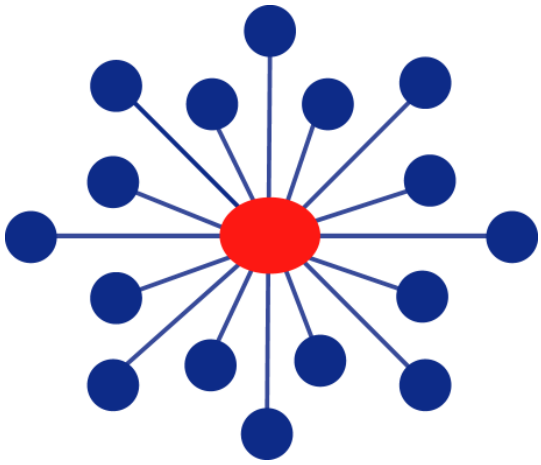

NIDA CTN Protocol 0051

Extended-Release Naltrexone vs. Buprenorphine for Opioid Treatment (X:BOT)

Lead Investigator (LI): John Rotrosen, MD
Co-LI: Joshua Lee, MD, MSc
Edward Nunes, MD

Project Manager: Patricia Novo, MPH

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PROTOCOL DEVELOPMENT TEAM

Genie L. Bailey, MD
Gregory S. Brigham, PhD
Arthur L. Caplan, PhD
Allan J. Cohen, MA, MFT
Marc Fishman, MD
Michael T. French, PhD
Mary Jeanne Kreek, MD
Walter Ling, MD
Dennis McCarty, PhD
Larissa J. Mooney, MD
Susan A. Murphy, PhD
Dominic Sisti, PhD
George Woody, MD

EMMES:
Robert Lindblad, MD
Ro Shauna Rothwell, PhD
Dee Blumberg, PhD
Don Stablein, PhD
Paul Van Veldhuisen, PhD
Colleen Allen, MPH
Jeanine May, PhD
Dagmar Salazar, MS

CCTN:
Petra Jacobs, MD
David Liu, MD
Steven Sparenborg, PhD
Geetha Subramaniam, MD
Betty Tai, PhD
Paul G. Wakim, PhD

TABLE OF CONTENTS

1.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ALT	Alanine Aminotransferase
ASI-Lite	Addiction Severity-Index-Lite
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BP	Blood Pressure
BUP	Buprenorphine
BUP-NX	Buprenorphine+Naloxone (Suboxone®)
CAP	College of American Pathologists
CCC	Clinical Coordinating Center
CFR	Code of Federal Regulations
CHRT	Concise Health Risk Tracking
CLIA	Clinical Laboratory Improvement Amendment of 1988
CNS	Central Nervous System
CoC	Certificate of Confidentiality
CRF	Case Report Form
CTN	Clinical Trials Network
CTP	Community Treatment Program
DEA	Drug Enforcement Agency
DHHS	Department of Health and Human Services
DSC	Data and Statistics Center
DSM-5	Diagnostic and Statistical Manual of Mental Disorders Fifth Edition
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ERC	Ethics Review Committee
FDA	Food and Drug Administration
FTND	Fagerström Test for Nicotine Dependence
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
HAM-D	Hamilton Depression Scale
HBsAB	Hepatitis B surface antibody
HBsAG	Hepatitis B surface antigen
HCV	Hepatitis C Virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	Heart Rate
IND	Investigational New Drug
IRB	Institutional Review Board
IM	Intramuscular
IV	Intravenous
LFTs	Liver Function Tests (AST, ALT, albumin and bilirubin)
LI	Lead Investigator
MD	Medical Doctor
MDMA	Methylenedioxymethamphetamine (Ecstasy)
MedDRA	The Medical Dictionary for Regulatory Activities
Mg	Milligrams

MM	Medical Management
MOP	Manual of Operations
NDA	New Drug Application
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
NMS	Non-Study Medical and Other Services
NP	Nurse Practitioner
NTX	Naltrexone
NX	Naloxone
OHRP	Office for Human Research Protections
PA	Physician Assistant
PI	Principal Investigator
PLG	Polylactide-co-glycolide
QA	Quality Assurance
RAB	Risk Assessment Battery
RAP-C	Research Advisory Panel of California
RRTC	Regional Research and Training Center
SAE	Serious Adverse Event
SC	Subcutaneous
SOWS	Subjective Opiate Withdrawal Scale
TAU	Treatment as Usual
TLFB	Timeline Follow-Back
UDS	Urine Drug Screen
VA	Veterans Administration
VAS	Visual Analog Scale
XR-NTX	Extended-Release Naltrexone (Vivitrol®)

2.0 CTN-0051 SYNOPSIS AND SCHEMA

For opioid-dependent patients in the U.S. and most of the rest of the world, detoxification or detoxification followed by short term residential treatment, with the goal of achieving long-term abstinence from opioid misuse is a mainstay of treatment. Nonetheless, the majority of patients treated in this way will relapse to opioid misuse, leading to a costly and ineffectual cycle of readmission for repeated detoxifications.

