TONIX PHARMACEUTICALS

TNX-102 SL (CYCLOBENZAPRINE HCL SUBLINGUAL TABLETS)

TNX-CY-P301

A PHASE 3, DOUBLE-BLIND, RANDOMIZED, MULTICENTER, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF TNX-102 SL TAKEN DAILY AT BEDTIME IN PATIENTS WITH MILITARY-RELATED PTSD

(PROTOCOL NO. TNX-CY-P301)

"HONOR STUDY"

Original Protocol Release Date: 06 October 2016

Date of Amendment 01: 03 February 2017

Date of Amendment 02: 28 March 2017

Date of Amendment 03: 18 May 2018

Date of Amendment 04: 29 October 2019

US IND No. 115936

Sponsor:
Tonix Pharmaceuticals, Inc. (Tonix)
509 Madison Avenue, Suite 306
New York, NY 10022

[redacted]

INVESTIGATOR'S AGREEMENT

I have read the TNX-CY-P301 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

Role in Study	Name	Email Address and Telephone Number
Responsible Physicians	[redacted]	[redacted]
24-Hour Emergency Contact	[redacted]	[redacted]
[redacted]		

2. SYNOPSIS

Name of Sponsor/Company:
Tonix Pharmaceuticals, Inc.

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

Name of Active Ingredient:
Cyclobenzaprine HCl

Title of Study:
A Phase 3, Double-Blind, Randomized, Multicenter, Placebo-Controlled Study to Evaluate the Efficacy and Safety of TNX-102 SL Taken Daily at Bedtime in Patients with Military-Related PTSD (Protocol No. TNX-CY-P301)

Study center(s): Approximately 45 centers in the United States

Study center(s) participating in the post-study pharmacogenomic assessment: 5 of the 45 centers that participated in the randomized, double-blind, placebo-controlled protocol

Studied period (years): 1.5	**Phase of development: 3**
Estimated date first patient enrolled: February 2017 Estimated date last patient completed: January 2019 **Studied period (months) for the post-study pharmacogenomic assessment: 3** Estimated date first patient enrolled: November 2019 Estimated date last patient completed: January 2020	

Objectives:

Primary:

To evaluate the efficacy of TNX-102 SL (cyclobenzaprine HCl sublingual tablets) in the treatment of military-related posttraumatic stress disorder (PTSD)

Secondary:

To evaluate the safety of TNX-102 SL (cyclobenzaprine HCl sublingual tablets) in the treatment of military-related posttraumatic stress disorder (PTSD)

Methodology:

This is a 12-week, multicenter, randomized, double-blind, placebo-controlled, fixed-dose study that will investigate the efficacy and safety of 5.6 mg TNX-102 SL (2 x 2.8 mg tablets)—a sublingual formulation of cyclobenzaprine. Following successful screening and randomization, eligible patients will have a telephonic visit at week 2 and then return regularly to the study clinic for monthly visits for assessments of efficacy and safety.

There will be a total of 6 study visits over approximately 13-17 weeks of study participation, including Screening (Visit 1), Randomization (Day 0, Visit 2), a phone visit after 2 weeks of treatment and in-clinic visits after 4, 8, and 12 weeks of treatment. A total of approximately 550 patients will be randomized in a 1:1 ratio to placebo or TNX-102 SL 5.6 mg (2 x 2.8 mg tablets).

Approximately 15 patients that successfully completed the TNX-CY-P301 study will be invited back to participate in a post-study pharmacogenomic assessment.

Number of patients (planned):

Approximately 550 patients will be randomized. Randomized patients who withdraw will not be replaced.

Approximately 15 patients will be invited to participate in a post-study pharmacogenomic assessment.

Diagnosis and main criteria for inclusion:

Inclusion criteria (assessed at Screening Visit 1):

1. Male or female between 18 and 75 years of age, inclusive, with military service (defined as active duty military, National Guard, reservist, veteran or military contractor). Identification confirming military service will be checked prior to randomization; medical monitor approval will be required for potential patients unable to provide evidence of prior service.
2. Diagnosed with current PTSD as determined by the Clinician-Administered PTSD Scale (CAPS-5) for Diagnostic and Statistical Manual of Mental Disorders-Version 5 (DSM-5) and of sufficient symptom severity, defined as all of the following at Screening Visit 1 using the Diagnostic version (1-month recall):
    a. The A criterion is 1=YES, and
    b. At least ONE item of the B criterion items must have a score of ≥2, and
    c. At least ONE item of the C criterion items must have a score of ≥2, and
    d. At least TWO items of the D criterion items must have a score of ≥2, and
    e. At least TWO items of the E criterion items must have a score of ≥2, and
    f. The F item 22 criterion is 1=YES (≥1 month duration of symptoms)
    g. At least ONE item of the G items must have a score of ≥2, and
    h. The total CAPS-5 score (of items 1 through 20 is) ≥33.
3. Index trauma(s) resulting in PTSD must meet the following:
    a. DSM-5 criterion A for PTSD as described in the CAPS-5 and Criterion A – Assessment Form (CA-AF), and
    b. Must have occurred in 2001 or later, and
    c. Must be military service-related (either occurrence during military service, including during National Guard service or as reservist), and
    d. Must have occurred when the patient was ≥18 years of age.
4. Willing and able to withdraw and refrain from opioids for the course of the study.
5. Willing to refrain from use of all other formulations of cyclobenzaprine for the course of the study.
6. Willing and able to refrain from antidepressants, antipsychotics, mood stabilizers, anticonvulsants, benzodiazepines, non-benzodiazepine hypnotics, buspirone, stimulants (e.g. amphetamines, methylphenidate, modafinil, armodafinil), prazosin and trazodone for the course of the study.
7. Capable of reading and understanding English and able to provide written informed consent to participate.
8. If female, either not of childbearing potential (defined as postmenopausal for at least one year or surgically sterile [e.g., bilateral tubal ligation; bilateral oophorectomy; hysterectomy, etc.])

or practicing one of the following medically acceptable methods of birth control throughout the study:

a. Hormonal methods such as oral, implantable, injectable, or transdermal contraceptives for a minimum of one full cycle (based on the patient's usual menstrual cycle period) before study drug administration;
b. Intrauterine device (IUD);
c. Double-barrier method (condoms, sponge, diaphragm, or vaginal ring with spermicidal jellies or cream);
d. In sexually-exclusive relationship with vasectomized male partner, or in same-sex relationship with no plans for artificial or other forms of insemination.

9. Willing and able to comply with all protocol-specified requirements.
10. If patient has received trauma-focused treatment (e.g., cognitive behavioral therapy for PTSD, prolonged exposure therapy, desensitization therapy, etc.) must have been completed at least three months prior to the Baseline visit, and there can be no plans to initiate this type of therapy during study. General psychotherapy that was in process at time of Screening may be continued during the trial, but no new initiation of treatment is allowed during the trial after enrollment.
11. Separate written, signed informed consent will be required if the patient is to participate in the post-study pharmacogenomic assessment. To be eligible to participate in the pharmacogenomic assessment, the patient must have been randomized, had at least one post-baseline CAPS-5 assessment, and received active study drug in the TNX-CY-P301 study.

Exclusion Criteria

1. Increased risk of suicide on the basis of the investigator's judgment and/or the results of the Mini International Neuropsychiatric Interview, Version 7.0.2 (M.I.N.I. 7.0.2) conducted at Screening and the Columbia Suicide Severity Rating Scale (C-SSRS) conducted at Screening and/or Baseline. Any of the following will be exclusionary:
   a. High suicidality based on a M.I.N.I. Module B score ≥ 17 (Screening); or,
   b. Patient answers YES to either M.I.N.I. question B10 or B11 (Screening); or,
   c. Patient meets criteria for CURRENT Suicidal Behavior Disorder on the M.I.N.I (Screening); or,
   d. C-SSRS Type 4 or Type 5 ideation within 6 months of Screening or at the Baseline visit; or,
   e. Any suicidal behavior in the past 12 months as identified by the C-SSRS at Screening or Baseline.
2. Increased risk of suicide, based on the investigator's judgment that is of a severity that is not appropriate for outpatient management, or that warrants additional therapy excluded by the protocol.
3. Significant (e.g., moderate or severe) comorbid traumatic brain injury (TBI) by history. Based on past history and investigator's judgment, patients with mild TBI are eligible.
4. Evidence of severe depression at screening or baseline (Visits 1 or 2) based on the investigator's judgment and collaborative pre-randomization review by the investigator and medical monitor(s) of the patient's psychiatric history, presenting symptomatology, M.I.N.I.

7.0.2 (including Major Depressive Episode and Suicidality modules), C-SSRS, CAPS-5, and BDI-II assessments.

5. Clinically significant laboratory abnormalities based on screening laboratory tests and/or medical history in the investigator's opinion, including a Thyroid Stimulating Hormone (TSH) level >1.5 times the upper limit of normal and aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 3 times the upper limit of normal (if persistent upon repeat). Patients with treated thyroid conditions and TSH levels ≤ 1.5 times the upper limit of normal will be eligible to participate in the study.
6. Diagnosed with clinically significant cardiac disease (e.g., significant arrhythmia or heart block, heart failure, or recent myocardial infarction [within the past 2 years]) or QTcF >450 msec (male) or >470 msec (female) on the screening electrocardiogram (ECG).
7. Current evidence of human immunodeficiency virus (HIV) infection based on screening laboratory results or medical history, or clinically significant hepatitis B or C infection as defined by current treatment or liver function tests (e.g., aspartate aminotransferase [AST] or alanine aminotransferase [ALT] > 3 times the upper limits of normal).
8. Use of antidepressant medication within 2 months of baseline, with the exception of trazodone at doses ≤ 150 mg per day or tricyclic antidepressants at doses ≤25 mg per day, which instead require a 1-week drug-free interval prior to the Baseline visit.
9. Unable to successfully wash out of the following medications during screening, or in whom washout is medically inadvisable: anticonvulsants, mood stabilizers, anti-psychotic agents, opioids, benzodiazepines, non-benzodiazepine hypnotics (zolpidem; eszopiclone, zaleplon), buspirone, trazodone, stimulants (e.g., amphetamine mixed salts, methylphenidate, lisdexamphetamine, dextroamphetamine, modafanil, armodafanil), atomoxetine, or any medication known to be a potent (strong) cytochrome P450 subtype 3A4 (CYP3A4) inhibitor, or St. John's wort. **Note**: Use of caffeine and/or nicotine is permitted.
10. Unable to successfully wash out of alpha-adrenergic antagonists and/or agonists (e.g., prazosin, terazosin, doxazosin, tamsulosin, silodosin, tizanidine, clonidine, guanfacine) or when washout is medically inadvisable.
11. Positive results for illegal or abused substances other than cannabis at Screening or Baseline or history of alcohol/substance use disorder during the preceding 6 months as defined by the screening M.I.N.I. 7.0.2. Patients who utilize alcohol/cannabis but do not meet criteria for alcohol/substance use disorder are otherwise suitable for the study provided that, in the judgment of the Investigator, this usage will not interfere with the patient's ability to complete the study or provide reliable data.
12. Any clinically significant, uncontrolled, or unstable medical or surgical condition that could affect a patient's ability to participate in the study or potentially compromise a patient's well-being during the study, including patients with a history of untreated or uncontrolled angle-closure glaucoma.
13. Diagnosis of DSM-5-defined bipolar disorder I, II or unspecified, schizophrenia, schizoaffective disorder, obsessive-compulsive disorder, major depressive disorder (MDD)

with psychotic features, other psychotic disorder, or antisocial personality disorder as confirmed by the M.I.N.I. Version 7.0.2.

14. History within the past 2 years of violent behavior unrelated to military duties or associated work.
15. Anticipated need for surgery that might confound results or interfere with patient's ability to comply with the protocol.
16. Female patients who are pregnant or lactating.
17. History of serotonin syndrome, severe allergic reaction or bronchospasm or known hypersensitivity to cyclobenzaprine or the excipients in TNX-102 SL or placebo formulations.
18. Seizure disorder other than history of childhood febrile seizures.
19. Current sleep apnea not well controlled by Continuous Positive Airway Pressure (CPAP) or oral (mouthpiece) devices. Patients with mild obstructive sleep apnea or those well controlled by CPAP or oral (mouthpiece) devices are allowed at the discretion of the investigator.
20. Patients with a body mass index (BMI) > 45.
21. Has received any other investigational drug within 30 days before Screening or has taken cyclobenzaprine within 21 days of the Randomization visit.
22. Previous participation in any other study with TNX-102 SL.
23. Any existing oral medical or dental condition, or tongue piercings, that could potentially interfere with sublingual administration of study drug, or history of severe or unexplained oral or oropharyngeal swelling or edema.
24. Family member of investigative staff.
25. In the process of litigating for compensation for a psychiatric disorder. Patients who are in the process of applying for VA benefits or who have a settled claim are eligible.

Randomization Criteria: All of the following must be met before the patient is eligible for randomization at Visit 2:

1. Patient continues to meet all inclusion and exclusion criteria, including urine and blood test results, and
2. Visit 2 total CAPS-5 score ≥ 33 ("Symptom Severity" version using 1-week recall), and
3. At Visit 2, patient is not severely depressed (based on the investigator's judgment and Visit 2 C-SSRS, CAPS-5, and BDI-II, and considering the pre-randomization collaborative review by the investigator and medical monitor(s) of the patient's Visit 1 psychiatric history, presenting symptomatology, M.I.N.I. 7.0.2, C-SSRS, CAPS-5, and BDI-II assessments), and
4. No active suicidal intent or plan, based on Investigator's judgment, and Visit 2 C-SSRS responses (e.g., no C-SSRS Type 4-5 ideation or suicidal behavior since Visit 1).

Investigational product, dosage and mode of administration:

Name: TNX-102 SL (cyclobenzaprine HCl sublingual tablets)

Dose, route, frequency: 2 tablets of 2.8 mg of TNX-102 SL taken simultaneously and sublingually (under the tongue) each day at bedtime starting on Day 0 for 12 weeks.

Duration of treatment:

12 weeks

Reference therapy, dosage and mode of administration:

Name: Placebo

Dose, route, frequency: 2 placebo tablets taken simultaneously and sublingually (under the tongue) each day at bedtime starting on Day 0 for 12 weeks.

Criteria for evaluation:

Primary Efficacy Endpoint:

- The mean change from baseline (Visit 2) in the Total CAPS-5 score after 12 weeks of treatment evaluated at Visit 6.

