromycin		ranitidine
	tipranavir		ranolazine
	troleandomycin		tacrolimus
	voriconazole		tipranavir/ritonavir
			ticagrelor
			zileuton

Source: Table 3-2,
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

APPENDIX 3. AMRIX® PACKAGE INSERT (DATED MAY 2018)

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AMRIX safely and effectively. See full prescribing information for AMRIX.

AMRIX® (cyclobenzaprine hydrochloride extended-release capsules), for oral use
Initial U.S. Approval: 1977

INDICATIONS AND USAGE
AMRIX is a muscle relaxant indicated as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions. (1)
Limitations of Use:
- AMRIX should be used only for short periods (up to 2 or 3 weeks) (1)
- AMRIX has not been found effective in the treatment of spasticity or cerebral palsy (1)

DOSAGE AND ADMINISTRATION
- Recommended adult dose for most patients is 15 mg taken once daily. Some patients may require 30 mg taken once daily (2)
- Recommended to take doses at approximately same time each day (2)
- Instruct patients to swallow AMRIX capsules intact or to sprinkle capsule contents on a tablespoon of applesauce and swallow immediately without chewing (2)
- Use for periods longer than 2 or 3 weeks is not recommended (2)

DOSAGE FORMS AND STRENGTHS
- Extended-release capsules: 15 and 30 mg (3)

CONTRAINDICATIONS
- Hypersensitivity to any component of this product (4)
- Concomitant use of monoamine oxidase (MAO) inhibitors or within 14 days after their discontinuation (4)
- During acute recovery phase of myocardial infarction, and in patients with arrhythmias, heart block or conduction disturbances, or congestive heart failure (4)
- Hyperthyroidism (4)

AMRIX® (cyclobenzaprine hydrochloride extended-release capsules)

WARNINGS AND PRECAUTIONS
- Serotonin syndrome has been reported with cyclobenzaprine when used in combination with other serotonergic drugs (5.1)
- Cyclobenzaprine is structurally related to tricyclic antidepressants which have been reported to produce adverse cardiovascular effects or CNS depressant effects (5.2)
- Use in the elderly is not recommended (5.3)
- Use in patients with hepatic impairment is not recommended (5.4)
- Use with caution in patients with a history of urinary retention, angle-closure glaucoma, increased intraocular pressure and in patients taking anticholinergic medications (5.5)

ADVERSE REACTIONS
Most common adverse reactions (incidence ≥3% in any treatment group and greater than placebo): dry mouth, dizziness, fatigue, constipation, nausea, dyspepsia, and somnolence (6)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals at 1-888-483-8279 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS
- MAO Inhibitors: Life-threatening interactions may occur (4, 7)
- Serotonergic Drugs: Serotonin syndrome has been reported (5.1, 7)
- CNS Depressants: Effects of alcohol, barbiturates, and other CNS depressants may be enhanced (5.2, 7)
- Tramadol: Seizure risk may be enhanced (7)
- Guanethidine: Antihypertensive effect may be blocked (7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 5/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
AMRIX® (cyclobenzaprine hydrochloride extended-release capsules) is indicated as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions. Improvement is manifested by relief of muscle spasm and its associated signs and symptoms, namely, pain, tenderness, and limitation of motion.
Limitations of Use:
- AMRIX should be used only for short periods (up to two or three weeks) because adequate evidence of effectiveness for more prolonged use is not available and because muscle spasm associated with acute, painful musculoskeletal conditions is generally of short duration and specific therapy for longer periods is seldom warranted.
- AMRIX has not been found effective in the treatment of spasticity associated with cerebral or spinal cord disease or in children with cerebral palsy.

2 DOSAGE AND ADMINISTRATION
The recommended adult dose for most patients is one (1) AMRIX 15 mg capsule taken once daily. Some patients may require up to 30 mg/day, given as one (1) AMRIX 30 mg capsule taken once daily or as two (2) AMRIX 15 mg capsules taken once daily.
- It is recommended that doses be taken at approximately the same time each day.
- Use of AMRIX for periods longer than two or three weeks is not recommended *[see Indications and Usage (1)]*.

Instruct patients to swallow AMRIX capsules intact. Alternatively, the contents of the AMRIX capsule may be sprinkled over applesauce and then swallowed. This method is appropriate only for patients able to reliably swallow the applesauce without chewing. Other foods have not been tested and should not be substituted for applesauce. Instruct the patient to:
- Sprinkle the contents of the capsule onto a tablespoon of applesauce and consume immediately without chewing.
- Rinse the mouth to ensure all of the contents have been swallowed.
- Discard any unused portion of the AMRIX capsules after the contents have been sprinkled on applesauce.