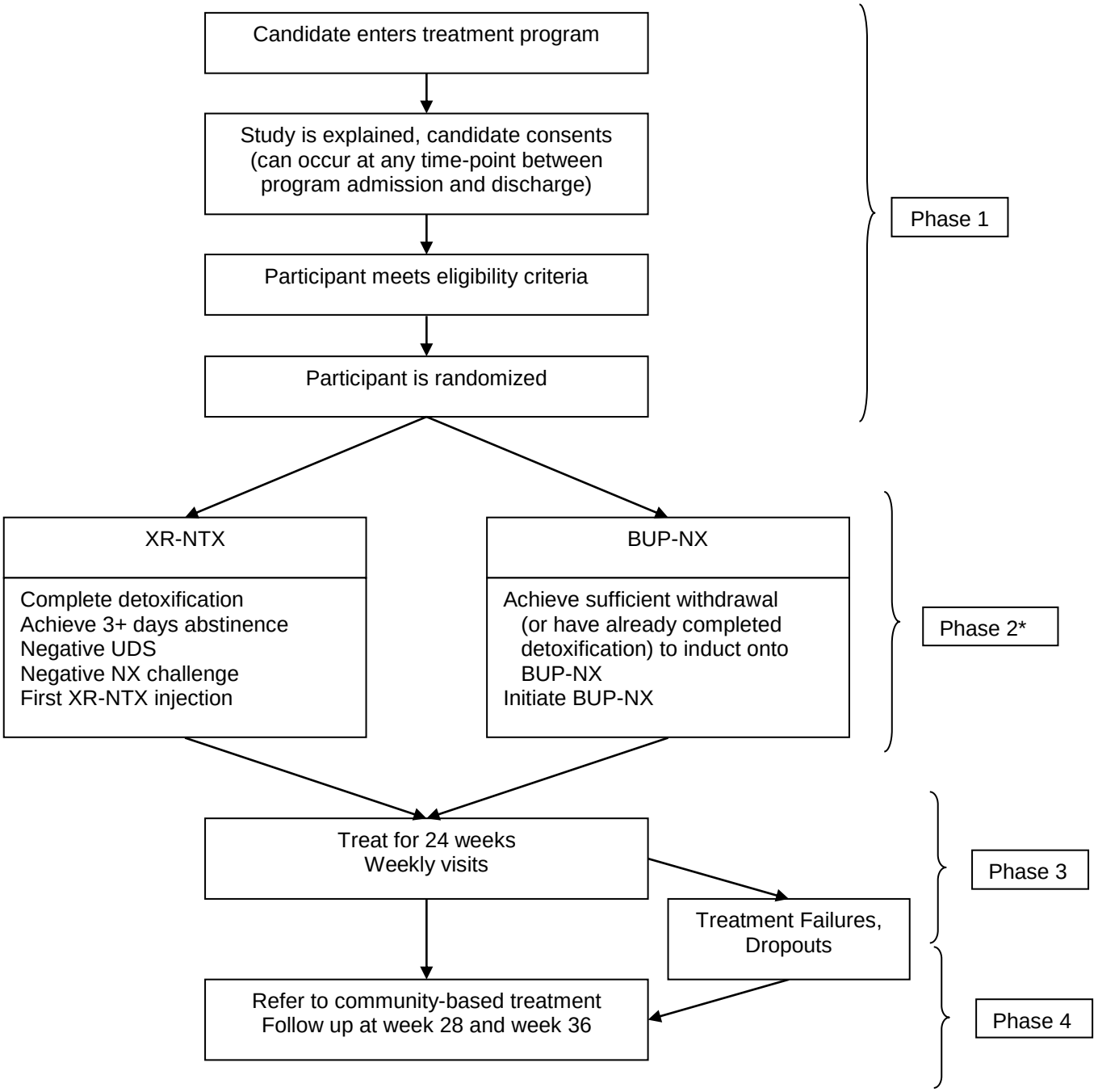
The overarching goal of CTN-0051 is to foster adoption of new relapse-prevention pharmacotherapies in community-based treatment programs (CTPs) where these could have a substantial public health impact. To this end CTN-0051 will assess the comparative effectiveness of extended release injectable naltrexone (XR-NTX, Vivitrol®), an opioid antagonist recently approved and indicated for the prevention of relapse to opioid dependence, versus buprenorphine-naloxone (BUP-NX, Suboxone®), a high affinity partial agonist indicated for maintenance treatment of opioid dependence, as pharmacotherapeutic aids to recovery.

The study is conducted in 8 CTN-affiliated CTPs that provide or partner with detoxification services (inpatient/residential) which have the capacity to maintain participants opioid-free for approximately 3-7 days, have the capacity to provide medication-assisted therapy, and can provide a minimum of one group or individual counseling session per week during the 24-week treatment period. Up to 600 eligible participants will be randomized to treatment with XR-NTX or BUP-NX for 24 weeks (sufficient to include 350 participants who are randomized more than 72 hours after their last opioid). To maximize generalizability, the point of randomization is flexible, from shortly after program admission until just prior to program discharge. A data analysis modification (assessment of whether the early vs. late randomizers have a differential treatment effect and if so, time to relapse will be estimated for early and late randomizers separately) will occur if differential treatment initiation is a problem for cases randomized prior to completing detoxification (i.e., significantly fewer early randomizers are able to complete detoxification and XR-NTX induction).

The primary goal of the study is to estimate the difference, if one exists, between XR-NTX and BUP-NX in the distribution of the time to relapse (i.e., loss of persistent abstinence) during the 6-month trial. The primary outcome measure is the time to the event, with the event called relapse. Secondary objectives are to: (1) compare outcome on XR-NTX versus BUP-NX across a range of clinical safety and secondary efficacy domains, (2) explore demographic, clinical, and genetic predictors of successful treatment and moderators of differential effectiveness (i.e., what variables may help clinicians choose which of these treatments is best for a given patient), and (3) collect a limited dataset to permit analyses of economic costs and benefits of the two treatments.

Toward the end of the 24-week treatment period, participants are referred for follow-up care in the community (which could include pharmacotherapy if desired and available), and follow-up outcomes are assessed at week 28 and week 36 after randomization. For participants receiving BUP-NX, who do not wish to continue, or for whom community resources are not available, the study provides a two-week BUP-NX taper.

Figure 1: CTN-0051 Schema



***The window for induction remains open into Phase 3 (until week 22).

3.0 CTN-0051 TIMELINE

Study activities are expected to last up to 38 months at participating sites. A phased startup, with two or three sites starting several months before the others, is anticipated. The timeline is as follows:

- Study start up (IRB approvals, hiring, training): up to 3 months
- Enrollment: up to 24 months
- Treatment: 6 months
- Follow-up: 3 months
- Data lock: 2 months

4.0 INTRODUCTION

4.1 Background and Rationale

Opioid dependence is a chronic relapsing disorder, conveying serious risks including disability, incarceration, transmission of blood-borne infections, and death from opioid overdose. There is now nearly a half century of overwhelming evidence that agonist substitution, initially with methadone and more recently with buprenorphine, is both efficacious in clinical trials and effective in the community in promoting and sustaining abstinence and reducing risks associated with opioid dependence.[1,2] Despite this, "drug-free" non-medication-based strategies, such as short-term detoxification followed by psychosocial counseling, while associated with high relapse rates, remain a mainstay of treatment in U.S. community-based settings.[3,4] Reasons include negative societal, institutional and personal attitudes toward agonists, individual preference to be "drug-free", and limited access to medication and providers. Naltrexone (NTX), a full mu-opioid antagonist, has been FDA-approved for opioid pharmacotherapy since the 1980s, but in its orally administered form it is largely ineffective, it has virtually no place as first-line opioid treatment, and it is little used in the community.[5-6] Two recent studies of XR-NTX (Comer et al.[7], testing Depotrex®, Biotech Inc., in New York City and Philadelphia; and Krupitsky et al.[8], testing Vivitrol®, Alkermes Inc., in Russia) support efficacy of XR-NTX compared to placebo injections.