Secondary Efficacy Endpoints: The first two secondary efficacy endpoints listed below are considered key secondary endpoints and will be tested in that order:

- CGI-I score (analyzed as a continuous variable) after 12 weeks of treatment.
- Change from baseline in the SDS total score after 12 weeks of treatment.

A fixed sequence procedure will be applied to the key secondary efficacy endpoints to adjust for multiplicity and to control for overall type I error.

Other Secondary Efficacy Endpoints:

- Change from baseline in patients' quality of sleep using the PROMIS Sleep Disturbance scale after 12 weeks of treatment.
- Change from baseline in the disruption of work/school activities assessed using the SDS after 12 weeks of treatment.
- Change from baseline in disruption of social life/ leisure activities assessed using the SDS after 12 weeks of treatment.
- Change from Baseline in the disruption of family life/home responsibilities assessed using the SDS after 12 weeks of treatment.
- Change from baseline in CAPS-5 Arousal and Reactivity (Criterion E) score after 12 weeks of treatment.
- Change from baseline in CAPS-5 Intrusion symptoms (Criterion B) score after 12 weeks of treatment.
- Change from baseline in CAPS-5 Persistent Avoidance (Criterion C) score after 12 weeks of treatment.
- Change from baseline in CAPS-5 Negative Cognition and Mood (Criterion D) score after 12 weeks of treatment.
- Change from baseline in CAPS-5 Sleep Disturbance (item E-6) score after 12 weeks of treatment.
- Change from baseline in CAPS-5 Exaggerated Startle (item E-4) score after 12 weeks of treatment.
- PGIC score after 12 weeks of treatment.
- Proportion of patients with a PGIC score of "much improved" or "very much improved" after 12 weeks of treatment

- Proportion of patients with a treatment response on the CGI-I defined as a CGI-I score of "much improved" or "very much improved" after 12 weeks of treatment.
- Proportion of patients with a Total CAPS-5 score of 0 –10 (asymptomatic/few symptoms) after 12 weeks of treatment.
- Proportion of patients with a Total CAPS-5 score of 0-22 (asymptomatic or mild PTSD/subthreshold) after 12 weeks of treatment.
- Proportion of patients with Response, defined as a ≥ 10-point improvement from baseline in Total CAPS-5 score after 12 weeks of treatment.
- Proportion of patients with Loss of Diagnosis, defined as Response AND no longer meeting DSM-5 symptom criteria in any one or more of the four clusters (B, C, D, E) after 12 weeks of treatment.
- Proportion of patients in Remission, defined as Loss of Diagnosis AND Total CAPS-5 score ≤ 10 after 12 weeks of treatment.
- Proportion of patients achieving sustained Remission, defined as Loss of Diagnosis AND Total CAPS-5 score ≤ 10 after both 8 weeks AND 12 weeks of treatment.
- Proportion of patients with a ≥50% improvement from baseline in Total CAPS-5 score after 12 weeks of treatment.
- Change from baseline in BDI-II score after 12 weeks of treatment.
- Change from baseline in CAPS-5 Reckless or Self-Destructive Behavior (item E-2) score after 12 weeks of treatment.

Exploratory Endpoints: Any exploratory endpoints will be delineated in the SAP.

Safety

Safety will be assessed by:

- Adverse events (AE) and serious AEs (SAEs) throughout the entire duration of the study, including detailed assessment of AEs involving the oral cavity
- Changes from baseline in clinical laboratory test results
- Changes from baseline in vital signs and weight
- Change from baseline in BDI-II
- Changes from baseline indicative of increased suicidal ideation or behavior as assessed by the Columbia Suicide Severity Rating Scale (C-SSRS)
- Changes from baseline in patient-rated Changes in Sexual Functioning Questionnaire Short-Form (CSFQ-14)
- Changes from baseline in patient-rated morning sedation as assessed by the Morning Treatment-Related Sedation Score (MTRSS)

Statistical methods:

Analysis Populations

- Safety Population (SAFETY): All patients who receive at least one dose of investigational product, analyzed as treated.
- Modified Intent-to-Treat Population (mITT): All randomized patients who have at least a baseline and one post-baseline CAPS-5 assessment, analyzed as randomized.

Efficacy Analyses

The primary efficacy analysis will use a mixed model repeated measures (MMRM) approach to estimate mean change from baseline in the Total CAPS-5 score evaluated after 12 weeks of treatment in the TNX-102 SL 5.6 mg and placebo arms. The model will include all patients in the mITT population, and missing values will be imputed using a multiple imputation (MI) approach. The dependent variable will be the observed change from baseline in total CAPS-5 score at each post-randomization visit. Covariates in the model will include the fixed categorical effects of treatment, site, sex, current tobacco use status, presence of current MDE, visit and treatment by visit interaction, as well as the continuous fixed covariates of baseline score and baseline score by visit interaction.

MMRM methodology will be utilized for the secondary endpoints as appropriate. Binary data, e.g., CGI-I response, will be analyzed using a Cochran-Mantel-Haenszel (CMH) test controlling for the randomization stratification variable of presence of current MDE, analyzed separately at each visit. Patients with missing data will be analyzed as though they are non-responders for binary endpoints. A fixed sequence procedure will be applied to the key secondary efficacy endpoints to adjust for multiplicity and to control for overall type I error.

Safety Analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version in use at the start of the study and will be summarized overall and by preferred term and system organ class. 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. Actual values and changes from Baseline for clinical laboratory test results, vital sign measurements, BDI-II scores, CSFQ-14, and morning sedation scores from the MTRSS will be summarized at endpoint using descriptive statistics (n, mean, SD, median, minimum, and maximum).

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

Interim Analysis

One planned interim analysis for the purposes of sample size reassessment and to assess stopping early for either futility or success will be performed. The interim analysis will be conducted when approximately 50% of the total planned enrollment is evaluable for efficacy. The specific details of this analysis and the efforts to maintain blinding integrity will be described in detail in an Interim Statistical Analysis Plan (ISAP) that will be finalized prior to any analysis. This analysis will be performed by an independent unblinded analysis group. Results of this assessment will be provided to an Independent Data Monitoring Committee (IDMC). Details of the interim analysis procedure and steps to maintain treatment blinding of the study team will be described in the ISAP and the IDMC Charter.

Sample Size Estimation

The study is planned to enroll approximately 550 patients total in a 1:1 randomization, that is, 275 patients in each of the placebo and TNX-102 SL 5.6 mg groups. [redacted]

[redacted]

Pharmacogenomic Analyses

Potential genetic determinants of treatment response will be examined by the assessment of genetic variants in relation to treatment outcome and adverse events. A blood sample will be obtained from patients who have signed a separate informed consent form for the pharmacogenomic analyses. The blood sample will be obtained at a separate post-study visit only after the patient has agreed to be tested and has signed the separate pharmacogenomics informed consent form.

The first step of the pharmacogenomic analyses will involve exome sequencing and analysis for allelic polymorphisms related to treatment response to TNX-102 SL, and potentially utilized to develop a pharmacogenomic test for determining likelihood of treatment response to TNX-102 SL. In addition, relationship between oral adverse events and selected allelic polymorphisms will be explored.

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

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4. 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
ANCOVA	Analysis of covariance
AR	α2-adrenoreceptors
AST	Aspartate Aminotransferase
BDI-II	Beck Depression Inventory–II
BMI	Body Mass Index
BOCF	Baseline observation carried forward
BUN	Blood urea nitrogen
CAPS-5	Clinician Administered PTSD Scale (for DSM-5)
CA-AF	Criterion A – Assessment Form
CBP	Cyclobenzaprine
CSFQ-14	Changes in Sexual Functioning Questionnaire Short Form
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression- Improvement from Initiation of Treatment
CI	Confidence Interval
CMH	Cochran–Mantel–Haenszel
CNS	Central Nervous System
CoC	Certificates of Confidentiality
CPAP	Continuous Positive Airway Pressure
CRF	Case Report Form
CRO	Contract Research Organization
C-SSRS	Columbia Suicide Severity Rating Scale
CYP3A4	Cytochrome P450 subtype 3A4
DSM-5	Diagnostic and Statistical Manual of Mental Disorders (Version 5)
e.g.	*Exempli gratia* (for example)
EC	Ethics Committee

Abbreviation or Specialist Term	**Explanation**
eCRF	Electronic case report form
ECG	Electrocardiogram
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HCl	Hydrochloride
HEENT	Head, Eyes, Ears, Nose and Throat
HIPAA	Health Insurance Portability and Accountability Act
HIV_1	Human immunodeficiency virus type 1
HIV_2	Human immunodeficiency virus type 2
i.e.	*id est* (that is)
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IR	Immediate-release
ISAP	Interim Statistical Analysis Plan
IUD	Intrauterine device
IWR	Interactive Web Response
LEC-5	Life Events Checklist for DSM-5
LOCF	Last observation carried forward
M.I.N.I.	Mini International Neuropsychiatric Interview
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
mCPP	meta-chlorophenylpiperazine
MCV	Mean corpuscular volume
MDD	Major Depressive Disorder

Abbreviation or Specialist Term	**Explanation**
MDE	Major Depressive Episode
MedDRA	*Medical Dictionary for Regulatory Activities*
Mg	Milligram(s)
MI	Multiple imputation
mITT	Modified Intent-to-Treat
MMRM	Mixed Model Repeated Measures
msec	Millisecond(s)
MTRSS	Morning Treatment-Related Sedation Scale
N, n	Number (of patients)
NA	Not applicable
NDA	New Drug Application
NREM	Non-rapid eye movement
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
OND	Operation New Dawn
PCL	PTSD Checklist
PGIC	Patient Global Impression of Change (Since Baseline) Scale
PI	Principal Investigator
PO	*per os* (by mouth)
PRN	*pro re nata* (as needed)
PROMIS	Patient-Reported Outcome Measurement Information System
PTSD	Post-Traumatic Stress Disorder
QTcF	QT corrected for heart rate using Fridericia's formula
RBC	Red blood cell
REM	Rapid eye movement
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard deviation
SDS	Sheehan Disability Scale

Abbreviation or Specialist Term	Explanation
SL	Sublingual
SOP	Standard Operating Procedures
SPI	Safety Planning Intervention
SWS	Slow wave sleep
TBI	Traumatic brain injury
TEAE	Treatment Emergent Adverse Event
TNX-102 SL	Cyclobenzaprine HCl sublingual tablets
TSH	Thyroid Stimulating Hormone
US	United States
VA	Veteran's Administration
WBC	White blood count
WHO	World Health Organization

5. INTRODUCTION

TNX-102 SL is a tablet for sublingual administration containing cyclobenzaprine HCl [3-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-N,N-dimethyl-1-propanamine hydrochloride]. TNX-102 SL 2.8 mg tablets are under development by Tonix Pharmaceuticals, Inc. (Tonix) as a treatment for posttraumatic stress disorder (PTSD).

The active ingredient in TNX-102 SL, cyclobenzaprine HCl (CBP), has been approved for use in the United States (US) since 1977, originally as FLEXERIL® 10-mg oral tablets indicated as an adjunct to rest and physical therapy for the relief of muscle spasm associated with acute, painful musculoskeletal conditions. The usual dose for this indication is 30 mg or 15 mg per day taken as 10 mg TID or 5 mg TID, respectively. The FLEXERIL brand of immediate-release (IR) cyclobenzaprine tablets has been discontinued since May 2013. Generic cyclobenzaprine is available and marketed in a variety of strengths including 5-, 7.5- and 10-mg IR tablets. AMRIX® (AMRIX® Prescribing Information, 2016), an extended-release capsule of cyclobenzaprine was approved in 2007 in the US as a New Drug Applications (NDA) and is currently available in 15- and 30-mg, taken once a day for the same indication as FLEXERIL in the US. Both FLEXERIL and AMRIX are indicated for 2-3 weeks use only. No cyclobenzaprine product has been approved for use in PTSD by Food and Drug Administration (FDA), Health Canada, or in any other country.

As its primary pharmacologic action in relief of muscle spasm, cyclobenzaprine has been shown to decrease skeletal muscle hyperactivity in several animal models through central mechanisms involving blockade of either α_2-adrenoreceptors (Barnes et al, 1980) (AR) or serotoninergic 5-HT_{2A} receptors (Kobayashi et al, 1996; Honda et al, 2003). Cyclobenzaprine acts primarily in the central nervous system (CNS) at the brain stem rather than at the spinal cord level, and does not act directly at the neuromuscular junction or directly on skeletal muscle.

In addition to these primary pharmacologic actions, cyclobenzaprine has been observed to increase restorative sleep in fibromyalgia patients, which was correlated with improvement in daytime symptoms in a proof-of-concept study conducted by Vela Pharmaceuticals (Protocol No. VPI CY 0001.1) (Moldofsky et al, 2011) using low dose cyclobenzaprine (TNX-102 capsules). The rationale for testing cyclobenzaprine as a treatment for PTSD is based on known effects of cyclobenzaprine on CNS receptors and, in part, on the relationship of fibromyalgia and PTSD to disturbed and non-restorative sleep.

PTSD is characterized by symptom clusters that include re-experiencing (intrusion) symptoms, avoidant behaviors, negative mood and cognitions, and heightened arousal and reactivity, the array of which develops and persists following exposure to a severely traumatic event. It is well established that sleep disturbances are common among individuals with PTSD that has developed in response to combat traumas (Mellman et al, 1995; Pietrzak et al, 2010; Neylan et al, 1998) and sexual assault (Steine et al, 2012), including military sexual trauma (Kelly et al, 2011). Among military personnel returning from OEF/OIF/OND deployments to Afghanistan and Iraq, sleep disturbances are considered the most frequent and severe of the PTSD symptoms (McLay et al, 2010). Sleep disturbances are considered core features of PTSD and are components of two of the main symptom clusters of PTSD including distressing dreams (re-experiencing cluster) and insomnia and restless sleep (hyperarousal cluster) (Krakow et al, 2001; Spoormaker et al, 2008). Problems with sleep are not only thought to significantly exacerbate

daytime symptoms of PTSD but also increase the likelihood of comorbid complications such as depression and substance use disorders as well as suicidal behaviors (Krakow et al, 2002; Saladin et al, 1995; Krakow et al, 2000), a particularly critical problem in PTSD (Oquendo et al, 2003; Sareen et al, 2005). Moreover, because of a direct relationship between sleep disturbance in PTSD and suicidal ideation, it is suggested that targeting sleep disturbance may help prevent suicidal behaviors in PTSD (Betts et al, 2013).