3 DOSAGE FORMS AND STRENGTHS
Extended-release capsules in the following strengths:
- 15 mg: Capsules are orange/orange and are embossed in blue ink with "15 mg" on the body, and Cephalon "C" logo, "Cephalon," and a dashed band on the cap.
- 30 mg: Capsules are blue/red and are embossed in white ink with "30 mg" on the body, and Cephalon "C" logo, "Cephalon," and a dashed band on the cap.

4 CONTRAINDICATIONS
- Hypersensitivity to any component of this product. These adverse reactions may manifest as an anaphylactic reaction, urticaria, facial and/or tongue swelling, or pruritus. Discontinue AMRIX if a hypersensitivity reaction is suspected.
- Concomitant use of monoamine oxidase (MAO) inhibitors or within 14 days after their discontinuation. Hyperpyretic crisis seizures and deaths have occurred in patients receiving cyclobenzaprine (or structurally similar tricyclic antidepressants) concomitantly with MAO inhibitor drugs.
- During the acute recovery phase of myocardial infarction, and in patients with arrhythmias, heart block or conduction disturbances, or congestive heart failure.
- Hyperthyroidism.

5 WARNINGS AND PRECAUTIONS

5.1 Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome has been reported with cyclobenzaprine when used in combination with other drugs, such as selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), tramadol, bupropion, meperidine, verapamil, or MAO inhibitors. The concomitant use of AMRIX with MAO inhibitors is contraindicated *[see Contraindications (4)]*. Serotonin syndrome symptoms may include mental status changes (e.g., confusion, agitation, hallucinations), autonomic instability (e.g., diaphoresis, tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g., tremor, ataxia, hyperreflexia, clonus, muscle rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Treatment with AMRIX and any concomitant serotonergic agents should be discontinued immediately if the above reactions occur and supportive symptomatic treatment should be initiated. If concomitant treatment with AMRIX and other serotonergic drugs is clinically warranted, careful observation is advised, particularly during treatment initiation or dose increases.

5.2 Tricyclic Antidepressant-like Effects

Cyclobenzaprine is structurally related to the tricyclic antidepressants, e.g., amitriptyline and imipramine. Tricyclic antidepressants have been reported to produce arrhythmias, sinus tachycardia, prolongation of the conduction time leading to myocardial infarction and stroke *[see Contraindications (4)]*. AMRIX may enhance the effects of alcohol, barbiturates, and other CNS depressants.

Some of the more serious central nervous system (CNS) reactions noted with the tricyclic antidepressants have occurred in short-term studies of cyclobenzaprine for indications other than muscle spasm associated with acute musculoskeletal conditions, and usually at doses somewhat greater than those recommended for skeletal muscle spasm. If clinically significant CNS symptoms develop, consider discontinuation of AMRIX.

5.3 Use in the Elderly

As a result of a 40% increase in cyclobenzaprine plasma levels and a 56% increase in plasma half-life following administration of AMRIX in elderly subjects as compared to young adults, use of AMRIX is not recommended in the elderly *[see Clinical Pharmacology (12.3)]*.

5.4 Use in Patients with Hepatic Impairment

As a result of two-fold higher cyclobenzaprine plasma levels in subjects with mild hepatic impairment, as compared to healthy subjects, following administration of immediate-release cyclobenzaprine and because there is limited dosing flexibility with AMRIX, use of AMRIX is not recommended in patients with mild, moderate, or severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

5.5 Atropine-like Action

Because of its atropine-like action, AMRIX should be used with caution in patients with a history of urinary retention, angle-closure glaucoma, increased intraocular pressure, and in patients taking anticholinergic medication.

6 ADVERSE REACTIONS

Most Common Adverse Reactions in the AMRIX Clinical Trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data described below reflect exposure to AMRIX in 253 patients in 2 clinical trials. AMRIX was studied in two double-blind, parallel-group, placebo-controlled, active-controlled trials of identical design *[see Clinical Studies (14)]*. The study population was composed of patients with muscle spasms associated with acute painful musculoskeletal conditions. Patients received 15 mg or 30 mg of AMRIX taken orally once daily, cyclobenzaprine immediate-release (IR) 10 mg three times a day, or placebo for 14 days.