In October 2010, largely on the basis of the Russian trial and an earlier U.S. safety study (Alkermes ALK21-006 and ALK21-006-EXT), the FDA approved Vivitrol® for the "prevention of relapse to opioid dependence". Patients and treatment programs now have a remarkable opportunity to choose between two pharmacologically distinct and opposite treatment approaches, XR-NTX and BUP-NX, each with established efficacy. Yet, little is known about XR-NTX implementation in U.S. community-based settings, and the FDA's decision has been criticized insofar as (1) the FDA "accepted a single trial of injectable naltrexone in Russia, unpublished at the time, as primary evidence of efficacy", and (2) "the study did not adequately assess risk of post-treatment overdose".[9, 10] Since agonist therapy is prohibited in Russia, these authors question the use of these "data to gain approval in the USA – where methadone and buprenorphine are widely available".

Regardless of the merit of these concerns, the data from the Russian placebo-controlled efficacy trial do not directly address the effectiveness, comparative effectiveness, safety, and costs of XR-NTX in U.S. community-based populations and treatment programs. There are few, if any, data to guide choice and to direct patient-centered treatment decisions. It is in this context that our primary goals are to learn and inform the field about XR-NTX implementation in the community and to compare that to BUP-NX – specifically with regard to population and treatment program characteristics associated with successful outcomes – to foster more widespread adoption of new pharmacotherapies and prevent relapse. Our aims are to clearly address key questions emerging from the availability of mechanistically opposite treatment options and to develop pilot data to inform future studies. Overall, are the two approaches (XR-NTX vs. BUP-NX) essentially equally effective? Are there demographic, and/or clinical factors associated with favorable treatment outcome overall, or that predict better outcome with one approach vs. the other? What treatment-program characteristics are associated with success with each of the treatments?

A key design consideration to highlight early in this introduction is that induction from active opioid use onto XR-NTX and BUP-NX differs substantially. Ideally (though not necessarily typically) BUP-NX induction is initiated in the very early phase of opioid withdrawal and BUP-NX maintenance is pursued instead of opioid detoxification. In contrast, because naltrexone is a full

mu antagonist that will precipitate withdrawal, induction is deferred until full detoxification has been completed and a patient has been fully opioid-free for several days. In this study, participants may be inducted onto BUP-NX at various points during a detoxification admission and during or after a detoxification taper, while all XR-NTX-randomized participants will need to complete detoxification. To maximize recruitment and generalizability, randomization may occur at any time up to 15 days following consent, affording the CTP and the patient maximum flexibility as to the timing of decision-making during the detoxification process or soon after. While BUP-NX induction often occurs as part of office-based prescribing to active opioid users and does not involve a detoxification start point, BUP-NX induction during or following detoxification *is* common practice in detoxification units and during post-detoxification aftercare, particularly as patients entering a treatment facility are often in crisis, not yet aware of the full menu of treatment options, and often don't recognize or accept that they are unlikely to succeed in aftercare without medication. Further, for many patients, information about access to – and third-party payment for – BUP-NX maintenance is often not available until late in the course of a detoxification admission, if it is available at all. For these reasons, it is not uncommon to initiate BUP-NX treatment during or following detoxification, and there are CTN CTPs that have standard operating procedures for this. Further, in discussions with clinical sites for this trial, it has become clear that in many parts of the U.S., medication treatment is not available for most opioid-dependent patients, due to a combination of lack of services or practitioners and lack of third-party coverage. Hence, there is a large population of opioid-dependent patients who enter detoxification programs to which the findings of the proposed trial should generalize. To maximize generalizability, the point of randomization is flexible, from shortly after program admission until just prior to program discharge. A data analysis modification (assessment of whether the early vs. late randomizers have a differential treatment effect and if so, time to relapse will be estimated for early and late randomizers separately) will occur if differential treatment initiation is a problem for cases randomized prior to completing detoxification (i.e., significantly fewer early randomizers are able to complete detoxification and XR-NTX induction).

4.2 Naltrexone (NTX) and Extended-Release Naltrexone (XR-NTX)

NTX is a potent opioid antagonist with high affinity for the mu-opioid receptor. In the U.S. it is approved for use in treating opioid dependence and alcohol dependence. It is highly efficacious in preventing relapse to opioid dependence provided that it is taken as prescribed, but adherence with oral naltrexone is problematic and leads to extremely high dropout rates, with the occasional exception of treatment in criminal justice and other settings where relapse may be linked to severe adverse consequences.[11-13] This has led to intensive efforts – including NIDA- and NIAAA-funded grants to small businesses – to develop long-acting naltrexone preparations that can be administered as an injection or placed as an implant once per month or less frequently.[14,15]

XR-NTX (Vivitrol®, NTX-containing polylactide-co-glycolide [PLG] biodegradable sterile microspheres suspended in a diluent) is delivered by monthly injection into the muscles of the upper outer quadrant of the buttock. Each vial of microspheres contains 380 mg NTX which are suspended by adding a diluent that comes with the product and shaking for about a minute prior to injection of the "full" (less dead-space) content of the vial. Plasma concentrations of NTX and 6-beta naltrexol (its main active metabolite) after a single XR-NTX injection are detectable for at least 30 days. Consistent with this, in human laboratory studies with Vivitrol® and Depotrex®, essentially complete blockade of opioid agonist effects is seen for 30 days.[16-17] To maintain blockade beyond 30 days, XR-NTX must be re-administered. Long-term use of NTX and XR-NTX is not associated with tolerance, dependence, addiction or withdrawal on discontinuation. NTX and XR-NTX will, however, precipitate withdrawal in individuals physiologically dependent on opioids.