A growing body of evidence suggests that sleep disruption plays an important causal role in the pathogenesis of PTSD (Koren et al, 2002; Mellman et al, 2002; McLay et al, 2010; Wright et al, 2011). Moreover, sleep disturbance is a frequent residual complaint after successful PTSD treatment, a finding that applies to both psychological and pharmacological treatment (Spoormaker et al, 2008). Evidence is now emerging that pharmacological targeting of sleep disturbance in PTSD, in which self-reported and polysomnographic improvement in sleep parameters is achieved, can account for over 90% of the variance in improvement in PTSD severity ratings and work/school function (Krystal et al, 2013).

Understanding of PTSD pathophysiology has been greatly advanced due to heuristic models of trauma based on animal work on fear conditioning and extinction (Yehuda & LeDoux, 2007; Maren et al, 2013). Human studies of fear memory and stress responsiveness have highlighted the potential role of sleep, particularly rapid eye movement (REM) sleep, in affective and memory processes (Pace-Schott et al, 2015; Yoo et al, 2007; Pace-Schott et al, 2009). There is evidence for the hypothesis that sleep disturbances play a critical role in PTSD by compromising sleep-dependent affective and memory processing that may be key for recovery from PTSD (Yehuda & LeDoux, 2007).

5.1. Sleep and PTSD

Subjective sleep disturbance, characterized by non-restorative sleep, frequent awakenings and distressing dreams and nightmares related to the trauma, is a core feature of PTSD (Spoormaker et al, 2008). Clinical observations focusing on the nature of sleep complaints suggest dysregulation in both REM and non-rapid eye movement (NREM) sleep in PTSD (Woodward et al, 2000; Germain et al, 2013). Meta-analysis of polysomnography (PSG) studies in both military veterans and adult civilians suggest modest indices of sleep disruption in PTSD using these traditional measures, with greater stage 1 (light) sleep, reduced slow wave sleep (SWS), and greater REM density compared with individuals without PTSD (Kobayashi et al, 2007). Quantitative EEG, in which high frequency beta and gamma activity are considered indices of central arousal during sleep, has indicated both greater beta activity during NREM and lesser beta activity during REM sleep in PTSD, as well as disturbances in delta activity, and heart rate differences between REM and NREM related to the amount of REM sleep (Woodward et al, 2002; Neylan et al, 2003; Halász et al, 2004; Woodward et al, 2000). Such changes are consistent with the pathophysiology of PTSD, which involves hypervigilance and exaggerated responses to both external and internal stimuli, and which are putatively indicative of heightened nocturnal sympathetic noradrenergic activity (Berridge et al, 2012; Breslau et al, 2005; Capaldi et al, 2011).

A recent evaluation of treatment algorithms for PTSD found that addressing fragmented sleep and nightmares consistently improves all symptom domains in PTSD, such that targeting sleep-related symptoms has been recommended as an initial step for treatment of all patients with

PTSD (Bajor et al, 2011). Prazosin, a centrally acting α_1-adrenoreceptor antagonist, has been repeatedly demonstrated to provide improvements on subjective measures of sleep disturbance and PSG in both civilian and combat related trauma (Raskind et al, 2003; Taylor et al, 2008; Raskind et al, 2007; Raskind et al, 2013). It is notable that prazosin treatment has also been reported to improve non-sleep symptoms in PTSD (Taylor et al, 2006; Raskind et al, 2007), however, a recently reported large (N=304) multicenter VA cooperative study (#563) failed to show improvement on total CAPS score with prazosin (https://clinicaltrials.gov/ct2/show/results/NCT00532493).

Normal NREM sleep is associated with a reduction in sympathetic nervous system drive and increase in parasympathetic nervous system drive (Berridge et al, 2012; Pace-Schott et al, 2015). In PTSD, there is evidence that the nocturnal secretion of norepinephrine remains high, which could be a factor resulting in fragmented REM sleep. Since cyclobenzaprine shares α_1-adrenoreceptor antagonist activity with prazosin, cyclobenzaprine may have similar therapeutic effects on sleep disturbances in PTSD based on this molecular target.

In addition to the efficacy evidence demonstrated in the TNX-102 SL Phase 2 study (Section 5.1.1), the potential clinical utility of cyclobenzaprine in treating PTSD is also supported by the promising results of studies with agents that share a molecular mechanism of antagonism of the 5-HT_{2A} receptor (Hertzberg et al, 1996; Warner et al, 2001; Davidson et al, 1998; Hertzberg et al, 1998; Hidalgo et al, 1999; Davis et al, 2004; Connor et al, 1999; Bahk et al, 2002; Kim et al, 2005; Lewis, 2002; Davidson et al, 2003). The 5-HT_{2A} blocking activity of cyclobenzaprine may be crucial to the aforementioned enhancement of sleep-dependent memory processing believed to be necessary for recovery from PTSD (Datta & O'Malley 2013; Karshima et al, 2010; Siwek et al, 2014; Data et al, 2008). Another of cyclobenzaprine's high affinity receptors, also where it acts as an antagonist, is the H_1 receptor, which has been shown to have antianxiety effects (Llorca et al, 2002), play a role in wake promotion (Monti et al 2011; Huang et al, 2006), and has been implicated in emotional processing (Serafim et al, 2012, 2013) known to be sleep-dependent. Thus, in summary, the pharmacodynamic profile of cyclobenzaprine's CNS receptor activities appears well-suited for treating PTSD based on its potential to combine the activities on sleep and emotional memory processing of the α_1-adrenergic receptor antagonist prazosin, 5-HT_{2A} receptor antagonist antidepressants, and histaminergic H_1 antagonists.

5.1.1. Brief Summary of Prior Clinical Experience and Dose Rationale

[redacted]

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary Objective

To evaluate the efficacy of TNX-102 SL (cyclobenzaprine HCl sublingual tablets) in the treatment of military-related PTSD.

6.2. Secondary Objectives

To evaluate the safety of TNX-102 SL (cyclobenzaprine HCl sublingual tablets) in the treatment of military-related PTSD.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a Phase 3, 12-week, randomized, multicenter, double-blind, placebo-controlled, fixed dose study that will investigate the efficacy and safety of TNX-102 SL 5.6 mg (2 x 2.8 mg tablets) taken daily at bedtime for the management of military-related PTSD. This study is to be conducted at approximately 45 investigational sites in the United States.

The total duration of this study over 6 visits will be approximately 13-17 weeks, with 12 weeks of treatment duration and a variable length of screening. This study will consist of a Screening visit (Visit 1, Days −35 to −8), Randomization visit (Visit 2, Day 0), telephone visit (Visit 3, Week 2) and three monthly in-clinic visits (Visits 4, 5 and 6 at Weeks 4, 8, and 12).

Eligible patients who provide written informed consent to participate will have study assessments performed at Screening, including counseling regarding any required washout and instructions to refrain from use of excluded medications throughout the study.

The length of the pre-randomization screening period is variable (7 to 35 days) in order to accomplish wash-out of previous medications, where appropriate, and allow for return of clinical laboratory results necessary to confirm eligibility. At Visit 2, patients will return to the site for additional baseline assessments and randomization (Day 0), when, if they meet all study randomization criteria, they will be randomly assigned in a 1:1 ratio to receive placebo or TNX-102 SL 5.6 mg. Patients will take the study drug sublingually daily at bedtime, starting on the day that they are randomized and continuing for 12 weeks (or to early termination). A dynamic randomization procedure will be employed at Visit 2 to minimize trial-wide imbalances between the treatment groups for site, sex, current tobacco/nicotine use (yes/no) and presence (yes/no) of current Major Depressive Episode (MDE) based on the Mini International Neuropsychiatric Interview, Version 7.0.2 (M.I.N.I. 7.0.2) conducted at Visit 1.

Patients who test positive for cocaine, ecstasy (MDMA), methamphetamine or other non-disclosed illicit drugs (other than marijuana) should be screen-failed. In addition, patients who meet M.I.N.I. criteria outlined in the entry criteria for alcohol/substance use disorder over the 6 months prior to Screening should be screen-failed.

Patients suffering from depression are eligible for the study, provided their depression does not pose an undue risk to their well-being (e.g., suicidal risk) or warrant treatment with

antidepressants or other excluded treatments. The investigator will evaluate each patient's medical and psychiatric history, current symptomatology, and the results of the MINI 7.0.2, BDI-II, C-SSRS, and CAPS-5 from Visits 1 and 2, to determine whether it is appropriate for the patient to participate in the study. In addition, each patient will undergo medical monitor pre-randomization review to ensure agreement with the investigator's assessment.

NOTE: Patients who use alcohol/marijuana but do not meet criteria for alcohol/substance use disorder (per Diagnostic and Statistical Manual of Mental Disorders [Version 5; DSM-5]) are otherwise suitable for the study provided that, in the judgment of the Investigator, this usage will not interfere with the patient's ability to complete the study or provide reliable data. Information related to marijuana and alcohol use will be collected at Screening.

Patients with evidence of hepatic impairment secondary to hepatitis B or C at screening, or who are undergoing treatment for hepatitis, should be excluded. Patients with stable and asymptomatic disease whose hepatic enzymes (aspartate aminotransferase [AST] or alanine aminotransferase [ALT]) satisfy the study's entry criteria (< 3 times the upper limits of normal), may be allowed to proceed with randomization with prior Medical Monitor approval.

CAPS-5, M.I.N.I. 7.0.2 and Columbia Suicide Severity Rating Scale (C-SSRS) interviews will be conducted by an approved and qualified individual(s) at each site who has successfully completed training on each instrument.

If a patient scores a 2 or 3 on the suicidal ideation section of the C-SSRS at any visit (including the Screening visit), the investigator and patient should work together to implement a Safety Planning Intervention (SPI). As described in detail in Section 11.3.3, the recommended SPI for this study is the plan developed by Barbara Stanley, PhD and Gregory Brown, PhD which has been adopted by the U.S. 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.

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

7.2. Number of Patients and Treatment Assignment

A total of approximately 550 patients will be randomized in a 1:1 ratio to treatment with TNX-102 SL 5.6 mg (2 x 2.8 mg) tablets or identical SL placebo tablets. See Section 13.2 for details regarding potential sample size adjustment.

7.3. Study Endpoints

7.3.1. Primary efficacy endpoint

The primary efficacy endpoint will be the mean change from baseline in the total Clinician Administered PTSD Scale-Version 5 (CAPS-5) at Week 12.

7.3.2. Secondary efficacy endpoints

7.3.2.1. Key Secondary Efficacy Endpoints

The first two secondary efficacy endpoints listed below are considered key secondary endpoints and will be tested in that order:

- CGI-I score (analyzed as a continuous variable) after 12 weeks of treatment.
- Change from baseline in the SDS total score after 12 weeks of treatment.

A fixed sequence procedure will be applied to the key secondary efficacy endpoints to adjust for multiplicity and to control for overall type I error.

7.3.2.2. Other Secondary Efficacy Endpoints

- Change from baseline in patients' quality of sleep using the PROMIS Sleep Disturbance scale after 12 weeks of treatment.
- Change from baseline in the disruption of work/school activities assessed using the SDS after 12 weeks of treatment.
- Change from baseline in disruption of social life/ leisure activities assessed using the SDS after 12 weeks of treatment.
- Change from Baseline in the disruption of family life/home responsibilities assessed using the SDS after 12 weeks of treatment.
- Change from baseline in CAPS-5 Arousal and Reactivity (Criterion E) score after 12 weeks of treatment.
- Change from baseline in CAPS-5 Intrusion symptoms (Criterion B) score after 12 weeks of treatment.
- Change from baseline in CAPS-5 Persistent Avoidance (Criterion C) score after 12 weeks of treatment.
- Change from baseline in CAPS-5 Negative Cognition and Mood (Criterion D) score after 12 weeks of treatment.
- Change from baseline in CAPS-5 Sleep Disturbance (item E-6) score after 12 weeks of treatment.
- Change from baseline in CAPS-5 Exaggerated Startle (item E-4) score after 12 weeks of treatment.
- PGIC score after 12 weeks of treatment.
- Proportion of patients with a PGIC score of "much improved" or "very much improved" after 12 weeks of treatment
- Proportion of patients with a treatment response on the CGI-I defined as a CGI-I score of "much improved" or "very much improved" after 12 weeks of treatment.
- Proportion of patients with a Total CAPS-5 score of 0 –10 (asymptomatic/few symptoms) after 12 weeks of treatment.

- Proportion of patients with a Total CAPS-5 score of 0-22 (asymptomatic or mild PTSD/subthreshold) after 12 weeks of treatment.
- Proportion of patients with Response, defined as a ≥ 10-point improvement from baseline in Total CAPS-5 score after 12 weeks of treatment.
- Proportion of patients with Loss of Diagnosis, defined as Response AND no longer meeting DSM-5 symptom criteria in any one or more of the four clusters (B, C, D, E) after 12 weeks of treatment.
- Proportion of patients in Remission, defined as Loss of Diagnosis AND Total CAPS-5 score ≤ 10 after 12 weeks of treatment.
- Proportion of patients achieving sustained Remission, defined as Loss of Diagnosis AND Total CAPS-5 score ≤ 10 after both 8 weeks AND 12 weeks of treatment.
- Proportion of patients with a ≥50% improvement from baseline in Total CAPS-5 score after 12 weeks of treatment.
- Change from baseline in BDI-II score after 12 weeks of treatment.
- Change from baseline in CAPS-5 Reckless or Self-Destructive Behavior (item E-2) score after 12 weeks of treatment.

7.3.3. Exploratory efficacy endpoints

Any exploratory endpoints will be delineated in the SAP.

7.3.4. Safety

Safety will be assessed by:

- Adverse events (AE) and serious AEs (SAEs) throughout the entire duration of the study, including detailed assessment of AEs involving the oral cavity
- Changes from baseline in clinical laboratory test results
- Changes from baseline in vital signs and weight
- Change from baseline in BDI-II
- Changes from baseline indicative of increased suicidal ideation or behavior as assessed by the Columbia Suicide Severity Rating Scale (C-SSRS)
- Changes from baseline in patient-rated Changes in Sexual Functioning Questionnaire Short-Form (CSFQ-14)
- Changes from baseline in patient-rated morning sedation as assessed by the Morning Treatment-Related Sedation Score (MTRSS)

7.3.5. Pharmacogenomic Endpoints

In this present study, we propose to examine potential genetic determinants of treatment response and particular adverse events by studying the patient's genomic profile in relation to treatment outcome and presence or absence of the adverse events. A single blood sample will be obtained at an unscheduled post-study visit, with invited participants first providing separate written, signed informed consent for pharmacogenomic analysis. The final list of pharmacogenomic endpoints will be delineated in the SAP for the pharmacogenomic portion of the study.