The most common adverse reactions (incidence ≥3% in any treatment group and greater than placebo) were dry mouth, dizziness, fatigue, constipation, nausea, dyspepsia, and somnolence (see Table 1).

Table 1: Incidence of the Most Common Adverse Reactions Occurring in ≥ 3% of Patients in any Treatment Group* and Greater Than Placebo in the Two Phase 3, Double-Blind AMRIX Trials

	Placebo	AMRIX 15 mg	AMRIX 30 mg
	N=128	N=127	N=126
Dry mouth	2%	6%	14%
Dizziness	2%	3%	6%
Fatigue	2%	3%	3%
Constipation	0%	1%	3%
Somnolence	0%	1%	2%
Nausea	1%	3%	3%
Dyspepsia	1%	0%	4%

*AMRIX 15 mg QD, AMRIX 30 mg QD, or cyclobenzaprine IR tablets TID

Additional Adverse Reactions from Clinical Studies and Postmarketing Experience

The following adverse reactions have been reported in clinical studies or postmarketing experience with AMRIX, cyclobenzaprine IR, or tricyclic drugs. Because some of these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

In a postmarketing surveillance program of cyclobenzaprine IR, the adverse reactions reported most frequently were drowsiness, dry mouth, and dizziness and adverse reactions reported in 1% to 3% of the patients were: fatigue/tiredness, asthenia, nausea, constipation, dyspepsia, unpleasant taste, blurred vision, headache, nervousness, and confusion.

The following adverse reactions have been reported in postmarketing experience (AMRIX or cyclobenzaprine IR), in clinical studies of cyclobenzaprine IR (incidence <1%), or in postmarketing experience with other tricyclic drugs:

Body as a Whole: Syncope; malaise; chest pain; edema.

Cardiovascular: Tachycardia; arrhythmia; vasodilatation; palpitation; hypotension; hypertension; myocardial infarction; heart block; stroke.

Digestive: Vomiting; anorexia; diarrhea; gastrointestinal pain; gastritis; thirst; flatulence; edema of the tongue; abnormal liver function and rare reports of hepatitis, jaundice, and cholestasis; paralytic ileus, tongue discoloration; stomatitis; parotid swelling.

Endocrine: Inappropriate ADH syndrome.

Hematologic and Lymphatic: Purpura; bone marrow depression; leukopenia; eosinophilia; thrombocytopenia.

Hypersensitivity: Anaphylaxis; angioedema; pruritus; facial edema; urticaria; rash.

Metabolic, Nutritional, and Immune: Elevation and lowering of blood sugar levels; weight gain or loss.

Musculoskeletal: Local weakness; myalgia.

Nervous System and Psychiatric: Seizures, ataxia; vertigo; dysarthria; tremors; hypertonia; convulsions; muscle twitching; disorientation; insomnia; depressed mood; abnormal sensations; anxiety; agitation; psychosis, abnormal thinking and dreaming; hallucinations; excitement; paresthesia; diplopia; serotonin syndrome; neuroleptic malignant syndrome; decreased or increased libido; abnormal gait; delusions; aggressive behavior; paranoia; peripheral neuropathy; Bell's palsy; alteration in EEG patterns; extrapyramidal symptoms.

Respiratory: Dyspnea.

Skin: Sweating; photosensitization; alopecia.

Special Senses: Ageusia; tinnitus.

Urogenital: Urinary frequency and/or retention; impaired urination; dilatation of urinary tract; impotence; testicular swelling; gynecomastia; breast enlargement; galactorrhea.

7 DRUG INTERACTIONS

Based on its structural similarity to tricyclic antidepressants, AMRIX may have life-threatening interactions with MAO inhibitors *[see Contraindications (4)]*, may enhance the effects of alcohol, barbiturates, and other CNS depressants, may enhance the seizure risk in patients taking tramadol, or may block the antihypertensive action of guanethidine and similarly acting compounds.

Postmarketing cases of serotonin syndrome have been reported during combined use of cyclobenzaprine and other drugs, such as SSRIs, SNRIs, TCAs, tramadol, bupropion, meperidine, verapamil, or MAO inhibitors *[see Warnings and Precautions (5.1)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B: There are no adequate and well-controlled studies of AMRIX in pregnant women. Because animal reproduction studies are not always predictive of human response, AMRIX should be used during pregnancy only if clearly needed. No treatment-related effects on embryofetal development were observed in mice and rabbits at approximately 3 and 15 times the maximum recommended human dose (MRHD), respectively (on a mg/m² basis at maternal doses of 20 mg/kg/day in both mice and rabbits).