As a consequence of its extended duration of action and "assured" treatment adherence, XR-NTX may dramatically and favorably alter the limited effectiveness profile associated with orally administered NTX. By ensuring 30-day medication adherence with a single injection, and thereby establishing a ~30 day mu-opioid antagonist blockade, the likelihood of an individual re-establishing opioid dependence during this period is very low. The two clinical trials cited above (Comer et al.[7], and Krupitsky et al.[8]) support efficacy for XR-NTX preparations compared to placebo injections.

The 2006 Comer et al. study[7] was a proof-of-concept, 2-month randomized, placebo-controlled trial with a subcutaneously administered product (Depotrex®, Biotek Inc.), and showed that long-acting injectable naltrexone in conjunction with outpatient counseling produced superior treatment retention to placebo, providing "evidence of the feasibility, efficacy, and tolerability of long-lasting antagonist treatments for opioid dependence".

The Krupitsky et al. study[8] was conducted in 2008 and 2009 in 13 sites in Russia, and was sponsored by the manufacturer, Alkermes Inc. Following inpatient detoxification, 250 opioid-dependent patients were randomized to XR-NTX (Vivitrol®) or placebo, double-blind monthly injections, for 6-months, during which all patients received outpatient counseling. The percent of opioid abstinent weeks, by weekly urine toxicology, was the primary outcome. A response profile analysis compared the cumulative percent of patients at each level of the outcome (percent opioid-free weeks) between the active XR-NTX and placebo conditions. The difference between the response profiles was significant ($p < .0002$), with the median patient on XR-NTX having 90% abstinent weeks compared to 35% abstinent weeks for the median patient on placebo. Total abstinence (100% opioid-free weeks) was reported in 45 (35.7%) subjects in the XR-NTX group versus 28 (22.6%) subjects in placebo group ($p < .03$). Retention in treatment for the full 6 months was 53% on XR-NTX, compared to 38% on placebo ($p < .02$). The 6-month retention rate in the 50% range is similar to that observed in clinical trials of buprenorphine.[2] Patients treated with XR-NTX showed an approximately 50% sustained reduction in craving compared to no change in craving in the placebo group ($p < .005$). XR-NTX was generally well tolerated. Data from this pivotal trial supported Alkermes' supplemental NDA for treatment of opioid dependence.

***Prescribing and Safety*:** Details on XR-NTX (Vivitrol®) prescribing, pharmacokinetics and pharmacodynamics, metabolism and elimination, safety and toxicity are in Appendix C.

4.3 Buprenorphine (BUP) and Buprenorphine/Naloxone Combination (BUP-NX)

Buprenorphine (BUP) is a lipophilic thebaine derivative with a high binding affinity at the mu-opioid receptor where it has partial agonist effects, and at the kappa opioid receptor where it is a competitive antagonist. Like many opioids it was initially commercially developed as an analgesic. In October 2002, the FDA approved BUP for detoxification and maintenance treatment of opioid dependence. For these indications BUP is marketed as Subutex® (Reckitt Benckiser), and in a 4:1 ratio combination with naloxone (BUP-NX), as Suboxone® (Reckitt Benckiser). The BUP-NX combination was developed to limit abuse liability and diversion.[18-22] Generic formulations of BUP-NX are now available. Recently Reckitt Benckiser began marketing a sublingual BUP-NX film and this is the formulation that is used in the present study. Numerous clinical trials, many of them conducted through a NIDA/VA Cooperative Studies Program partnership and others by the NIDA Clinical Trials Network, involving thousands of participants, have overwhelmingly established both efficacy and effectiveness of BUP-NX in the community.[21,23-32] BUP and BUP-NX are safe and effective alternatives to methadone[27,28,30,33-36], and enable significant and substantial improvement over time in psychosocial functioning.[37]

Maximal drug effects typically occur at approximately 8 to 16 mg, although sublingual daily doses up to 32 mg have been safely administered for a period of up to a year.[27,34,38] Variability in individual dosing addresses the range and severity of opioid dependence across patients. Because of BUP's lipophilicity and high affinity to the mu-opioid receptor, less-frequent-than-daily dosing is possible for some patients.[39] BUP's slow dissociation from mu-opioid receptors contributes to its long duration of action and smooth day-to-day course, and minimizes symptoms and signs of withdrawal upon cessation.[40,41]

Owing to its partial agonist properties, BUP has limited respiratory depressant effects, low toxicity even at high doses, and limited risk with overdose.[42,43] At sufficient doses, BUP blocks the effects of exogenous opioids[44,45] and can both reduce illicit use and afford some level of protection against overdose. BUP has abuse potential, though in contrast to full agonists like methadone, this is limited, likely also a consequence of partial agonist properties.[38, 45-51][38,44] Although there is a ceiling on BUP's respiratory depressant effects[38], interactions with other CNS depressants such as benzodiazepines and alcohol are potentially dangerous[52,53] and patients should be cautioned to avoid acute binge use of CNS depressants.[54] Because BUP is metabolized by cytochrome P-450 3A4[55], drugs that inhibit or induce this system can affect BUP levels. Known inhibitors include erythromycin, ketoconazole, grapefruit juice and certain HIV protease inhibitors[56] which may increase BUP levels. Inducers include phenobarbital, carbamazepine, and phenytoin which could reduce BUP levels and lead to withdrawal symptoms[54] though this has not been observed clinically.

Unlike methadone, BUP-NX is typically prescribed in office-based treatment settings which makes it an ideal comparator for XR-NTX, particularly at a time when there is a movement to expand treatment from traditional addictions specialty programs to mainstream healthcare settings. Office-based BUP-NX permits patients to receive medication by prescription to be taken at home for days, weeks or even months, thereby avoiding the requirement for frequent (often daily) attendance at methadone maintenance programs and its associated stigma. Patients can return to a more "normal" life in a relatively short time span. BUP-NX treatment may either be long or short term, however much of the available evidence (much of it from CTN studies[32,57-59]) suggests a high rate of relapse on discontinuation even after several months of treatment. Many participants in CTN studies have expressed the strong desire to use BUP-NX as a maintenance medication rather than a short-term treatment or a detoxification agent.[32, 59] Of note, an expanding number of addictions specialty programs as well as medical primary care settings, HIV clinics and other mainstream programs, have implemented sustainable outpatient addictions pharmacotherapy initiatives with BUP-NX.