7.4. Efforts to Minimize Missing Data

It is important to avoid missing data from clinical trials. The following strategies are designed to minimize drop-outs and missing data in this study:

- Providing patients with greater background on the nature of placebo-controlled clinical trials and explaining that completing this study, regardless of the patient's level of treatment response, is essential to understanding whether TNX-102 SL may be helpful to others in the treatment of PTSD. Sites will explain that the study is not designed to benefit the individual patient but, rather, can only provide useful information for future therapeutics.
- Minimizing the burden on patients, with visits scheduled generally every 4 weeks (with reasonable visit window flexibility). Clinical site personnel will also receive guidance regarding the special considerations necessary when dealing with patients with military PTSD.
- Training of site personnel on the importance of minimizing missing data
- Providing payment for patients' time and effort at clinic visits, based on the duration of assessments and as approved by the Institutional Review Board. Reimbursement for travel expenses to and from the clinic sites may also be provided to further minimize the financial burden of participating in the study.
- Utilizing repeated assessments of outcome measures and analytical approaches that most appropriately compensate for missing data.

8. SELECTION AND WITHDRAWAL OF PATIENTS

8.1. 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. If medications are to be withdrawn for the explicit purpose of participation in this study, the patient must first sign an informed consent form before the withdrawal or down titration of any medication is initiated.

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 post-study pharmacogenomic assessment. Additional information is provided in Section 15.3.

8.2. Inclusion Criteria

Patients enrolled in this study will be volunteer patients. Eligible patients must meet all of the following inclusion criteria during the screening period:

1. Male or female between 18 and 75 years of age, inclusive, with military service (defined as active duty military, National Guard, reservist, veteran or military contractor) Identification confirming military service will be checked prior to randomization; medical monitor approval will be required for potential patients unable to provide evidence of prior service.
2. Diagnosed with current PTSD as determined by the Clinician-Administered PTSD Scale (CAPS-5) for Diagnostic and Statistical Manual of Mental Disorders-Version 5 (DSM-5) and of sufficient symptom severity, defined as all of the following at Screening Visit 1 using the Diagnostic version (1-month recall):
    a. The A criterion is 1=YES, and
    b. At least ONE item of the B criterion items must have a score of ≥2, and
    c. At least ONE item of the C criterion items must have a score of ≥2, and
    d. At least TWO items of the D criterion items must have a score of ≥2, and
    e. At least TWO items of the E criterion items must have a score of ≥2, and
    f. The F item 22 criterion is 1=YES (≥1 month duration of symptoms)
    g. At least ONE item of the G items must have a score of ≥2, and
    h. The total CAPS-5 score (of items 1 through 20 is) ≥33.
3. Index trauma(s) resulting in PTSD must meet the following:
    a. DSM-5 criterion A for PTSD as described in the CAPS-5 and Criterion A – Assessment Form (CA-AF), and
    b. Must have occurred in 2001 or later, and
    c. Must be military service related (either occurrence during military service, including during National Guard service or as reservist), and
    d. Must have occurred when the patient was ≥18 years of age.
4. Willing and able to withdraw and refrain from opioids for the course of the study.
5. Willing to refrain from use of all other formulations of cyclobenzaprine for the course of the study.
6. Willing and able to refrain from antidepressants, antipsychotics, mood stabilizers, anticonvulsants, benzodiazepines, non-benzodiazepine hypnotics, buspirone, stimulants (e.g. amphetamines, methylphenidate, modafinil, armodafinil), prazosin and trazodone for the course of the study.
7. Capable of reading and understanding English and able to provide written informed consent to participate.
8. If female, either not of childbearing potential (defined as postmenopausal for at least one year or surgically sterile [e.g., bilateral tubal ligation; bilateral oophorectomy;

hysterectomy, etc.]) or practicing one of the following medically acceptable methods of birth control throughout the study:

a. Hormonal methods such as oral, implantable, injectable, or transdermal contraceptives for a minimum of one full cycle (based on the patient's usual menstrual cycle period) before study drug administration;
b. Intrauterine device (IUD);
c. Double-barrier method (condoms, sponge, diaphragm, or vaginal ring with spermicidal jellies or cream);
d. In sexually-exclusive relationship with vasectomized male partner, or in same-sex relationship with no plans for artificial or other forms of insemination.

9. Willing and able to comply with all protocol-specified requirements.
10. If patient has received trauma-focused treatment (e.g., cognitive behavioral therapy for PTSD, prolonged exposure therapy, desensitization therapy, etc.) must have been completed at least three months prior to the Baseline visit, and there can be no plans to initiate this type of therapy during study. General psychotherapy that was in process at time of Screening may be continued during the trial, but no new initiation of treatment is allowed during the trial after enrollment.
11. Separate written, signed informed consent will be required if the patient is to participate in the post-study pharmacogenomic assessment. To be eligible to participate in the Pharmacogenomic assessment, the patient must have been randomized, had at least one post-baseline CAPS-5 assessment, and received active study drug in the TNX-CY-P301 study.

8.3. Exclusion Criteria

Eligible patients who meet any of the following criteria during the screening period should be excluded from the study:

1. Increased risk of suicide on the basis of the investigator's judgment and/or the results of the Mini International Neuropsychiatric Interview, Version 7.0.2 (M.I.N.I. 7.0.2) conducted at Screening and the Columbia Suicide Severity Rating Scale (C-SSRS) conducted at Screening and/or Baseline. Any of the following will be exclusionary:
    a. High suicidality based on a M.I.N.I. Module B score ≥ 17 (Screening); or,
    b. Patient answers YES to either M.I.N.I. question B10 or B11 (Screening); or,
    c. Patient meets criteria for CURRENT Suicidal Behavior Disorder on the M.I.N.I (Screening); or,
    d. C-SSRS Type 4 or Type 5 ideation within 6 months of Screening or at the Baseline visit; or,
    e. Any suicidal behavior in the past 12 months as identified by the C-SSRS at Screening or Baseline.
2. Increased risk of suicide, based on the investigator's judgment that is of a severity that is not appropriate for outpatient management, or that warrants additional therapy excluded by the protocol.

3. Significant (e.g., moderate or severe) comorbid traumatic brain injury (TBI) by history. Based on past history and investigator's judgment, patients with mild TBI are eligible.
4. Evidence of severe depression at screening or baseline (Visits 1 or 2) based on the investigator's judgment and collaborative pre-randomization review by the investigator and medical monitor(s) of the patient's psychiatric history, presenting symptomatology, M.I.N.I. 7.0.2 (including Major Depressive Episode and Suicidality modules), C-SSRS, CAPS-5, and BDI-II assessments.
5. Clinically significant laboratory abnormalities based on screening laboratory tests and/or medical history in the investigator's opinion, including a Thyroid Stimulating Hormone (TSH) level >1.5 times the upper limit of normal and aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 3 times the upper limit of normal (if persistent upon repeat). Patients with treated thyroid conditions and TSH levels ≤ 1.5 times the upper limit of normal will be eligible to participate in the study.
6. Diagnosed with clinically significant cardiac disease (e.g., significant arrhythmia or heart block, heart failure, or recent myocardial infarction [within the past 2 years]) or QTcF >450 msec (male) or >470 msec (female) on the screening electrocardiogram (ECG).
7. Current evidence of human immunodeficiency virus (HIV) infection based on screening laboratory results or medical history, or clinically significant hepatitis B or C infection as defined by current treatment or liver function tests (e.g., aspartate aminotransferase [AST] or alanine aminotransferase [ALT] > 3 times the upper limits of normal).
8. Use of antidepressant medication within 2 months of baseline, with the exception of trazodone used at doses ≤ 150 mg per day or tricyclic antidepressants at doses ≤25 mg per day, which instead require a 1-week drug-free interval prior to the Baseline visit.
9. Unable to successfully wash out of the following medications during screening, or in whom washout is medically inadvisable: anticonvulsants, mood stabilizers, anti-psychotic agents, opioids, benzodiazepines, non-benzodiazepine hypnotics (zolpidem; eszopiclone, zaleplon), buspirone, trazodone, stimulants (e.g., amphetamine mixed salts, methylphenidate, lisdexamphetamine, dextroamphetamine, modafanil, armodafanil), atomoxetine, or any medication known to be a potent (strong) cytochrome P450 subtype 3A4 (CYP3A4) inhibitor, or St. John's wort. **Note**: Use of caffeine and/or nicotine is permitted.
10. Unable to successfully wash out of alpha-adrenergic antagonists and/or agonists (e.g., prazosin, terazosin, doxazosin, tamsulosin, silodosin, tizanidine, clonidine, guanfacine) or when washout is medically inadvisable.
11. Positive results for illegal or abused substances other than cannabis at Screening or Baseline or history of alcohol/substance use disorder during the preceding 6 months as defined by the screening M.I.N.I. 7.0.2. Patients who utilize alcohol/cannabis but do not meet criteria for alcohol/substance use disorder are otherwise suitable for the study provided that, in the judgment of the Investigator, this usage will not interfere with the patient's ability to complete the study or provide reliable data.
12. Any clinically significant, uncontrolled, or unstable medical or surgical condition that could affect a patient's ability to participate in the study or potentially compromise a

patient's well-being during the study, including patients with a history of untreated or uncontrolled angle-closure glaucoma.

13. Diagnosis of DSM-5-defined bipolar disorder I, II or unspecified, schizophrenia, schizoaffective disorder, obsessive-compulsive disorder, major depressive disorder (MDD) with psychotic features, other psychotic disorder, or antisocial personality disorder as confirmed by the M.I.N.I. Version 7.0.2.
14. History within the past 2 years of violent behavior unrelated to military duties or associated work.
15. Anticipated need for surgery that might confound results or interfere with patient's ability to comply with the protocol.
16. Female patients who are pregnant or lactating.
17. History of serotonin syndrome, severe allergic reaction or bronchospasm or known hypersensitivity to cyclobenzaprine or the excipients in TNX-102 SL or placebo formulations.
18. Seizure disorder other than history of childhood febrile seizures.
19. Current sleep apnea not well controlled by Continuous Positive Airway Pressure (CPAP) or oral (mouthpiece) devices. Patients with mild obstructive sleep apnea or those well controlled by CPAP or oral (mouthpiece) devices are allowed at the discretion of the investigator.
20. Patients with a body mass index (BMI) > 45.
21. Has received any other investigational drug within 30 days before Screening or has taken cyclobenzaprine within 21 days before Randomization visit.
22. Previous participation in any other study with TNX-102 SL.
23. Any existing oral medical or dental condition, or tongue piercings, that could potentially interfere with sublingual administration of study drug, or history of severe or unexplained oral or oropharyngeal swelling or edema.
24. Family member of investigative staff.
25. In the process of litigating for compensation for a psychiatric disorder. Patients who are in the process of applying for VA benefits or who have a settled claim are eligible.

8.4. Randomization Criteria

The following randomization criteria must be satisfied at the Visit 2 Baseline Randomization Visit in order for the patient to be eligible to continue in the study. Only those patients meeting all of the following randomization criteria are eligible for randomization:

1. Patient continues to meet all inclusion and exclusion criteria, including urine and blood test results, and
2. Visit 2 total CAPS-5 score ≥ 33 ("Symptom Severity version using 1-week recall), and

3. At Visit 2, patient is not severely depressed (based on the investigator's judgment and Visit 2 C-SSRS, CAPS-5, and BDI-II, and considering the pre-randomization collaborative review by the investigator and medical monitor(s) of the patient's Visit 1 psychiatric history, presenting symptomatology, M.I.N.I. 7.0.2, C-SSRS, CAPS-5, and BDI-II assessments).
4. No active suicidal intent or plan, based on Investigator's judgment, and Visit 2 C-SSRS responses (e.g., no C-SSRS Type 4-5 ideation or suicidal behavior since Visit 1).

8.5. Prior and Concomitant Medications

Many concomitant medications are prohibited during this study because this study has been designed to evaluate the safety and efficacy of monotherapy with TNX-102 SL tablets for the treatment of PTSD. The goal of the study is to recruit patients who are not currently using other medications to treat their PTSD, or who are not clearly benefitting from any of the medications that would need to be discontinued in order to enter this study. Since many patients with PTSD may already be taking one or more excluded medications when screened, Principal Investigators should use extreme caution when determining whether a patient, in their clinical judgment, can be safely withdrawn from current medications that are being used to treat PTSD or are otherwise excluded from the protocol.

Eligible patients will not be receiving treatment with antidepressants, antipsychotic agents, mood stabilizers or anticonvulsants. In addition, eligible patients will not have taken antidepressants within 2 months of the Baseline visit. This time frame is intentionally long because it is not considered appropriate for patients to discontinue antidepressants solely to enter the study. An exception is made for the use of low-dose tricyclic agents at doses ≤ 25 mg per day, or trazodone at doses ≤ 150 mg per day, either of which may be discontinued for the purpose of enrollment but requires a 1-week medication-free period prior to randomization, as described below.

Patients also must be willing and able to discontinue use of benzodiazepines, non-benzodiazepines and certain other medications frequently used to treat PTSD; e.g., prazosin; trazodone; topiramate. Discontinuation of any of these agents should only be considered if/when the patient's clinical condition and stability will not be adversely affected.

Unless otherwise stated, excluded medications (e.g., trazodone, prazosin, topiramate, alpha-adrenergic agonists or antagonists [e.g., prazosin; tamsulosin; terazosin; doxazosin, silodosin, alfuzosin, clonidine, guanfacine], buspirone, benzodiazepines, and non-benzodiazepine hypnotics [zolpidem, zaleplon, eszopiclone]) will require a 1-week drug-free period prior to the Baseline visit (Visit 2). Similarly, all opioid medications, including tramadol and tapentadol, are excluded medications. Patients on chronic opioids are not appropriate candidates for participation, but there may be patients with occasional PRN opioid usage or who were recently on a short course for acute pain who may be appropriate if, in the clinical judgement of the Investigator, they could be safely tapered and remain opioid free for the week before baseline visit and throughout the 12 weeks of the study. The screening period of up to 35 days is provided to ensure a safe tapering rate and discontinuation of excluded medications, per Investigator's discretion, leading up to the 1-week medication-free period required before the randomization/baseline visit.