Nonteratogenic Effects

Cyclobenzaprine has been shown to adversely affect pup postnatal development when dams were treated with the drug during pregnancy and lactation periods in rats. This study found that cyclobenzaprine decreased pup body weight and survival at approximately ≥3 times the MRHD (on a mg/m² basis at maternal doses of 10 and 20 mg/kg/day in rats).

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because cyclobenzaprine is closely related to the tricyclic antidepressants, some of which are known to be excreted in human milk, caution should be exercised when AMRIX is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of AMRIX have not been studied in pediatric patients.

8.5 Geriatric Use

Clinical studies of AMRIX did not include sufficient numbers of patients aged 65 and over to determine the safety and efficacy of AMRIX in the elderly population. The plasma concentration and half-life of cyclobenzaprine are substantially increased in the elderly when compared to the general patient population. Accordingly, use of AMRIX is not recommended in the elderly *[see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*.

8.6 Hepatic Impairment

The use of AMRIX is not recommended in patients with mild, moderate, or severe hepatic impairment *[see Warnings and Precautions (5.4) and Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.3 Dependence

Pharmacologic similarities among the tricyclic drugs require that certain withdrawal symptoms be considered when AMRIX is administered, even though they have not

been reported to occur with this drug. Abrupt cessation of treatment after prolonged administration rarely may produce nausea, headache, and malaise. These are not indicative of addiction.

10 OVERDOSAGE

Although rare, deaths may occur from overdosage with AMRIX. Multiple drug ingestion (including alcohol) is common in deliberate cyclobenzaprine overdose. **As management of overdose is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment.** Signs and symptoms of toxicity may develop rapidly after cyclobenzaprine overdose; therefore, hospital monitoring is required as soon as possible.

10.1 Manifestations

The most common effects associated with cyclobenzaprine overdose are drowsiness and tachycardia. Less frequent manifestations include tremor, agitation, coma, ataxia, hypertension, slurred speech, confusion, dizziness, nausea, vomiting, and hallucinations. Rare but potentially critical manifestations of overdose are cardiac arrest, chest pain, cardiac dysrhythmias, severe hypotension, seizures, and neuroleptic malignant syndrome. Changes in the electrocardiogram, particularly in QRS axis or width, are clinically significant indicators of cyclobenzaprine toxicity. Other potential effects of overdosage include any of the symptoms listed under *Adverse Reactions (6)*.

10.2 Management

General

As management of overdose is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment. In order to protect against the rare but potentially critical manifestations described above, obtain an ECG and immediately initiate cardiac monitoring. Protect the patient's airway, establish an intravenous line, and initiate gastric decontamination. Observation with cardiac monitoring and observation for signs of CNS or respiratory depression, hypotension, cardiac dysrhythmias and/or conduction blocks, and seizures is necessary. If signs of toxicity occur at any time during this period, extended monitoring is required. Monitoring of plasma drug levels should not guide management of the patient. Dialysis is probably of no value because of low plasma concentrations of the drug.

Gastrointestinal Decontamination

All patients suspected of an overdose with AMRIX should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage and emesis is contraindicated.

Cardiovascular

A maximal limb-lead QRS duration of 0.10 seconds may be the best indication of the severity of the overdose. Serum alkalinization, to a pH of 7.45 to 7.55, using intravenous sodium bicarbonate and hyperventilation (as needed), should be instituted for patients with dysrhythmias and/or QRS widening. A pH >7.60 or a pCO_2 <20 mmHg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium, or phenytoin. Type 1A and 1C antiarrhythmics are generally contraindicated (e.g., quinidine, disopyramide, and procainamide).

CNS

In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with benzodiazepines or, if these are ineffective, other anticonvulsants (e.g., phenobarbital, phenytoin). Physostigmine is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies, and then only in close consultation with a poison control center.

Psychiatric Follow-Up

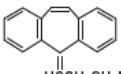
Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Psychiatric referral may be appropriate.