Prescribing and Safety: Details on BUP-NX (Suboxone®) prescribing, pharmacokinetics and pharmacodynamics, metabolism and elimination, safety and toxicity are in Appendix D.

4.4 Significance to the Field

Advantages of XR-NTX include that it affords a 30-day duration of action, confirmed administration with no uncertainty about compliance, and virtually no abuse potential or diversion risk. Disadvantages are that XR-NTX is expensive, that it requires monthly injection, and that currently very little is known about its implementation, effectiveness, comparative effectiveness, safety and costs in U.S. community-based treatment settings. In contrast, much more is known about BUP-NX, the advantages of which include being widely embraced by patients and by the treatment community. Disadvantages are that there remain barriers to more widespread BUP-NX use including high cost, lack of third-party coverage, shortages of trained providers, concerns about abuse and diversion, and, not least, not all patients respond favorably. Clinical trials suggest that approximately 50% of patients started on buprenorphine will be retained in treatment after six months, a good result for a chronic relapsing disorder such

as opioid dependence; but the flip side of this is that 50% will have dropped out. Further, despite decades of success, “negative” views about agonist-based maintenance therapy persist amongst many individuals and institutions in the broader community and amongst many patients and providers who prefer a “drug-free” approach (i.e., free of narcotic or addictive drugs such as methadone, BUP or BUP-NX; in this context “drug-free” does not equate to “medication-free”, for example non-addictive medication such as XR-NTX). For institutions and individuals preferring “drug-free” treatment, XR-NTX may be a potent tool in facilitating “medication-assisted recovery”.

CTN-0051 has the potential to: (1) address critical clinical questions, (2) foster adoption of new pharmacotherapies via community-based specialty and mainstream treatment settings, and (3) advance public health (opioid misuse, associated infections, associated criminal justice consequences, direct and indirect costs of addiction, etc.) by improving and expanding effective treatment.

5.0 CTN-0051 OBJECTIVES

5.1 Primary Objective

The primary goal of the study is to estimate the difference, if one exists, between XR-NTX and BUP-NX in the distribution of the time to relapse (i.e., loss of persistent abstinence) during the 6-month trial.

The primary outcome measure is the time to the event, with the event called relapse. By definition individuals are abstinent at the time of randomization. Relapse occurs if the participant is using any non-protocol prescribed opioids regularly starting at day 21 post-randomization or thereafter. Operationally, relapse is defined as either: (a) four consecutive opioid use weeks, or (b) seven consecutive days of use by self-report. A use week is defined as any week during which a participant self-reports at least one day of use during that week, provides a urine sample positive for non-protocol opioids, or fails to provide a urine sample. Self-report of opioid (heroin or prescription opioids) and other substance use is ascertained at each weekly study visit using the Timeline Follow-Back for each day leading back to the previous visit. Urine is collected at each study visit and tested for opioids. In the event that a participant reports no use, but their urine test indicates use, the week is considered a use week. Missing urine samples are classified as positive. The time of the event occurs at the start of the qualifying clinical event period (e.g., first of the 7 consecutive use days or start of the 4 consecutive weeks of use).

5.2 Secondary Objectives

Secondary objectives are to:

1. Compare outcome on XR-NTX versus BUP-NX for the following domains:
   a. Proportion successfully inducted onto assigned medication.
   b. Safety, as measured by adverse events and serious adverse events, including opioid overdose episodes, both during the 6-month trial and during the 3-month follow-up period.
   c. Opioid abstinence, as measured by the Timeline Follow-Back (TLFB) (self-report days using opioids), proportion of opioid-positive urine tests.
   d. Misuse of alcohol and other drugs of abuse (e.g., cocaine, other stimulants, cannabis, benzodiazepines), by self-report and urine drug screens.
   e. Tobacco use, as measured by the Fagerström Test for Nicotine Dependence (FTND).
   f. Craving for opioids, and for other drugs, measured by Visual Analog Scales (VAS).
   g. Depressive, anxiety, and subacute withdrawal symptoms (typical constellation is fatigue, anorexia, and insomnia), as measured by the Hamilton Depression Scale (17-item) (HAM-D) and the Subjective Opioid Withdrawal Scale (SOWS).
   h. Problems related to drug abuse, as measured by the Addiction Severity-Index-Lite (ASI-Lite) and EuroQol (EQ-5D).
   i. HIV risk behavior over time, as measured by the Risk Assessment Battery (RAB).
   j. Cognitive function, as measured by performance on brief pen and paper tasks (Trail Making Test Parts A and B, Stroop).
2. Explore baseline demographic, clinical, and genetic features as predictors of opioid use outcome over the 6-month trial (main effect of predictors), and as moderators of differential treatment effect (moderator by treatment interaction).
3. Collect a limited dataset to permit analyses of economic costs and benefits of the two treatments.

6.0 STUDY DESIGN

6.1 Overview of Protocol Study Design

This is a multi-center, two-arm, 6-month (24-week), parallel-group, open-label, randomized controlled trial to examine the comparative effectiveness and safety of XR-NTX versus BUP-NX. Candidates are individuals seeking treatment for opioid dependence (heroin or prescription opioids) who are admitted to an inpatient (detoxification and/or short term residential treatment) program for treatment of substance dependence. The study is conducted in 8 CTPs that: (a) provide or partner with opioid detoxification services (inpatient/residential) which have the capacity to maintain participants opioid-free, (b) have the capacity to initiate patients onto XR-NTX or BUP-NX, (c) have the capacity to maintain participants on XR-NTX or BUP-NX for the duration of the 24-week trial, (d) have a sufficient flow of patients completing detoxification and who do not routinely receive long-term medication-assisted therapy as to provide a sufficient population of potential participants to achieve study enrollment goals, and (e) can provide a minimum level of outpatient care (at least one group and/or individual counseling session per week) for 24 weeks. Candidates are consented, screened, and randomized at the time of admission, during detoxification or during early abstinence. Participants meeting all eligibility criteria are randomized to one of two treatment conditions, XR-NTX or BUP-NX. Treatment is for 24 weeks in the context of a protocol-directed medical management treatment program and individual or group psychosocial counseling. Research visits occur weekly, until relapse criteria are met, for collection of urine samples and safety and other assessments. XR-NTX is administered by injection on an approximately every-four-week basis; BUP-NX is provided for take-home, initially on a weekly basis, transitioning to an every-two-week and then to an every-four-week schedule. Medical management for both conditions is on a similar (weekly, transitioning to every-two-weeks, to every-four-weeks) schedule. The primary outcome measure is the time to the event of relapse. XR-NTX is provided as Vivitrol®. BUP-NX is provided as Suboxone® film.