Other medications capable of modifying the pharmacologic activity of TNX-102 SL (e.g., α-adrenergic agonists/antagonists; potent CYP3A4 inhibitors) will also be excluded, and discontinuing these medications should only be considered if clinically acceptable. A list of CYP3A4 inhibitors is provided in 0; only those considered potent or strong inhibitors (in the left-hand column) are excluded medications.

8.5.1. Allowed Concomitant Medications

It is ideal to have all patients participating in the study go without any hypnotic agents for the entire double-blind period of the study. Yet there may be instances in which patients' insomnia symptoms need to be addressed with a concomitant treatment. In these instances, the Investigator should recommend use of an antihistamine-based OTC hypnotic, such as Benadryl® or generic diphenhydramine 25-50 mg, for a limited period (e.g. no more than a few nights in a row). Patients should be asked to keep track of their use of such sleeping remedies, and again, chronic nightly use should be avoided whenever possible.

Melatonin is considered an allowable concomitant medication but its usage should have been stable for at least 30 days prior to baseline and usage should remain stable during the study. If diphenhydramine is ineffective, the treating Investigator should contact the medical monitor to discuss alternative options.

Allergy medications and cold remedies containing adrenergic agonist decongestants such as pseudoephedrine or phenylephrine should be avoided unless absolutely necessary (and in such cases when considered absolutely necessary, they should be avoided in the evening or at bedtime to minimize their interference with sleep). Sympathomimetics such as adrenergic agonist decongestants have the potential to acutely worsen PTSD symptoms and therefore could confound the assessment of TNX-102 SL versus placebo for treatment of PTSD.

Other prescription or over-the-counter medications not specifically excluded by entry criteria typically may be continued during the study, with the expectation that chronic medications should have been used in a stable fashion for at least 30 days prior to randomization. Sites should contact the medical monitor for any questions about whether a concomitant medication may be continued during the study or if it would be acceptable to taper an excluded medication.

8.6. Withdrawal Criteria

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 10.5.1.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Study Drug Packaging, and Labeling and Storage

Study drug supplies will be packaged identically so as to maintain the integrity of the study blind. The study medication bottles will be labeled minimally with the following information: study number TNX-CY-P301, sponsor name and address, bottle number, 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. Two bottles will be dispensed to each patient at Visit 2 (baseline), Visit 4 (Week 4) and Visit 5 (Week 8); this will provide the patient with 80 tablets to cover the 4 weeks of dosing 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 the second 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 be instructed 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 both 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 excursions (15-30°C/59-86°F) as defined in the Study Reference Manual (IP Receipt and Storage) are permitted without the sponsor's approval.

9.2. Dosing Instructions

Patients will be instructed to take **two** tablets of their assigned study drug (TNX-102 SL 2.8 mg tablets or placebo tablets) sublingually, placed simultaneously **under the tongue**, each evening at bedtime starting at bedtime on evening of Day 0 (Day of Visit 2) and continuing without interruption for 12 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 SL 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 2 (two) 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.

9.3. Dispensing Instructions

Each patient who has met the randomization criteria (Section 8.3) will be assigned 2 double-blind treatment bottles at Visit 2 via the IWRS, with a unique, but otherwise random bottle number that is generated when the study coordinator successfully completes randomization procedures. Patients will also be assigned two new treatment bottles at Visits 4 and 5 via the IWRS. The bottle numbers provided by the Interactive Web Response (IWR) system at these visits will tell the site which treatment bottles have been assigned to the patient.

In the event of loss of study medication, new medication will be provided by the IWR system, when appropriately requested by the site and/or the sponsor or designee.

Study treatments for the double-blind treatment phase are either:

Treatment A: 2 × TNX-102 SL 2.8 mg tablets ("TNX-102 SL") to be taken sublingually once daily at bedtime.

Treatment B: 2 × placebo tablets ("placebo") to be taken sublingually once daily at bedtime.

9.4. Release of Clinical Study Supplies to the Investigator

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

9.5. Study Drug Accountability and Reconciliation

All patients will be expected to bring their bottles of study medication with them to all study visits. At each study visit, the site staff will inspect the medication bottles, and perform a count of the tablets remaining in the bottles and document this 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. Patients will be asked for an explanation if the count of returned study drug tablets indicates a discrepancy between the expected number of tablets dosed and the number returned in the bottles. If it is found that the patient is not taking the study medication as expected, the patient will be re-counseled with instructions, and this should be noted in the patients' records. A deviation should be recorded on any patient who is less than 70% compliant with dosing between visits.

If the patient fails to return any of the 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. If more than 8 tablets cannot be accounted for at any of the visits where drug is returned (week 4, 8 or 12), the investigator will be asked to evaluate the situation, and a written summary of this evaluation should be added to the source and entered onto the case report form (CRF). Situations where replacement drug is requested, or when more than 8 tablets 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 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.

10. STUDY VISITS AND PROCEDURES

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

10.1. Visit 1 (Screening: Day -35 to -7)

10.1.1. Informed Consent

Before the potential patient has undergone any study-related screening procedures, including any downward titration or withdrawal of medications, 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 Case Report Form (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 post-study pharmacogenomic assessment.

10.1.2. Screening Overview

Screening Visit 1 will start a variable length screening period. The length of the screening period is to be no shorter than 7 days, but may be as long as 35 days in order to accommodate medication taper and discontinuation or other study requirements.

If the patient is eligible to continue in the study, and does not need to discontinue any excluded medication, the patient may be scheduled to return for Visit 2 (Randomization) in 7 (or more) days, assuming all screening evaluations have been completed, including confirmation of acceptable laboratory and ECG results. If the patient needs to undergo taper and discontinuation of excluded medication, the Investigator will generate a written down titration schedule for the patient and will schedule Visit 2 such that the date of Visit 2 is at least 1 week after the date of the final dose of any excluded medication. If additional clinic visits are deemed necessary by the investigator for clinical monitoring of the patient before scheduling Visit 2, such visits will be recorded as unscheduled visits.

10.1.3. Patient Numbering

All screened patients will be assigned a unique concatenated 6-digit site-patient number (e.g., 102-112) by the IWR system. A screening log or system documenting the following information will be recorded and maintained, and will include the patient's initials, screening number, whether the patient was ultimately randomized or not, and if not randomized, the reason the patient was excluded/screen-failed.

10.1.4. Screening and Assessments/Procedures

The following screening assessments/procedures will be completed in the following general order:

- Obtain written informed consent to participate

- Obtain demographics, including alcohol, nicotine/tobacco (smoking and/or chewing), and marijuana use
- Obtain medical history
- Obtain prior and current medication history, including all prior PTSD therapies and other treatments for psychiatric indications
- Obtain psychiatric history (M.I.N.I. 7.0.2)
- Administer PTSD Rating Scales:
    - Life Events Checklist (LEC-5)
    - Criterion A – Assessment Form (CA-AF)
    - Clinician Administered PTSD Scale (CAPS-5) (Since Last Month version)
- Perform physical examination, including visual inspection of the oral cavity (including floor of mouth/sublingual area)
- Obtain vital signs, height, weight and BMI
- Draw samples for clinical laboratory tests for:
    - Chemistry, hematology, HIV and TSH, with free thyroxine also performed if TSH is outside the upper or lower limits of normal
    - Urine Drug Screen (central laboratory)
    - Serum pregnancy test (for women of child-bearing potential)
- Conduct 12-lead electrocardiogram
- Administer Depression/Suicidality Scales
    - Beck Depression Inventory (BDI-II)
    - Columbia Suicide Severity Rating Scale (C-SSRS, Baseline/Screening Version, with rater review of BDI-II prior to starting C-SSRS interview)
- Review inclusion/exclusion criteria

Only those patients meeting all of the inclusion and none of the exclusion criteria will be eligible to continue. NOTE: Final determination of eligibility based on clinical laboratory tests will be made when results have been returned.

Sites will be asked to complete and submit to the Tonix medical monitoring team key screening information. This information will be reviewed by the Tonix medical monitoring team to help ensure the selection of well-qualified patients. The specific requirements and timelines associated with this pre-randomization review process will be outlined in a separate document.

Once eligibility has been confirmed and authorization for randomization granted by a Tonix medical monitor, eligible patients will return to the clinic for Visit 2.

There is no requirement for Follow-Up visits for patients who are screen failures. Patients who fail to qualify should have their medication adjusted, as appropriate, per the judgment of the

Investigator and be released from the clinic. There will be no requirement to enter data into the electronic case report form (eCRF) for patients who are not randomized.

10.2. Visit 2 (Baseline: Day 0)

Visit 2 should be scheduled 7 to 35 days after Visit 1. Study procedures will be completed (including qualifying baseline assessments for the C-SSRS and CAPS-5). If the patient meets all randomization criteria, the patient will be randomized via the IWR system to receive double-blind study medication.

10.2.1. Pre-Randomization Assessments

The following assessments must be completed at Visit 2 to confirm that the patient is eligible for randomization. Upon arrival at the clinic, the following assessments should be done, preferably in this order:

- Assess occurrence of adverse events
- Update medical history (with changes since screening noted)
- Assess changes in medication history and concomitant medications
- Obtain vital signs and weight
- Administer CAPS-5 - "Symptom Severity Version", using 1-week recall
- Conduct urine drug screen (urine dipstick, only as necessary, if select Visit 1 tests were positive for excluded medications that required discontinuation prior to randomization)
- Conduct urine pregnancy test (for women of child-bearing potential)
- Perform visual examination of the oral cavity
- Have the patient complete the following outcome scales (in order):
    - SDS
    - PROMIS scale for sleep disturbance
    - MTRSS (assessment of sedation)
    - CSFQ-14
    - BDI-II (needs to be completed prior to the C-SSRS and reviewed by the C-SSRS rater at outset of C-SSRS interview)
- Administer the C-SSRS- Since Last Visit Version (with rater review of BDI-II prior to starting C-SSRS interview)

10.2.2. Randomization Criteria

Once all pre-randomization assessments have been completed, only those patients who meet all of the following randomization criteria will be eligible to continue:

1. Patient continues to meet all inclusion and exclusion criteria, including urine and blood test results, and

2. Visit 2 total CAPS-5 score ≥ 33 ("Symptom Severity" version using 1-week recall), and
3. At Visit 2, patient is not severely depressed (based on the investigator's judgment and Visit 2 C-SSRS, CAPS-5, and BDI-II, and considering the pre-randomization collaborative review by the investigator and medical monitor(s) of the patient's Visit 1 psychiatric history, presenting symptomatology, M.I.N.I. 7.0.2, C-SSRS, CAPS-5, and BDI-II assessments).
4. No active suicidal intent or plan, based on Investigator's judgment, and Visit 2 C-SSRS responses (e.g., no C-SSRS Type 4-5 ideation or suicidal behavior since Visit 1).

If the patient does not satisfy these randomization criteria, the patient has failed to qualify for this study and should be considered a screen failure, with the reason documented. With Medical Monitor approval, if the patient is otherwise considered a qualified and compliant patient, Visit 2 may be delayed to accommodate situations in which extenuating or short-term circumstances do not warrant screen failure.

If the patient does satisfy these randomization criteria, then continue with the following:

- Randomize the patient via IWRS Randomization System
- Dispense 4-week supply (two bottles) of double-blind study medication
- Review patient instructions regarding study drug dosing (Section 9.2)
- Schedule next study visit

10.3. Visit 3 (Telephone Visit: Day 14)

Visit 3 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 adverse events, including any oral adverse events and whether an unscheduled visit is indicated for an examination of the oral cavity
- Review patient instructions regarding drug dosing.
- Administer the 'Since Last Visit' C-SSRS

After all of the items have been reviewed with the patient, the patient should be given an appointment to return to the clinic for Visit 4, and be re-instructed, as necessary, on dosing instructions, and reminded to bring study medication back to the clinic at their next visit.

10.4. Visit 4 and 5 (Weeks 4 through 8)

Visits 4 and 5 are similar study visits that are scheduled to be conducted after 4 and 8 weeks of treatment, respectively. Visit 4 should occur on Day 28 ± 5 days and Visit 5 should occur on Day 56 ± 5 days.

The following assessments and procedures are scheduled for these visits in the following general order:

- Collect study drug and assess compliance
- Assess occurrence of adverse events
- Update concomitant medications
- Obtain vital signs and weight
- Administer CAPS-5-"Symptom Severity Version" using 1-week recall
- Conduct urine pregnancy test (for women of child-bearing potential)
- Have the patient complete the following outcome scales (in order):
    - SDS
    - PROMIS scale for sleep disturbance
    - MTRSS (assessment of sedation)
    - PGIC
    - BDI-II (needs to be completed prior to the C-SSRS and reviewed by the C-SSRS rater at outset of C-SSRS interview)
- Administer C-SSRS - Since Last Visit Version
- Physician to assess CGI-I (needs to be completed once all other assessments are available for investigator to review)
- Dispense new bottles of double-blind study medication as assigned by IWRS

After all of the assessments at each visit have been completed, the patient should be given an appointment to return to the clinic for the next scheduled visit, and be re-instructed, as necessary, on dosing instructions, and reminded to bring study medication back to the clinic at their next visit.

10.5. Visit 6 (Week 12)

Visit 6 should occur after 12 weeks of double-blind study drug treatment, scheduled at Day 84 -5 / +7 days. The following assessments and procedures are to be completed in the following general order:

- Collect study drug and assess compliance
- Assess occurrence of adverse events
- Update concomitant medications
- Obtain vital signs and weight
- Administer CAPS-5-"Symptom Severity Version" using 1-week recall
- Conduct urine pregnancy test (for women of child-baring potential). Serum pregnancy test may be done at Investigator's discretion.

- Draw samples for clinical laboratory tests for:
  - Chemistry and hematology
- Perform visual examination of oral cavity
- Have the patient complete the following outcome scales (in order):
  - SDS
  - PROMIS scale for sleep disturbance
  - MTRSS (assessment of sedation)
  - PGIC
  - CSFQ-14
  - BDI-II (needs to be completed prior to the C-SSRS and reviewed by the C-SSRS rater at outset of C-SSRS interview)
- Administer C-SSRS-Since Last Visit Version
- Physician to assess CGI-I (needs to be completed once all other assessments are available for investigator to review)

10.5.1. 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 adverse event (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

This study will attempt to obtain as complete information as possible on all participating patients. An effort must be made to contact the medical monitor prior to any patient's early termination. Each reason for early termination will be adjudicated. 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 study medication. NOTE: These visit procedures are not intended for patients who fail to qualify for randomization or for any other reason withdraw from the study prior to receipt of a dose of double-blind study drug.