Pediatric Management

The principles of management of child and adult overdosage are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

11 DESCRIPTION

AMRIX is a skeletal muscle relaxant which relieves muscle spasm of local origin without interfering with muscle function. The active ingredient in AMRIX extended-release capsules is cyclobenzaprine hydrochloride, USP. Cyclobenzaprine hydrochloride (HCl) is a white, crystalline tricyclic amine salt with the empirical formula $C_{20}H_{21}N$·HCl and a molecular weight of 311.9. It has a melting point of 217°C, and a pK_a of 8.47 at 25°C. It is freely soluble in water and alcohol, sparingly soluble in isopropanol, and insoluble in hydrocarbon solvents. If aqueous solutions are made alkaline, the free base separates. Cyclobenzaprine HCl is designated chemically as 3-(*5H*-dibenzo[*a,d*] cycloheptен-5-ylidene)-*N,N*-dimethyl-1-propanamine hydrochloride, and has the following structural formula:



$HCCH_2CH_2N(CH_3)_2 \cdot HCl$

AMRIX extended-release capsules for oral administration are supplied in 15 and 30 mg strengths. AMRIX capsules contain the following inactive ingredients: diethyl phthalate NF, ethylcellulose NF (Ethocel Standard 10 Premium), gelatin, Opadry® Clear YS-1-7006, sugar spheres NF (20-25 mesh), and titanium dioxide. AMRIX 15 mg capsules also contain D&C yellow #10, FD&C green #3, and FD&C red #40. AMRIX 30 mg capsules also contain FD&C blue #1, FD&C blue #2, FD&C red #40, and FD&C yellow #6.

AMRIX® (cyclobenzaprine hydrochloride extended-release capsules)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Cyclobenzaprine relieves skeletal muscle spasm of local origin without interfering with muscle function. Cyclobenzaprine has not been shown to be effective in muscle spasm due to central nervous system disease. In animal models, cyclobenzaprine reduced or abolished skeletal muscle hyperactivity. Animal studies indicate that cyclobenzaprine does not act at the neuromuscular junction or directly on skeletal muscle. Such studies show that cyclobenzaprine acts primarily within the central nervous system at the brain stem as opposed to the spinal cord level, although an overlapping action on the latter may contribute to its overall skeletal muscle relaxant activity. Evidence suggests that the net effect of cyclobenzaprine is a reduction of tonic somatic motor activity, influencing both gamma (γ) and alpha (α) motor systems. Pharmacological studies in animals demonstrated a similarity between the effects of cyclobenzaprine and the structurally related tricyclic antidepressants, including reserpine antagonism, norepinephrine potentiation, potent peripheral and central anticholinergic effects, and sedation. Cyclobenzaprine caused slight to moderate increase in heart rate in animals.

12.3 Pharmacokinetics

Absorption

Following single-dose administration of AMRIX 15 mg and 30 mg in healthy adult subjects (n=15), C_{max}, $AUC_{0\text{-}168h}$ and $AUC_{0\text{-}\infty}$ increased in an approximately dose-proportional manner from 15 mg to 30 mg. The time to peak plasma cyclobenzaprine concentration (T_{max}) was 7 to 8 hours for both doses of AMRIX.

A food effect study conducted in healthy adult subjects (n=15) utilizing a single dose of AMRIX 30 mg demonstrated a statistically significant increase in bioavailability when AMRIX 30 mg was given with food relative to the fasted state. There was a 35% increase in peak plasma cyclobenzaprine concentration (C_{max}) and a 20% increase in exposure ($AUC_{0\text{-}168h}$ and $AUC_{0\text{-}\infty}$) in the presence of food. No effect, however, was noted in T_{max} or the shape of the mean plasma cyclobenzaprine concentration versus time profile. Cyclobenzaprine in plasma was first detectable in both the fed and fasted states at 1.5 hours.

When the contents of AMRIX capsules were administered by sprinkling on applesauce, it was found to be bioequivalent to the same dose when administered as an intact capsule.

In a multiple-dose study utilizing AMRIX 30 mg administered once daily for 7 days in a group of healthy adult subjects (n=35), a 2.5-fold accumulation of plasma cyclobenzaprine levels was noted at steady-state.

Metabolism and Excretion

Cyclobenzaprine is extensively metabolized and is excreted primarily as glucuronides via the kidney. Cytochromes P-450 3A4, 1A2, and, to a lesser extent, 2D6, mediate N-demethylation, one of the oxidative pathways for cyclobenzaprine. Cyclobenzaprine has an elimination half-life of 32 hours (range 8-37 hours; n=18); plasma clearance is 0.7 L/min following single-dose administration of AMRIX.