The Protocol will proceed in four phases (see Figure 1).

Phase 1: Informed Consent, Screening, and Randomization (Days -15 through Day 0): This phase begins with informed consent during the index admission, and initiates enrollment, the conduct of all study-specific procedures and the collection of study data. During the first several days of an index admission, clinical and/or research staff provide information about the study to potential participants (for scheduled admissions this information may be provided in advance of the admission). Guidelines for opioid detoxification are provided in the study MOP; data on detoxification utilization are collected. This phase may take place from 1 day up to 15 days. Following final review and confirmation of all eligibility criteria, randomization may proceed. Randomization may take place on the same day as informed consent and screening if recent liver function results are available, but in most cases takes place 2 or 3 days later. Regardless of when randomization takes place, the date of randomization is defined as “Day 0”.

Phase 2: Induction (Day 0 through Day 156): Following randomization, participants are inducted onto their assigned active medication condition and treated as outpatients for 24 weeks per protocol. Guidelines for induction onto XR-NTX and onto BUP-NX are provided in the study MOP. Following induction, XR-NTX is administered by injection approximately every 4 weeks; and BUP-NX is quickly titrated upwards to maintenance doses. Induction should occur as soon as practicable following randomization, but may occur as late as week 22. Participants continue into Phases 3 and 4 for research visits, even if not yet inducted onto their assigned medication.

Phase 3: Active Treatment (Week 1 through Week 24): Following randomization, participants are inducted as soon as practicable and treated per their assigned active medication condition

and followed as outpatients until 24 weeks post-randomization. Assessment visits occur weekly until relapse criteria are met. Participants whose induction onto their assigned study medication is delayed will also attend weekly research visits. Medical management visits will initially occur weekly, transition to every two weeks and then to every four weeks. In order to retain participants in treatment, and consistent with good practice, we permit flexibility with dosing (see section 8.5). The window for Visit 1 is -3/+6 days to accommodate induction; however, induction may occur after Visit 1. A +/- 3-day window is permissible for subsequent weekly visits. For participants who relapse and/or become lost to follow up, a -3/+28 day window is permissible to complete the EOT visit. Participants who relapse will discontinue study medication and weekly research visits, but should be encouraged to attend the week 24 and follow up visits at weeks 28 and 36.

Phase 4: Post Treatment Follow-up (Week 25 through Week 36): Toward the end of the 24-week treatment period, participants are referred for follow-up care in the community (which could include continuation of medication, if available, indicated, and desired), and follow-up outcomes are assessed at week 28 and week 36 post-randomization. For participants receiving BUP-NX, who do not wish to continue, or for whom community resources are not available, the study provides a two-week BUP-NX taper. A -3/+28 day window is permissible for the scheduled week 28 visit and a +/- 4 week window is permissible for the scheduled week 36 visit.

6.2 Treatment Initiation

To maximize generalizability, this study is designed to permit entry of participants throughout opioid detoxification and early abstinence. While XR-NTX can only be administered to individuals who have completed detoxification, the percentage of participants who are randomized early that are able to successfully initiate antagonist therapy is unknown. A risk to this study plan is that a differentially large percentage of individuals may be unable to initiate XR-NTX versus buprenorphine therapy. The study includes an adaptive strategy such that if at a single time point a statistically lower treatment initiation rate is observed in “early” entry cases, then the study will be revised to:

(a) Exclude further early entry cases and analyze them separately; and
(b) Expand the total accrual target to maintain the initial design power for the late entry cases.

This assessment occurred after the entry of 100 cases randomized early in the detoxification process (e.g., prior to 3 opioid-free days).

6.3 Duration of Study and Visit Schedule

Each participant is engaged in the overall study for approximately 9 months as follows:

- Up to 15 days: Consent, screening and randomization.
- 24 weeks: Weekly research visits for 24 weeks; and active treatment, once inducted, up to week 24 post-randomization.
- 12 weeks: Follow-up, with visits at weeks 28 and 36 post-randomization.

7.0 STUDY POPULATION

Study participants are treatment-seeking heroin- and/or prescription opioid-dependent volunteers, without chronic pain requiring opioid therapy, who are willing to accept "agonist-based" or "antagonist-based" therapy. Randomization is stratified by (1) treatment site, and (2) baseline opioid use (high level use [≥6 bags {or equivalent} IV heroin/day] vs. all others [i.e., <6 bags {or equivalent} IV heroin/day and other routes of administration or other opioids]).

7.1 Inclusion Criteria

1. Male or female;
2. 18 years of age and older;
3. Meet DSM-5 criteria for opioid-use disorder (heroin and/or prescription opioids);
4. Have used opioids other than as specifically prescribed within thirty days prior to consent;
5. Seeking treatment for opioid dependence and willing to accept "agonist-based" or "antagonist-based" therapy;
6. In good-enough general health, as determined by the study physician on the basis of medical history, review of systems, physical exam and laboratory assessments, to permit treatment with XR-NTX or BUP-NX;
7. Able to provide written informed consent;
8. Able to speak English sufficiently to understand the study procedures and provide written informed consent to participate in the study;
9. If female of childbearing potential, be willing to practice an effective method of birth control for the duration of participation in the study.