If the patient withdraws prior to the week 2 (visit 3) visit window (before day 11), the following assessments and procedures are to be completed at this visit in the following general order:

- Document reason for early termination
- Collect study drug and assess compliance
- Assess occurrence of adverse events
- Update concomitant medications
- Obtain vital signs and weight
- Conduct urine pregnancy test (for women of child-bearing potential). Serum pregnancy test may be done at Investigator's discretion.
- Draw samples for clinical laboratory tests for:
    - Chemistry and hematology
- Perform visual examination of oral cavity
- Have the patient complete the following outcome scales (in order):
    - MTRSS (assessment of sedation)
    - CSFQ-14
    - BDI-II (needs to be completed prior to the C-SSRS and reviewed by the C-SSRS rater at outset of C-SSRS interview)
- Administer C-SSRS – Since Last Visit Version

If the patient withdraws after the week 2 (visit 3) visit window (on or after day 11), the following assessments and procedures are to be completed at this visit in the following general order:

- Document reason for early termination
- Collect study drug and assess compliance
- Assess occurrence of adverse events
- Update concomitant medications
- Obtain vital signs and weight
- Administer the CAPS-5-"Symptom Severity Version" using 1-week recall
- Draw samples for clinical laboratory tests for:
    - Chemistry and hematology
    - Serum pregnancy test (for women of child-bearing potential)
- Conduct visual examination of oral cavity
- Have the patient complete the following outcome scales (in order):
    - SDS
    - PROMIS scale for sleep disturbance

  - MTRSS (assessment of sedation)
  - PGIC
  - CSFQ-14
  - BDI-II (needs to be completed prior to the C-SSRS and reviewed by the C-SSRS rater at outset of C-SSRS interview)
- Administer C-SSRS- Since Last Visit Version
- Physician to assess CGI-I (needs to be completed once all other assessments are available for investigator to review)

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

10.5.2. 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 results, physical examination, or other findings. If an additional study visit is warranted, or occurs, the date and nature of the visit will be documented in the CRF and in the source documents.

Patients who call to report an oral AE that is a lesion of some form should be brought back to the clinic for an unscheduled oral exam if deemed appropriate. In the case in which the AE is solely sensory in nature (such as oral hypoaesthesia) *and* the patient reports there is no discernable associated lesion, an unscheduled oral exam is not required but may be arranged if the investigator determines it to be clinically appropriate.

10.6. Pharmacogenomic Assessment (Post-Study)

For patients who participated in P301 and are invited back to the site for participation in the optional pharmacogenomics assessment after having finished their participation, the patients will be invited in for an unscheduled visit in which they first will learn about the pharmacogenomics study and sign a separate written pharmacogenomics informed consent form. Next, a blood sample is drawn and processed for pharmacogenomic analysis. Once completed, the patient is discharged from the pharmacogenomics portion of the study.

11. STUDY ASSESSMENTS

11.1. Screening Assessments

11.1.1. Psychiatric and Medical History

A psychiatric interview using the Mini International Neuropsychiatric Interview (M.I.N.I.-Version 7.0.2) and a comprehensive medical history will be obtained at screening in order to determine whether the patient is eligible for enrollment.

While patients with mild traumatic brain injury (TBI) are eligible to participate in the study, moderate and severe TBI are excluded. Mild TBI (or concussion) is one of the most common forms of combat-related injury. Based on self-report data, approximately 15% of troops engaged in active combat in Afghanistan and Iraq may have suffered a mild TBI (Hoge et al., 2008). A *history of TBI* is defined as any traumatically induced structural injury and/or physiological disruption of brain function as a result of an external force that is indicated by new onset or worsening of at least one of the following clinical signs, immediately following the event:

1. Any period of loss of or a decreased level of consciousness;
2. Any loss of memory for events immediately before or after the injury;
3. Any alteration in mental state at the time of the injury (e.g., confusion, disorientation, slowed thinking);
4. Neurological deficits (e.g., weakness, balance disturbance, praxis, paresis/plegia, change in vision, other sensory alterations, aphasia) that may or may not be transient;
5. Intracranial lesion.

Although *severity of TBI* depends in part on patient assessment in the days after a traumatic head injury, for the purposes of this protocol, mild TBI is defined as:

1. Normal structural brain imaging findings
2. Loss of consciousness not greater than 30 minutes after injury
3. Alteration of consciousness not greater than 24 hours after injury
4. Posttraumatic amnesia not more than 24 hours after injury
5. No ongoing neurological deficits (Note: tinnitus, headaches, or sleep disturbances that appeared to result from the head trauma would *not* be considered as ongoing neurological deficits and therefore should *not* be interpreted as meaning the person has a greater severity than mild TBI.)

In addition, the past medication history will be reviewed. Any psychiatric medication or PTSD therapies utilized during the patient's lifetime should be collected. Responses from the M.I.N.I. will serve to document the presence of other psychiatric conditions. The diagnosis and severity of PTSD will be based on the CAPS-5 (Section 11.2.1).

11.2. Efficacy Assessments

The primary efficacy endpoint and many of the secondary and exploratory efficacy endpoints in this study are derived from clinician-administered assessments which must be administered by qualified and trained individuals at each clinical site. Study specific training will be required before staff is 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 unless absolutely unavoidable due to the rater's absence from the clinic. 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, appropriate privacy and sufficient time to complete them.

11.2.1. Clinician-Administered PTSD Scale (CAPS-5)

The primary efficacy endpoint is the change from baseline (Visit 2) in total CAPS-5 score at Week 12 (Visit 6).

The CAPS-5 is an updated and validated version of a semi-structured interview that has been designed to assess the essential features of PTSD as defined by the DSM-5 (Weathers et al, 2013). The CAPS-5 affords the clinician flexibility to inquire about symptoms and diagnostic status over different time frames, such as past week, past month, and/or worst month for lifetime. For this study, a "Diagnostic" version of the CAPS-5 (lifetime and past month recall) will be utilized at the Screening visit to confirm the diagnosis of PTSD and determine eligibility based on symptom severity. A "Symptom Severity" version of the CAPS-5 (past week recall) will be completed by clinician at all other time points (Baseline [Visit 2] and after 4, 8, and 12 weeks of treatment [Visits 4, 5, and 6]). A CAPS-5 total score of 33 or above at both Screening ("Diagnostic" version) and Baseline ("Symptom Severity" version) is requisite for eligibility.

In addition to the total symptom score, the CAPS-5 affords the opportunity to examine clusters of symptoms, including Criterion B (intrusion symptoms), Criterion C (persistent avoidance), Criterion D (negative cognitions and mood), and Criterion E (arousal and reactivity), all of which will be secondary efficacy endpoints.

The CAPS-5 interview contains the following components:

- Life Events Checklist for DSM-5 (LEC-5): Completed by the patient at Screening Visit 1 only) and reviewed by the rater of the CAPS-5 interview at the start of the interview.
- PTSD Symptoms
    - Criterion A: the rater will review the patient-completed LEC-5 and then inquire into the qualifying index trauma (Criterion A) utilizing the study-specific Criterion A - Assessment Form (CA-AF) (Visit 1 only)
    - Criterion B: Items 1-5
    - Criterion C: Items 6-7
    - Criterion D: Items 8-14
    - Criterion E: Items 15-20
    - Criterion F: Items 21-22
    - Criterion G: Items 23-25
    - Global ratings: Items 26-28
    - Dissociative symptoms: Items 29-30

Further instruction on when to complete each component will be provided in the study specific versions of the CAPS-5 forms.

The LEC-5, which documents the patient's lifetime traumatic experiences, will be completed by the patient at Screening Visit 1 before the clinician administered CAPS-5. The CAPS-5 rater will be responsible for reviewing the answers on this form with the patient as part of the completion of the CAPS-5 Criterion A - Assessment Form in order to determine if the traumatic experience qualifies the patient for inclusion in the study. NOTE: If worst month lifetime PTSD symptoms resulted from earlier trauma(s), such as trauma(s) before age 18 or trauma(s) not related to military services, the prospective patient should be excluded from participation.

At Screening, the total CAPS-5 score (Diagnostic version with 1-month recall) must be ≥ 33 and must meet the other diagnostic criteria specified in Inclusion Criterion 2 (Section 8.2) in order for the patient to continue. At Baseline (Visit 2), the total CAPS-5 score (past week recall) must again be ≥ 33.

The CAPS-5 interview must be completed by a qualified and trained rater. This rater should be kept consistent for a given patient throughout the study. If circumstances require non-conformity with the single rater approach for any patient, this should be documented. Additional information regarding the conduct, rating, and scoring of the CAPS-5 instrument as well as the requirements for rater training will be provided separately.

11.2.2. Beck Depression Inventory (BDI-II)

The Beck Depression Inventory (BDI-II) is a 21-item measure of the severity of current depressive symptoms, extensively validated for use in both medical and mental health populations. While this instrument does not provide a psychiatric diagnosis of depression and has considerable overlap with PTSD associated symptoms (Resick et al, 2017), it does provide a continuous scale for measuring changes in the severity of symptomatology.

The patient will be asked to complete this questionnaire at all in-clinic study visits. At Visit 1 and Visit 2, patients whose responses are indicative of suicidal ideation, as defined by a response to Item #9 of ≥1 should be carefully evaluated and compared to the patient's C-SSRS responses, and appropriate intervention prescribed, if indicated. In addition, patients' BDI-II responses at Screening and Baseline (Visits 1 and 2) should be reviewed by the investigator as part of the comprehensive evaluation of the patient's psychiatric status and overall eligibility, since patients suffering from severe depression should be screen failed and referred for appropriate psychological evaluation or care, as necessary. After Visit 1, the responses to Item #9 should be monitored along with C-SSRS responses to ensure that there is no increase in suicidal ideation during the study, and the total score should also be monitored to ensure the patient's psychological status remains stable.

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

The CGI-I will be completed by an Investigator to evaluate the patient's status since initiation of treatment. The CGI-I, status since initiation of treatment, is the first key secondary efficacy endpoint in this study. The CGI-I should be completed toward the end of each in-clinic post-Baseline study visit once all of the assessments are available for the investigator's review.

11.2.3.1. CGI-I Assessments at Weeks 4, 8, and 12

Once the patient has been randomized, an Investigator will complete the CGI-I assessment after 4, 8, and 12 weeks of treatment (Visits 4 -6) in order to assess the overall change in the patient's status since Baseline and answer the following question:

Since the initiation of treatment at Visit 2, the patient is:

1 = Very much improved
2 = Much improved
3 = Minimally improved
4 = No change
5 = Minimally worse
6 = Much worse
7 = Very much worse

11.2.4. Patient Global Impression of Change (PGIC)

The PGIC is a validated, self-report instrument to gauge the patient's assessment of change in condition. This form will be completed by the patient after 4, 8 and 12 weeks of treatment (Visits 4, 5 and 6, respectively). The patient will answer a single question:

Since the initiation of study medication, overall, my PTSD symptoms are:

1 = Very much improved
2 = Much improved
3 = Minimally improved
4 = No change
5 = Minimally worse
6 = Much worse
7 = Very much worse

11.2.5. PROMIS Sleep (short form) 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 Sleep scale (short form 8a) will be assessed at Baseline (Visit 2) and after 4, 8, and 12 weeks of treatment (Visits 4, 5, and 6, respectively).

11.2.6. Sheehan Disability Scale (SDS)

The SDS scale is a self-report questionnaire that was designed to assess the patient's view of the degree to which symptoms have disrupted work, social life/ leisure activities, and family life/ home responsibilities during the past 1 week (Sheehan & Sheehan, 2008). In addition, the SDS asks the patient to provide the number of days or work lost as well as unproductive days in the past week. The SDS scale will be completed by the patient at Baseline (Visit 2), and after 4, 8, and 12 weeks of treatment (Visits 4, 5, and 6, respectively).

11.3. Safety Parameters

Safety will be assessed by evaluation of adverse events, responses on the C-SSRS and BDI-II, clinical laboratory tests, vital signs, weight, patient ratings of sexual function assessed by the CSFQ-14, and patient-rated assessments of morning sedation as assessed by the MTRSS.

11.3.1. Adverse Events (AEs)

Patients will be monitored for AEs throughout the study from the time that the patient signs an informed consent and 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, in the opinion of the patient and outside of their normal experience, should be reported as an adverse event.

If a patient reports an oral cavity adverse event, the Investigator should examine the oral cavity to confirm the presence or absence of any irritation or other signs. Additional details related to onset, duration, severity and reversibility of the oral cavity event will be documented (Section 11.3.5).

Additional information regarding definition and reporting requirements for adverse events, serious adverse events, and pregnancies is provided in Section 11.3.1.

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

The C-SSRS is a questionnaire 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 used 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.

There are multiple versions of this questionnaire. At Visit 1, the “baseline/screening” questionnaire will be administered and the recall periods will be “lifetime” and “within the past 6 months” for suicidal ideation, and “within the past year” for suicidal behaviors. Patients whose responses are indicative of suicidal ideation with intent and/or plan (e.g., Type 4-5 ideation) within the past 6 months or a history of prior suicidal behavior within the past year will be excluded from participation, with recommended referral for appropriate intervention.

At all subsequent visits (Visit 2 through 6), the "since last visit" questionnaire will be administered, and the recall period on this will be "since the last visit". Note that if there has been a significant change in responses indicative of increased suicide risk, appropriate intervention should be prescribed as described below.

11.3.3. Safety Planning Intervention (SPI)

The C-SSRS is completed at every visit in order to assess for changes in suicidality during the study. As a screening and baseline entrance criterion, patients exhibiting Type 4 or 5 ideation in the past 6 months or a history of suicidal behavior in the past 12 months are not eligible for the study due to this risk and should be referred for appropriate emergency care. If a patient scores a 4 or 5 at a clinic visit following randomization, the patient should be withdrawn from the study and referred for appropriate emergency care. If a patient scores a 4 or 5 at any clinic visit, it should be reported as a serious adverse event.