Special Populations

Elderly

Although there were no notable differences in C_{max} or T_{max}, cyclobenzaprine plasma AUC is increased by 40% and the plasma half-life of cyclobenzaprine is prolonged in elderly subjects greater than 65 years of age (50 hours) after dosing with AMRIX compared to younger subjects 18 to 45 years of age (32 hours). Pharmacokinetic characteristics of cyclobenzaprine following multiple-dose administration of AMRIX in the elderly were not evaluated.

Hepatic Impairment

In a pharmacokinetic study of immediate-release cyclobenzaprine in 16 subjects with hepatic impairment (15 mild, 1 moderate per Child-Pugh score), both AUC and C_{max} were approximately double the values seen in the healthy control group. The pharmacokinetics of cyclobenzaprine in subjects with severe hepatic impairment is not known.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies were conducted in CD-1 mice and Sprague-Dawley rats with cyclobenzaprine to evaluate its carcinogenic potential. In an 81-week carcinogenicity study, metastatic hemangiosarcoma was seen in 3 of 21 male mice at 10 mg/kg/day (2 times the MRHD on a mg/m^2 basis). In a 105-week carcinogenicity study, malignant astrocytoma was seen in 3 of 50 male rats at 10 mg/kg/day (3 times the MRHD on a mg/m^2 basis). There were no tumor findings in female mice or rats.

Cyclobenzaprine HCl was not mutagenic or clastogenic in the following assays: an *in vitro* Ames bacterial mutation assay, *in vitro* Chinese hamster ovary (CHO) cell chromosomal aberration test, and *in vivo* mouse bone marrow micronucleus assay.

Cyclobenzaprine HCl had no effects on fertility and reproductive performance in male or female rats at oral doses up to 20 mg/kg/day (6 times the MRHD on a mg/m^2 basis).

13.2 Animal Toxicology and/or Pharmacology

In a 67-week study with rats that received cyclobenzaprine at oral doses of 10, 20, or 40 mg/kg/day (3 to 15 times the MRHD on mg/m^2 basis), there were findings in the liver consisting of midzonal vacuolation with lipidosis for males and midzonal and centrilobular hepatocytic enlargement for females. In addition, there were findings of centrilobular coagulative necrosis. In the higher dose groups, these microscopic changes were seen after 26 weeks and even earlier in rats that died prior to 26 weeks; at lower doses, these changes were not seen until after 26 weeks.

In a 26-week study with Cynomolgus monkeys that received cyclobenzaprine at oral of doses of 2.5, 5, 10, or 20 mg/kg/day, one monkey at 20 mg/kg/day (15 times the MRHD

on mg/m² basis) was euthanized in week 17. Morbidity for this animal was attributed to findings of chronic pancreatitis, cholecystitis, cholangitis, and focal liver necrosis.

14 CLINICAL STUDIES

Efficacy was assessed in two double-blind, parallel-group, active-controlled, placebo-controlled studies of identical design of AMRIX 15 mg and 30 mg taken once daily, between 6:00 and 7:00 PM, cyclobenzaprine 10 mg three times a day, or placebo for 14 days in patients with muscle spasms associated with acute painful musculoskeletal conditions.

There were significant differences in the primary efficacy analysis, the patient's rating of medication helpfulness, between the AMRIX 15 mg group and the placebo group at Days 4 and 14 in one study and between the AMRIX 30 mg group and the placebo group at Day 4 in the second study.

Table 2: Patients' Rating of Medication Helpfulness - Study 1*

	Day 4		Day 14	
	Number of Patients (%)		Number of Patients (%)	
	Placebo (N = 64)	AMRIX 30 mg (N = 64)	Placebo (N = 64)	AMRIX 30 mg (N = 64)
Excellent	1 (2%)	3 (5%)	12 (19%)	15 (23%)
Very Good	5 (8%)	13 (20%)	9 (14%)	19 (30%)
Good	15 (23%)	22 (34%)	10 (16%)	15 (23%)
Fair	24 (38%)	20 (31%)	16 (25%)	10 (16%)
Poor	10 (16%)	5 (8%)	9 (14%)	4 (6%)
Missing	9 (14%)	1 (2%)	8 (13%)	1 (2%)

*Percentages are rounded to the nearest whole percent.