7.2 Exclusion Criteria

1. Serious medical, psychiatric or substance use disorder that, in the opinion of the study physician, would make study participation hazardous to the participant or compromise study findings or would prevent the participant from completing the study. Examples include:
   (a) Disabling or terminal medical illness (e.g., uncompensated heart failure, cirrhosis or end-stage liver disease) as assessed by medical history, review of systems, physical exam and/or laboratory assessments;
   (b) Severe, untreated or inadequately treated mental disorder (e.g., active psychosis, uncontrolled manic-depressive illness) as assessed by history and/or clinical interview;
   (c) Current severe alcohol, benzodiazepine, or other depressant or sedative hypnotic use likely to require a complicated medical detoxification (routine alcohol and sedative detoxifications may be included);
2. LFTs (ALT, AST) greater than 5 times upper limit of normal;
3. Suicidal or homicidal ideation that requires immediate attention;
4. Known allergy or sensitivity to buprenorphine, naloxone, naltrexone, polylactide-co-glycolide, carboxymethylcellulose, or other components of the Vivitrol® diluent;
5. Maintenance on methadone at doses of 30mg or greater at the time of signing consent;
6. Presence of pain of sufficient severity as to require ongoing pain management with opioids;
7. Pending legal action or other reasons that might prevent an individual from completing the study;
8. If female, currently pregnant or breastfeeding, or planning on conception;

9. Body habitus that, in the judgment of the study physician, precludes safe intramuscular injection of XR-NTX (e.g., BMI>40, excess fat tissue over the buttocks, emaciation).

7.2.1 Special Populations to Consider

This study is likely to enroll persons involved in the criminal justice system, many of whom are expected to be in treatment at the CTPs conducting this study. The study will not recruit persons incarcerated/detained in a correctional facility, but will not exclude parolees, probationers, or persons in sentencing diversion or drug court programs who are enrolled at participating CTPs. Some of these subjects may be classified as prisoners per 45 CFR 46 Subpart C.

7.3 CTP Sites

This multi-site trial involves 8 CTPs that: (a) provide or partner with opioid detoxification services (inpatient/residential) which have the capacity to maintain participants opioid-free, (b) have the capacity to initiate participants onto XR-NTX or BUP-NX while they are still in an inpatient/residential setting, (c) have the capacity to maintain participants on XR-NTX or BUP-NX for the duration of 24-week trial, (d) have a sufficient flow of patients completing detoxification and who do not routinely receive long-term medication-assisted therapy as to provide a sufficient population of potential participants to achieve study enrollment goals, and (e) can provide a minimum level of outpatient care (at least one group and/or individual counseling session per week) for 24 weeks.

8.0 STUDY PROCEDURES

Refer to Figure 1 (Study Schema).

8.1 Recruitment and Screening (Phase 1)

Recruitment efforts will vary per site, and may broadly include CTP staff education and distribution of study materials, community or participant-level outreach and advertisements, and the encouragement of word-of-mouth referrals among CTP patient populations. During (or prior to) the first several days of an index admission, clinical and/or research staff will provide information about the study to interested, potential participants.

8.1.1 Informed Consent (Phase 1)

At any point candidates may begin the informed consent and screening procedures. The timing of consent and screening procedures is flexible, and allows CTPs to customize recruitment, screening, and randomization procedures to accommodate local conditions. Obtaining consent and baseline data early in the admission will allow a full accounting of persons interested in study enrollment but then not choosing to or not able to enroll (screen fails), while enrollment towards the end or just after detoxification will allow participants initially exposed to enrollment to reconsider and join the trial several days later. Candidates for the study are given a current local IRB-approved copy of the Informed Consent Form to read. Appropriately qualified and trained study personnel explain all aspects of the study in lay language and answer all of the study candidate's questions. Candidates who remain interested after receiving an explanation of the study are given a short informed consent quiz to test his/her understanding of the project, the purpose and procedures involved, and the voluntary nature of his/her participation. Those who cannot successfully answer quiz items have the study re-explained by research staff with a focus on aspects they did not understand. Those who demonstrate understanding of the study and voluntarily agree to participate are asked to sign the Informed Consent Form. Participants will not be administered any assessments or study procedures prior to signing informed consent. Participants are also asked to sign a release of medical records request to permit study staff to access CTP records relating to the index admission, primarily for the purpose of accessing clinical laboratory information (e.g., liver function tests) to eliminate repeat testing and speed randomization.

8.1.2 Detoxification

Guidelines for protocol-guided opioid detoxification (to be initiated after informed consent and depending on when in the detoxification process consent is obtained) are provided in the study MOP. Data on the detoxification, including number of days on the unit and medications received, are collected.

8.1.3 Screening and Baseline Assessments (Phase 1)

Screening and baseline assessments are detailed in Section 11 and capture participant demographic, medical, psychiatric, drug use, and treatment history, quality of life and current health status, in addition to blood and urine testing. These assessments confirm eligibility/ineligibility. Screening may take place at any time during Phase 1. LFTs performed within 4 weeks prior to randomization (i.e., drawn as part of usual care) are acceptable. If LFT results are available at screening, and participants meet all eligibility criteria, randomization may proceed. Otherwise, final eligibility is determined upon confirmation of LFTs.

8.2 Randomization (Phase 1, Day 0)

Randomization follows final confirmation of eligibility.

While the timing of randomization can be variable, it is expected that each randomized participant will initiate his or her assigned treatment. Success in initiating assigned treatment is tracked.

8.3 Stratified Randomization

A restricted randomization plan is used with centralized, automated, randomized block assignments. Randomization is stratified by two factors, site and pre-detoxification level of opioid use. While there are important and otherwise uncharacterized differences between sites – including state and local treatment service environments, opioid misuse epidemiology, and patient-level customs regarding treatment, medications, and clinical trial participation – the level of heroin and other opioid use will likely be an important independent predictor of treatment retention and rates of negative urines as has been demonstrated in recent analysis of naltrexone opioid trials.[60-62] The level of opioid use at treatment entry is a binary classification, operationally defined as 6 or more bags (or equivalent) IV heroin per day (≥6 bags/day) over the 7 days prior to entry into the treatment program versus less than 6 bags (or equivalent) IV heroin per day (<6 bags/day) or other routes of administration or other opioids.

Timing of the randomization is important to execution of the design and may also be an important prognostic variable. All cases are classified into one of three groups at the time of randomization, those:
(a) randomized within 24 hours of last (licit or illicit) opioid use;
(b) randomized between 24 and 72 hours following last (licit or illicit) opioid use;
(c) randomized more than 72 hours following last (licit or illicit) opioid use.

Each of these groups represents different clinical scenarios commonly encountered in CTN CTPs. Group (a) represents early decision-making, at such a time as to avoid unnecessary detoxification for those choosing BUP-NX. For group (b), decision-making occurs later during detoxification, but while participants still need to surmount the detoxification hurdle to begin XR-NTX. Group (c) includes participants who can be readily inducted onto either medication.