If a patient scores a 2 or 3 on the suicidal ideation section of the C-SSRS at any visit (including the Screening visit), the investigator and patient should work together to implement a Safety Planning Intervention (SPI). In addition, if a post-baseline score of 2 or 3 represents a significant change from the patient's baseline status, it should be recorded as an adverse event. The recommended SPI for this study is the plan developed by Barbara Stanley, PhD and Gregory Brown, PhD which has been adopted by the U.S. 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. Additional information and training on the implementation of an SPI will be provided prior to initiation of the study.

11.3.4. Physical Examination

A complete physical examination will be performed at Screening Visit 1 only. At a minimum, the physical examination will include the following components: HEENT (head, eyes, ears, nose, and throat), neck, chest and lungs, cardiovascular, abdomen, skin, and musculoskeletal. The physical examination may exclude rectal, genitourinary, and breast examinations.

11.3.5. Visual Examination of Oral Cavity

A visual examination of the oral cavity should be done at Screening (Visit 1), Baseline (Visit 2) and after 12 weeks (Visit 6) of treatment and/or at Early Termination. 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 spontaneously reports an oral adverse event (other than transient sensory AEs such as tongue numbness, tingling or bitter taste) to confirm presence or absence of any irritation or other signs. Additional details related to onset, duration, severity and reversibility of oral events will be documented in the CRF.

11.3.6. Vital Signs, Height and Weight

Vital signs (sitting blood pressure and heart rate, respiratory rate, oral temperature, and weight) will be assessed at Screening (Visit 1), Baseline (Visit 2) and after 4, 8, and 12 weeks of treatment (Visits 4, 5, and 6/Early Termination). Height will be measured without shoes at Visit

1 only. The BMI will be a derived variable, based on height and weight entries. A BMI > 45 is an exclusion criterion.

11.3.7. Electrocardiogram (ECG)

A 12-lead ECG will be performed at Screening (Visit 1) and will be reviewed by the Investigator for the purpose of excluding from participation patients who have either a history of or current evidence of clinically significant cardiac disease (e.g., significant arrhythmias or heart block, heart failure, or myocardial infarction within the past 2 years) or a QTcF at Screening >450m/sec (males) or QTcF >470m/sec (females).

The ECG interpretation by the Investigator will be recorded in the CRF as normal, abnormal but clinically insignificant, or abnormal and clinically significant. In addition, the standard ECG parameters including rhythm, heart rate, and intervals for PR (or PQ), QRS, and QTcF (Fridericia's) corrections for heart rate will be recorded.

If the Investigator has any concerns about the eligibility of a patient or wishes to confirm his/her assessment, the Investigator should consult with the medical monitor for this study.

11.3.8. Clinical Laboratory Assessments

The clinical laboratory evaluations to be performed in this trial are listed in Table 2. Those marked as screening tests will be performed at screening only. All other tests will be performed at Screening (Visit 1) and after 12 weeks of treatment (Visit 6), or Early Termination. Clinical laboratory values may be repeated prior to randomization in order to confirm exclusionary levels for TSH, ALT and/or AST values. If these values remain persistently elevated upon repeat, the patient is not eligible for randomization.

With the exception of the urine pregnancy tests or the ad hoc urine drug test required at baseline for patients washing off excluded medications (e.g., opioids, benzodiazepines, amphetamines), 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.

A urine drug screen for drugs of abuse (including marijuana) will be collected at Screening Visit 1 and sent to the central laboratory for analysis. If the patient has a positive drug screen at Visit 1 and/or Visit 2 for anything other than marijuana, and the results cannot be explained by use of current allowable prescription medications, the patient should be excluded from the study. If the urine drug screen is positive at Visit 1 and the results can be explained by the use of current prescription medications (e.g., opioids, benzodiazepines, amphetamines) that will be discontinued during screening, the investigator must repeat the drug screen and obtain a negative result using an in-clinic urine dipstick drug screen prior to randomization to confirm eligibility for the study.

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)[a]	Hematocrit
Alkaline phosphatase	Hemoglobin
Aspartate aminotransferase (AST)[a]	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)	WBC differential
Creatine 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)	White blood cell (WBC) count
Sodium	
Thyroid-stimulating hormone (TSH)[c] at screening	**Serum Pregnancy Test at Screening[b]**
Free T4 only if TSH is outside of normal limits	**Urine Pregnancy Test (qualitative dipstick)[b]**
Human immunodeficiency virus types 1 and 2 (HIV_1 and HIV_2)	**Urine Drug Screen[d]**
Pharmacogenomic testing for invited participants at 5 study sites (optional) (Separate Visit post Week 12/ET)	

[a] Level greater than 3 times the upper limit of normal is an exclusion (if persistent upon repeat).

[b] Pregnancy testing for females of child-bearing potential only. A positive pregnancy test is exclusionary (Visit 1 or Visit 2) or mandates withdrawal from the study (all other visits).

[c] TSH level greater than 1.5 times higher than the upper limit of normal is exclusionary at Visit 1.

[d] Urine drug screening will be conducted on all patients at Screening and, if necessary, at Baseline in patients with a positive result at Screening who otherwise qualify for the study. For patients testing positive at the Screening visit for an excluded medication that will be discontinued during the screening interval, an in-clinic urine dipstick drug screen will be performed at the Baseline visit and must be negative for opioids, benzodiazepines, amphetamines and illicit drugs other than marijuana in order for the patient to be eligible for randomization.

11.3.9. Assessment of Changes in Sexual Function: Changes in Sexual Functioning Questionnaire Short-Form (CSFQ-14)

The Changes in Sexual Functioning Questionnaire Short-Form (CSFQ-14) (Keller et al. 2006) is validated scale with internal reliability designed to allow a patient to self-evaluate his or her sexual behaviors or problems in a number of areas. The CSFQ-14 will be administered at Baseline (Visit 2) and Week 12/ET (Visit 6). It yields a total score, three subscales corresponding to phases of the sexual response cycle (i.e. desire, arousal, orgasm), and five subscales corresponding to important dimensions of sexual functioning. It is considered a useful scale for assessing sexual side effects of medications. For all items, higher scores reflect higher sexual functioning. For 12 of the 14 items, higher sexual functioning corresponds to greater

frequency or enjoyment/pleasure (e.g. 1=never to 5 = every day). For two items (item 10, assessing loss of interest after arousal for women and priapism for men, and item 14, assessing painful orgasm), higher sexual functioning corresponds to lower frequency (e.g. 1=every day to 5=never). Items 10 and 14 are included in the total score but not in any scale score.

11.3.10. Assessment of Sedation: Morning Treatment-Related Sedation Score (MTRSS)

The Morning Treatment-Related Sedation Score (MTRSS) is designed to assess the patient's morning sedation at clinic visits. The MTRSS will be assessed at Baseline (Visit 2) and at Weeks 4, 8, and 12/ET (Visits 4, 5, and 6). The patient will complete the following questions:

A. On most mornings during the past week, I have awakened feeling:

0. Alert with no grogginess
1. Mildly groggy
2. Moderately groggy
3. Very groggy

B. If you reported any grogginess in the last week (responses 1-3), the grogginess lasted:

1. A few minutes
2. A short time (less than one hour)
3. A long time (more than one hour)

Note: if "Alert with no grogginess is selected in Part A, Part B is not answered, and the score for part B is 0.

11.4. Pharmacogenomic Assessment

For pharmacogenomic analysis, a single blood sample collected in one PAXgene DNA tube will be obtained from an invited group of patients at 5 study sites after participation in the main study has ended. Patients had to have received active drug during the main study, at least one CAPS-5 assessment post-Baseline, and the patient has provided separate written, signed informed consent for pharmacogenomic analysis. The blood sample will be sent by the site to the pharmacogenomics testing laboratory where first DNA is extracted from the whole blood sample, and subsequently exome sequencing is performed on the DNA. The purpose of this testing is to allow exome sequencing and analysis for genetic variants related to treatment response and presence or absence of adverse events to TNX-102 SL.

12. DEFINITIONS, RECORDING, AND REPORTING OF ADVERSE EVENTS

12.1. Definition of Adverse Events

According to International Conference on Harmonization (ICH) guidance E2A, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, an adverse event (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 treatment-emergent AE (TEAE) is an AE that either commenced following initiation of study treatment or was present prior to study treatment but increased in frequency or severity following initiation of study treatment.

12.2. Adverse Event Recording

12.2.1. Coding the Adverse Event

Standard medical terminology should be used in describing AEs. 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.

12.2.2. 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 patient 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 patient'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.

12.2.3. 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.

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

Any SAE that occurs at any time during the study, 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 facsimile and 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 1 working day 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 or dosage.

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

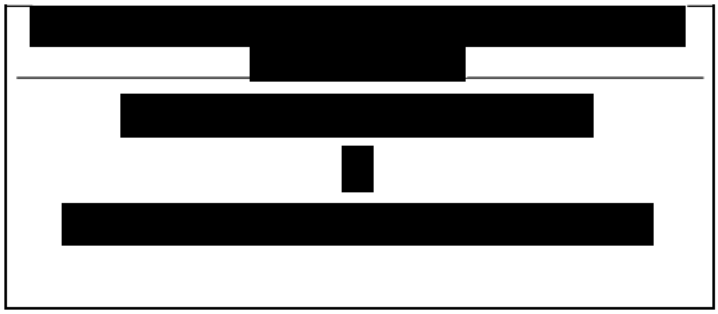
NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

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, during the per-protocol follow-up period, 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

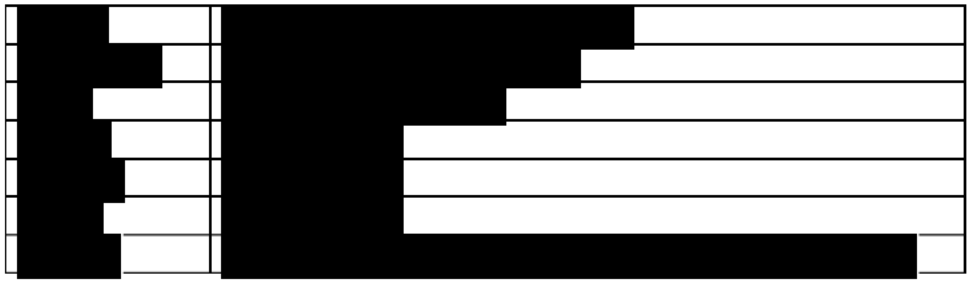
case records and other documents when requested. Telephone and e-mail reports must be confirmed promptly either by facsimile or by email. For reporting SAEs, one of Tonix's designated medical monitors should be called.

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 initial awareness of the event.**



Contact information for the Medical Monitors is provided below:

Table 3: Medical Monitoring Contact Information



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

The investigator, or the sponsor or designee in the case of a central Institutional Review Board (IRB), also must notify the 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.

12.4. Pregnancy

The active pharmaceutical product 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) and reported within 24 hours of the site's awareness to Tonix and/or its designee. 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.

13. STATISTICS

A full description of the statistical analyses to be performed at study completion will be provided in a Statistical Analysis Plan (SAP), which will be finalized prior to the interim analysis.

One interim analysis is planned (See Section 13.6) prior to the completion of the study. A full description of the interim analysis will be provided in an Interim Statistical Analysis Plan (ISAP), which will be finalized prior to the interim analysis.

Baseline will be defined as those values recorded closest to, but prior to administration of the first dose of study drug.

Unless otherwise noted, significance tests of treatment differences will be tested at the two-sided 0.05 level.

13.1. Populations for Analysis

The following populations will be defined for use in analyzing the efficacy and safety data in the study (see SAP for more details):

- Safety Population (SAFETY): All patients who receive at least 1 dose of study drug. All safety analyses and demographic/baseline characterization will be performed using this population, analyzed as treated, using the highest dose they were issued at any visit.
- Modified Intention-to-Treat Population (mITT): All randomized patients who have at least a baseline and one post-baseline CAPS-5 assessment. This is the primary population for efficacy analyses and patients will be analyzed based on their randomized treatment. See Section 10.5.1for early termination assessments.

13.2. Estimate of Sample Size

The study is planned to enroll approximately 550 patients total in a 1:1 randomization, that is, 275 patients in each of the placebo and TNX-102 SL 5.6 mg groups. [redacted]

13.3. Assessment of Demographic and Baseline Characteristics

Demographic and baseline characteristics such as age, gender, race/ethnicity, height, weight, BMI, presence of current major depressive episode, family status, education, employment status, and smoking history will be summarized by treatment group (TNX-102 SL and placebo) and overall using descriptive statistics.

Medical History will be coded using MedDRA and summarized by SOC and Preferred Term using frequency counts by treatment group.

13.4. Efficacy Analysis

13.4.1. Efficacy Endpoints

Primary Efficacy Endpoint:

The mean change from baseline (Visit 2) in the Total CAPS-5 score after 12 weeks of treatment evaluated at Visit 6.

Secondary Efficacy Endpoints: The first two secondary efficacy endpoints listed below are considered key secondary endpoints and will be tested in that order.

- CGI-I score (analyzed as a continuous variable) after 12 weeks of treatment.
- Change from baseline in the SDS total score after 12 weeks of treatment.

Other Secondary Efficacy Endpoints:

- Change from baseline in patients' quality of sleep using the PROMIS Sleep Disturbance scale after 12 weeks of treatment.
- Change from baseline in the disruption of work/school activities assessed using the SDS after 12 weeks of treatment.
- Change from baseline in disruption of social life/ leisure activities assessed using the SDS after 12 weeks of treatment.
- Change from Baseline in the disruption of family life/home responsibilities assessed using the SDS after 12 weeks of treatment.
- Change from baseline in CAPS-5 Arousal and Reactivity (Criterion E) score after 12 weeks of treatment.
- Change from baseline in CAPS-5 Intrusion symptoms (Criterion B) score after 12 weeks of treatment.
- Change from baseline in CAPS-5 Persistent Avoidance (Criterion C) score after 12 weeks of treatment.
- Change from baseline in CAPS-5 Negative Cognition and Mood (Criterion D) score after 12 weeks of treatment.
- Change from baseline in CAPS-5 Sleep Disturbance (item E-6) score after 12 weeks of treatment.