Table 3: Patients' Rating of Medication Helpfulness - Study 2*

	Day 4		Day 14	
	Number of Patients (%)		Number of Patients (%)	
	Placebo (N = 64)	AMRIX 15 mg (N = 63)	Placebo (N = 64)	AMRIX 15 mg (N = 63)
Excellent	1 (2%)	2 (3%)	10 (16%)	13 (21%)
Very Good	10 (16%)	12 (19%)	12 (19%)	21 (33%)
Good	14 (22%)	21 (33%)	13 (20%)	9 (14%)
Fair	16 (25%)	17 (27%)	14 (22%)	10 (16%)
Poor	19 (30%)	6 (10%)	12 (19%)	5 (8%)
Missing	4 (6%)	5 (8%)	3 (5%)	5 (8%)

*Percentages are rounded to the nearest whole percent.

In addition, one of the two studies demonstrated significant differences between the AMRIX 30 mg group and the placebo group in terms of patient-rated relief from local pain due to muscle spasm at Day 4 and Day 8, in patient-rated restriction of movement at Day 4 and Day 8, and in patient-rated global impression of change at Day 4, Day 8, and Day 14.

In both studies, there were no significant treatment differences between the AMRIX treatment groups and the placebo group in physician's global assessment, patient-rated restriction in activities of daily living, or quality of nighttime sleep.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

AMRIX extended-release capsules are available in 15 and 30 mg strengths, packaged in bottles of 60 capsules. AMRIX 15 mg capsules (NDC 63459-700-60) are orange/orange and are embossed in blue ink with "15 mg" on the body, and Cephalon "C" logo, "Cephalon", and a dashed band on the cap. AMRIX 30 mg capsules (NDC 63459-701-60) are blue/red and are embossed in white ink with "30 mg" on the body, and Cephalon "C" logo, "Cephalon", and a dashed band on the cap.

16.2 Storage and Handling

Dispense in a tight, light-resistant container as defined in the USP/NF.

Store at 25°C (77°F); excursions permitted to 15 - 30°C (59 - 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

- Instruct patients to swallow AMRIX capsules intact or to sprinkle capsule contents on a tablespoon of applesauce and swallow immediately without chewing.
- Advise patients to stop taking AMRIX and to notify their physician right away if they experience symptoms of an allergic reaction, such as difficulty breathing, hives, swelling of face or tongue, or itching.
- Advise patients that AMRIX should not be taken with MAO inhibitors or within 14 days after their discontinuation.
- Caution patients about the risk of serotonin syndrome with concomitant use of AMRIX and other drugs, such as SSRIs, SNRIs, TCAs, tramadol, bupropion, meperidine, verapamil, or MAO inhibitors. Advise patients of the signs and symptoms of serotonin syndrome *[see Warnings and Precautions (5.1)]* and instruct patients to seek medical care immediately if they experience these symptoms.

AMRIX® (cyclobenzaprine hydrochloride extended-release capsules)

- Advise patients to stop taking AMRIX and to notify their physician right away if they experience arrhythmias or tachycardia.
- Advise patients that AMRIX may enhance the impairment effects of alcohol. These effects may also be seen if AMRIX is taken with other CNS depressants.
- Caution patients about operating an automobile or other hazardous machinery until it is reasonably certain that AMRIX therapy will not adversely affect their ability to engage in such activities.
- Advise patients to take AMRIX at approximately the same time each day.

teva

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North Wales, PA 19454

Manufactured By:
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Vandalia, OH 45377

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US Patent Nos. 7387793, 7544372, 7790199, 7820203, 7829121, 9375410, 9399025

Patient Information
AMRIX® (am-rix)
(cyclobenzaprine hydrochloride)
Extended-Release Capsules

Read this Patient Information before you start taking AMRIX and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is AMRIX?

AMRIX is a prescription medicine used along with rest and physical therapy to help treat muscle spasm due to acute, painful musculoskeletal problems.

AMRIX should only be used for up to 2 or 3 weeks. It is not known if AMRIX is effective when used for longer periods.

It is not known if AMRIX is safe and effective in children.

Who should not take AMRIX?