- Change from baseline in CAPS-5 Exaggerated Startle (item E-4) score after 12 weeks of treatment.
- PGIC score after 12 weeks of treatment.
- Proportion of patients with a PGIC score of "much improved" or "very much improved" after 12 weeks of treatment
- Proportion of patients with a treatment response on the CGI-I defined as a CGI-I score of "much improved" or "very much improved" after 12 weeks of treatment.
- Proportion of patients with a Total CAPS-5 score of 0 –10 (asymptomatic/few symptoms) after 12 weeks of treatment.
- Proportion of patients with a Total CAPS-5 score of 0 -22 (asymptomatic or mild PTSD/subthreshold) after 12 weeks of treatment.
- Proportion of patients with Response, defined as a ≥ 10-point improvement from baseline in Total CAPS-5 score after 12 weeks of treatment.
- Proportion of patients with Loss of Diagnosis, defined as Response AND no longer meeting DSM-5 symptom criteria in any one or more of the four clusters (B, C, D, E) after 12 weeks of treatment.
- Proportion of patients in Remission, defined as Loss of Diagnosis AND Total CAPS-5 score ≤ 10 after 12 weeks of treatment.
- Proportion of patients achieving sustained Remission, defined as Loss of Diagnosis AND Total CAPS-5 score ≤ 10 after 8 weeks AND 12 weeks of treatment.
- Proportion of patients with a ≥50% improvement from baseline in Total CAPS-5 score after 12 weeks of treatment.
- Change from baseline in BDI-II score after 12 weeks of treatment.
- Change from baseline in CAPS-5 Reckless or Self-Destructive Behavior (item E-2) score after 12 weeks of treatment.

Exploratory Endpoints: Any exploratory endpoints will be delineated in the SAP.

13.4.2. Primary Efficacy Analysis

The primary efficacy analysis will use a mixed model repeated measures (MMRM) approach to estimate mean change from baseline in the Total CAPS-5 score evaluated after 12 weeks of treatment in the TNX-102 SL 5.6 mg and placebo arms. The model will include all patients in the mITT population, and the dependent variable will be the observed change from baseline in total CAPS-5 score at each post-randomization visit. Covariates in the model will include the fixed categorical effects of treatment, site, sex, current tobacco use status, presence of current MDE, visit and treatment by visit interaction, as well as the continuous fixed covariates of baseline score and baseline score by visit interaction. Missing data will be imputed via multiple imputation (MI), and details regarding the MI approach will be described in the SAP.

The primary analysis will be followed by several sensitivity analyses. Further details on sensitivity analyses can be found in the SAP.

13.4.3. Secondary Efficacy Analyses

MMRM methodology will be utilized for the continuous secondary endpoints, and analyses will be based on the mITT population. The dependent variable will be the observed change from baseline in the respective secondary endpoint at each post-randomization visit, with the exception of the CGI-I which does not have a baseline. Covariates in the model will include the fixed categorical effects of treatment, site, sex, current tobacco use status, presence of current MDE, visit and treatment by visit interaction (baseline score and baseline score by visit interaction will be included as appropriate).

Binary data will be analyzed using a Cochran-Mantel-Haenszel test controlling for the randomization stratification of presence of current MDE, analyzed separately at each visit. Patients with missing data will be analyzed as though they are non-responders. The primary time point of interest will be Week 12. Odds ratios and corresponding 95% confidence intervals will be presented.

To adjust for multiplicity and to control for overall type I error, a sequential test procedure will be applied to the key secondary efficacy endpoints. If the primary analysis produces a result that is statistically significant, a nominal significance level will be used for comparing the secondary endpoints in an ordered fashion. If the analysis for a secondary endpoint does not produce a statistically significant result, then the remaining secondary endpoint analyses will automatically be considered non-significant regardless of the p-value produced. In the case of an early stop or increase in sample size, the same methodology/critical value used for the primary endpoint will be applied to the key secondary endpoints for the purposes of the sequential testing. See the SAP for additional details.

The testing order for the two key secondary endpoints is as follows:

- CGI-I score (analyzed as a continuous variable) after 12 weeks of treatment.
- Change from baseline in the SDS total score after 12 weeks of treatment.

No other adjustments for multiplicity will be made and other p-values displayed in the output will be considered for descriptive summary purposes only and will not be used for formal inference. Full details regarding the statistical analyses for the listed endpoints will be provided in the SAP.

13.4.4. Exploratory Analyses

Exploratory efficacy analyses will be based on the mITT population. Details on exploratory efficacy analyses can be found in the SAP.

13.5. Safety Analyses

Safety will be assessed by:

- Adverse events and serious AEs throughout the entire duration of the study, including assessment of AEs involving the oral cavity

- Changes from baseline in clinical laboratory test results
- Changes from baseline in vital signs and weight
- Changes from baseline indicative of increased suicidal ideation or behavior as assessed by the C-SSRS
- Changes from baseline in BDI-II
- Changes from baseline in patient-rated sexual function as assessed by the CSFQ-14
- Changes from baseline in patient-rated morning sedation as assessed by the MTRSS

Adverse events will be coded using the latest version of MedDRA and will be summarized overall and by preferred term and system organ class. 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. Actual values and changes from Baseline for clinical laboratory test results, MTRSS scores, CSFQ-14 scores, BDI-II scores, and vital sign measurements will be summarized at endpoint using descriptive statistics (n, mean, SD, median, minimum, and maximum).

The number of patients with suicidal behaviors, ideations and acts based on the C-SSRS will be tabulated by treatment group and listed.

13.6. Interim Analyses

One planned interim analysis for the purposes of sample size reassessment and to assess stopping early for either futility or success will be performed. The interim analysis will be conducted when approximately 50% of the total planned enrollment is evaluable for efficacy.

An adaptive group sequential design will be used for early efficacy testing. The details of this testing will be described in an ISAP, which will be finalized prior to the interim analysis.

The interim analysis will be performed by an independent unblinded statistical group. Results of this assessment will be provided to an Independent Data Monitoring Committee (IDMC). The IDMC Charter will outline the roles and responsibilities of the IDMC as well as the interim analysis decision rules.

The following recommendations can be made at the time of the interim analysis: The IDMC will inform the Sponsor to increase the sample size by a fixed amount, keep the current sample size and continue, stop the study for futility, or stop the study early for success. If the study is stopped early for success based on the interim analysis results, currently randomized patients who have not yet completed the study will be offered an immediate transition into an open-label extension safety study (Protocol No. TNX-CY-P306).

14. PROCEDURES FOR MODIFYING THE PROTOCOL OR TERMINATING THE STUDY

14.1. 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.

14.2. 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.

15. ETHICAL CONSIDERATIONS

15.1. Ethical Conduct of the Study

This protocol is written in accordance with the principles established by the 18th World Medical Assembly General Assembly (Helsinki, 1964) 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 Good Clinical Practices (GCP) guidelines, Good Laboratory Practices (GLP) guidelines, local ethical and regulatory requirements, including the Federal Food, Drug and Cosmetic Act, U.S. applicable Code of Federal Regulations (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.

15.2. 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.

15.3. 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 serotoninergic medications (e.g., triptans) 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. Patients on MAOIs should not be considered for the study, and MAOIs should not be initiated during the study due to the additional safety concerns posed by this class of medication when used in combination with other serotoninergic drugs (such as cyclobenzaprine).

The patient should also be asked in the Informed Consent Form (ICF) for permission for the principal investigator or his designee to contact the patient's other personal physicians, as appropriate, concerning participation in the study. Separate written, signed informed consent must be obtained if the patient is to participate in the post-study optional pharmacogenomic assessment.

The method of obtaining and documenting informed consent and the contents of the ICF will comply with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, the requirements of 21 CFR Part 50, "Protection of Human Patients," the Health Insurance Portability and Accountability Act (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.

16. DATA HANDLING AND RECORDKEEPING

16.1. 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. Investigator can use the Certificate to avoid compelled "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. 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.

16.3. Data Handling

Unless otherwise specified, procedures, data collection and evaluation will be conducted as per the Standard Operating Procedures (SOPs) of the contract research organization (CRO). The investigator will assume the responsibility of ensuring the completeness and accuracy of the clinical data. All data will be verified for quality control and will also be patient to audits from Tonix or designee to ensure quality.

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.

16.4. 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.

16.5. Screening Records

A record generated by IWRS 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.

16.6. 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.

16.7. 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.

16.8. 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.

17. CONFIDENTIALITY

17.1. 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, **Certificates of Confidentiality** has been obtained from the FDA for the investigators to protect patients enroll in the study. Investigators can use the Certificate to avoid compelled "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.

17.2. 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.

17.3. 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.

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19. APPENDICES

APPENDIX 1. STUDY DESIGN AND SCHEDULE OF ASSESSMENTS

Period	Screening	Baseline	Double-Blind Treatment Period				Post-Study
Visit	**1**	**2**	**3[a]**	**4**	**5**	**6**	**7**
Study Week	**-5 to -1**	**0**	**2**	**4**	**8**	**12**	
Study Day	**-35 to -7**	**0**	**14 ± 3**	**28± 5**	**56 ± 5**	**84 -5/+7**	
Informed Consent	X						
Inclusion/Exclusion Criteria	X	X					
Randomization		X					
Psychiatric History (M.I.N.I. 7.0.2)	X						
Demographics and Medical History	X	X[b]					
Prior and Concomitant Medications	X	X	X	X	X	X	
Vital Signs, height[c], weight and BMI	X	X		X	X	X	
Physical Examination	X						
Inspection of oral cavity	X	X[d]				X	
12-Lead Electrocardiogram	X						
Pregnancy Test[e]	X[f]	X		X	X	X[f]	
Urine Drug Screen	X	X[g]					
Clinical Laboratory Assessments[h]	X					X	
HIV, and TSH	X						
Beck Depression Inventory (BDI-II)	X	X		X	X	X	
LEC-5	X						
CA-AF	X						
CAPS-5	X[i]	X[j, k]		X[k]	X[k]	X[k]	
C-SSRS	X[l]	X[m]	X[m]	X[m]	X[m]	X[m]	
CGI-I				X	X	X	
PGIC				X	X	X	
PROMIS-sleep (short form)		X		X	X	X	
CSFQ-14		X				X	
MTRSS		X		X	X	X	
SDS		X		X	X	X	

Period	Screening	Baseline	Double-Blind Treatment Period				Post-Study
Visit	**1**	**2**	**3[a]**	**4**	**5**	**6**	**7**
Study Week	**-5 to -1**	**0**	**2**	**4**	**8**	**12**	
Study Day	**-35 to -7**	**0**	**14 ± 3**	**28± 5**	**56 ± 5**	**84 -5/+7**	
Adverse Events		X	X	X	X	X	
Telephone Visit[a]			X				
Dispense Study Drug[n]		X		X	X		
Collect/ Count Study Drug Returned				X	X	X	
Informed Consent for Pharmacogenomic blood draw [o]							X
Pharmacogenomic blood draw (optional) [o]							X

Abbreviations: BDI-II = Beck Depression Inventory; BMI = Body Mass Index; CA-AF = Criterion A – Assessment Form; CAPS-5 = Clinician Administered PTSD Scale (for DSM-5); CSFQ-14=Changes in Sexual Functioning Questionnaire Short-Form; C-SSRS = Columbia-Suicide Severity Rating Scales; HIV = Human immunodeficiency virus; LEC-5 = Life Events Checklist for DSM-5; M.I.N.I = Mini International Neuropsychiatric Interview; MTRSS = Morning Treatment-Related Sedation Scale; PGIC = Patient Global Impression of Change; PROMIS = Patient Reported Outcomes Measurement Information System; SDS = Sheehan Disability Scale; TSH=Thyroid Stimulating Hormone;

[a] Week 2 visit will be performed via telephone. The patient will be asked about Adverse Events (including oral AEs), any change in medication, and study drug dosing and compliance and conduct the C-SSRS.

[b] Only updates from screening

[c] Height to be measured at Visit 1 only

[d] 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.

[e] Women of child-bearing potential only

[f] Serum pregnancy test required at Visit 1 only; all other pregnancy tests via urine dipstick performed in the clinic. Serum pregnancy test at Visit 6/Early Termination may be done at Investigator's discretion.

[g] Urine dipstick to confirm eligibility if Visit 1 results were positive for excluded medication requiring washout

[h] Chemistry and hematology

[i] Visit 1 CAPS-5 will utilize the "Diagnostic Version" (past month recall). Patients must meet criteria for diagnosis of PTSD and have a total score ≥33

[j] Total CAPS-5 score must be ≥33("Symptom Severity Version" using 1-week recall)

[k] CAPS-5 "Symptom Severity Version" using 1-week recall

[l] C-SSRS ("Baseline/Screening" Version)

[m] C-SSRS ("Since Last Visit" Version)

[n] Four-week supply of study medication will be dispensed at each dispensing visit. Must access IWR system in order to obtain correct bottle number to dispense

[o]The blood draw for the pharmacogenomic assessment will be obtained post study participation for an invited group of patients at 5 study sites. Separate written, signed informed consent is required if the patient is to participate in the optional pharmacogenomic assessment.

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** **clarithromycin** **cobicistat** **conivaptan** **danoprevir** **elvitegravir** **grapefruit juice** **indinavir** **itraconazole** **ketoconazole** **lopinavir** **mibefradil** **nefazodone** **nelfinavir** **paritaprevir** **posaconazole** **ritonavir** **saquinavir** **telaprevir** **telithromycin** **tipranavir** **troleandomycin** **voriconazole**	amprenavir aprepitant atazanavir cimetidine ciprofloxacin clotrimazole crizotinib cyclosporine darunavir/ritonavir diltiazem dronedarone erythromycin fluconazole fluvoxamine fosamprenavir imatinib tofisopam verapamil	alprazolam amiodarone amlodipine atorvastatin bicalutamide chlorzoxazone cilostazol fosaprepitant fluoxetine gingko goldenseal isoniazid istradefylline ivacaftor lapatinib lomitapide nilotinib oral contraceptives pazopanib ranitidine ranolazine tacrolimus 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 2016)

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

RECENT MAJOR CHANGES

Dosage and Administration (2) 05/2016

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)

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 1-800-896-5855 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: 05/2016

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

1

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 N=128	AMRIX 15 mg N=127	AMRIX 30 mg 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 has 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

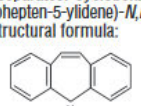
Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Psychiatric referral may be appropriate.

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*] cyclohepten-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.

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/m² 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/m² 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/m² 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/m² 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.

Distributed By:
Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454

Manufactured By:
Adare Pharmaceuticals, Inc.
Vandalia, OH 45377

AMR-008

US Patent Nos. 7387793, 7754372, 7790199, 7820203, 7829121

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

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 1-800-896-5855.

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.

TEVA CNS

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North Wales, PA 19454

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AMRPL-003
Revised May 2016

AMR-40470