Do not take AMRIX if you:

- are allergic to cyclobenzaprine or any of the ingredients in AMRIX. See the end of this Patient Information leaflet for a complete list of ingredients in AMRIX.
  Talk to your healthcare provider or get medical help right away if you have symptoms of an allergic reaction such as:
  - difficulty breathing
  - hives
  - swelling of your face or tongue
  - itching
- are taking certain antidepressants, known as monoamine oxidase (MAO) inhibitors or it has been 14 days or less since you stopped taking a MAO inhibitor. Ask your healthcare provider or pharmacist for a list of these medicines if you are not sure.
- have had a recent heart attack
- have heart rhythm problems (arrhythmias)
- have heart failure
- have an overactive thyroid (hyperthyroidism)

Talk to your healthcare provider before taking this medicine if you have any of the conditions listed above.

What should I tell my healthcare provider before taking AMRIX?

Before you take AMRIX, tell your healthcare provider if you:

- have a history of eye problems including glaucoma
- have heart problems or have had a heart attack
- have liver problems
- have trouble emptying your bladder (urinary retention)

- are pregnant or plan to become pregnant. It is not known if AMRIX will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if AMRIX passes into your breast milk. You and your healthcare provider should decide if you will take AMRIX or breastfeed.

AMRIX may affect the way other medicines work, and other medicines may affect how AMRIX works.

Tell your healthcare provider about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements.

Especially tell your healthcare provider if you take:

- a medicine to treat depression, mood, anxiety, psychotic, or thought disorders
- a pain medicine called tramadol or meperidine
- barbiturates or other medicines that depress your central nervous system (CNS depressants)
- a medicine that prevents nerve impulses (anticholinergic medicines)
- a medicine to help quit smoking called bupropion
- a blood pressure medicine called verapamil

Ask your doctor or pharmacist if you are not sure if you take any of the medicines listed above.

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider or pharmacist when you get a new medicine.

How should I take AMRIX?

- Take AMRIX exactly as your healthcare provider tells you to take it.
- Your healthcare provider will tell you how much AMRIX to take and when to take it.
- Your healthcare provider may change your AMRIX dose if needed.
- Take AMRIX around the same time every day.
- AMRIX should only be taken for short periods (up to two or three weeks).
- If you take too much AMRIX, call your doctor or go to the nearest hospital emergency room right away.

What should I avoid while taking AMRIX?

You should not drink alcohol until you know how AMRIX affects you. Taking AMRIX with alcohol or other medicines that depress your central nervous system can slow your thinking and physical response times.

Do not drive, operate machinery, or do other dangerous activities until you know how AMRIX affects you.

What are the possible side effects of AMRIX?

AMRIX may cause serious side effects that may lead to heart attack or stroke. Call your healthcare provider right away or go to the nearest hospital emergency room if you have:

- irregular or abnormal heartbeats (arrhythmias)
- fast heartbeat (tachycardia)

Serotonin syndrome is a serious medical condition that may happen when AMRIX is taken with certain other medicines. Call your healthcare provider right away or go to the nearest hospital emergency room if you become severely ill and have some or all of these symptoms:

- agitation, hallucinations, coma, or other changes in mental status
- coordination problems or muscle twitching (overactive reflexes)
- fast heartbeat, high or low blood pressure
- sweating or fever
- nausea, vomiting, or diarrhea
- muscle stiffness or tightness

The most common side effects of AMRIX include:

- dry mouth
- dizziness
- fatigue
- constipation
- nausea
- upset stomach
- drowsiness

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Tell your healthcare provider if you get any side effect that bothers you or that does not go away.

These are not all the possible side effects of AMRIX. For more information, ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store AMRIX?

- Store AMRIX at room temperature, between 59°F to 86°F (15°C to 30°C).
- Keep AMRIX in a tightly closed container, and keep AMRIX out of light.
- **Keep AMRIX and all medicines out of the reach of children.**

General information about the safe and effective use of AMRIX.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use AMRIX for a condition for which it was not prescribed. Do not give AMRIX to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information leaflet summarizes the most important information about AMRIX. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about AMRIX that is written for healthcare professionals.

For more information, go to www.AMRIX.com or call 1-888-483-8279.

What are the ingredients in AMRIX?

Active Ingredient: cyclobenzaprine hydrochloride USP

Inactive Ingredients: diethyl phthalate NF, ethylcellulose NF (Ethocel Standard 10 Premium), gelatin, Opadry® Clear YS-1-7006, sugar spheres NF (20-25 mesh), and titanium dioxide.

AMRIX 15 mg capsules also contain: D&C yellow #10, FD&C green #3, and FD&C red #40.

AMRIX 30 mg capsules also contain: FD&C blue #1, FD&C blue #2, FD&C red #40, and FD&C yellow #6.

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