Individuals in groups (a) and (b) comprise the early cases used in the decision rule assessment after 100 of these participants had entered.

8.4 Induction (Phase 2)

Following randomization, participants are inducted onto their assigned pharmacotherapy. Guidelines for detoxification and induction onto XR-NTX or BUP-NX are provided in the study MOP.

XR-NTX assignment: participants randomized to XR-NTX must complete/have completed a recent opioid detoxification, be ≥3 days removed from the last dose of opioid agonist (heroin, prescription opioids, methadone or buprenorphine), have a urine toxicology negative for the extended opioid spectrum, including methadone and buprenorphine, and have a negative naloxone challenge.

BUP-NX assignment: a) participants randomized during a buprenorphine-based detoxification will continue on buprenorphine, now as a daily maintenance dose. BUP-NX will be titrated over 1-3 days to a maintenance dose range of 8-24mg/day. Lower doses and doses up to 32mg/day may be prescribed with the approval of the site PI and Study Physician; b) participants randomized during a methadone-based detoxification will discontinue methadone, and be

inducted onto BUP-NX no less than 24 hours following the last methadone dose, after withdrawal symptoms have clearly emerged; c) participants randomized during a non-opioid-based detoxification or after completing a buprenorphine- or methadone-based detoxification may be inducted onto BUP-NX immediately or after a sufficient delay since last methadone dose.

8.5 Study Treatments (Phase 3)

Table 1: Treatment Visit Schedule

Study Week	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Medical Management Visits (both arms)		x	x	x	x	x		x		x		x		x		x		x				x				x
XR-NTX Administration		x*	x*	Approximately every 4 weeks, with final injection occurring no later than week 22.																						
BUP-NX Dispensing		x	x	x	x	x		x		x		x		x		x		x				x				x⁻

x*=the initial XR-NTX dose will depend on the length of time needed to complete detoxification and begin XR-NTX treatment; x⁻ = for BUP-NX taper where indicated

A. Medical Management: Both Arms

Both groups receive Medical Management (MM) clinical support from the same study clinicians (e.g., MD, DO, PA, NP, RN; working within the scope of their local licensure, clinical privileges and/or scope of practice) in unblinded fashion. MM is adapted from several recent studies of NTX, XR-NTX and BUP-NX, including the NIAAA COMBINE study[63], Krupitsky et al.[8], and CTN-0030 (POATS).[57] Briefly, MM sessions focus on establishing and maintaining patient-clinician rapport and partnership, education surrounding opioid addiction and treatment, establishing and maintaining a plan for XR-NTX or BUP-NX medication adherence, advice and encouragement to maintain abstinence, monitoring medication side effects and dose adjustments, and support for ancillary treatment, including weekly psychosocial counseling, 12-step involvement, and further community-based treatment. MM also provides guidelines for assessment and management of relapse in both arms. In contrast to studies specifically analyzing the effect of a trial's psychosocial interventions (i.e., the COMBINE trial or CTN-0030, POATS), and in keeping with a pragmatic, community-based comparative effectiveness trial, MM is broadly guided by provider training prior to study start and regular MM provider calls, a common progress note and the MM MOP, but is not subject to rigorous quality assurance procedures (i.e., audiotaping, manualization and QA audits). The study clinician assesses concomitant medications at each medical management visit. As this is not an IND study, and both medications are FDA approved for opioid dependence, the study data capture system does not include a concomitant medication case report form. MM visit schedules are the same for both arms, initially weekly (weeks 0-4), then every two weeks (weeks 4-16), and finally every four weeks (weeks 16, 20, 24). XR-NTX is injected at the MM visit approximately every 4 weeks with the final injection occurring no later than week 22. BUP-NX is dispensed at each MM visit through week 20. For all participants a final MM visit takes place on week 24 although no medication is dispensed (except for BUP-NX taper where this is indicated).

B. Psychosocial Counseling: Both Arms

Psychosocial counseling consists of outpatient counseling provided at the CTP. Selected sites agree to provide at least a minimum level of outpatient care that consists of at least one group and/or individual counseling session per week for up to 24 weeks. Data is collected from the clinic record or from the participant on counseling sessions attended. Participation in counseling sessions is voluntary. Failure to attend counseling sessions will not be considered to be a reason to be excluded from the trial.

8.5.1 XR-NTX Group

Prior to the naloxone challenge, participants randomized to XR-NTX must complete/have completed a recent opioid detoxification, be ≥3 days removed from the last dose of opioid agonist (heroin, prescription opioids, methadone or buprenorphine) and have a urine toxicology negative for all opioids, including buprenorphine. If initial UDS is positive, UDS is repeated daily until negative. Only then will the naloxone challenge take place.

8.5.1.1 XR-NTX Injections

Following a negative naloxone challenge (see MOP), XR-NTX monthly injections begin. XR-NTX (4cc, ~380mg of naltrexone base) is administered approximately every four weeks (with the final injection occurring no later than week 22), in the form of Vivitrol® which is obtained by NIDA or the NIDA contractor for distribution to the sites. XR-NTX injections may take place <4 weeks apart if there is clinical concern about non-adherence (participant is inconsistent in attending scheduled visits) or if clinical observation is that opioid craving and/or use re-emerge during the 4th week after the last injection; however, time between injections must always be at least 21 days. XR-NTX is administered by intramuscular injection to the buttocks (alternating sides) according to the injection preparation and administration procedures specified in the Vivitrol® product package insert (see Appendix C). These procedures are designed to minimize the risk of injection site reactions.

8.5.1.2 Ancillary Medications

Participants who experience withdrawal symptoms, sleeplessness, and/or depressive symptoms may be treated with ancillary medications (see guidelines in the study MOP). Depression is common in opioid-dependent patients and may adversely affect prognosis of naltrexone treatment.[60] Participants who show depressive symptoms may be treated with antidepressants and/or referred for psychiatric evaluation and treatment. In general, psychiatric or medical problems emerging during the study treatment period are handled by the CTP according to their usual practices for treatment and referral.

8.5.1.3 Handling of Missed XR-NTX Doses, Lapses, and Relapses

Use of illicit opioids presents different concerns in the management of patients receiving XR-NTX maintenance, compared to those receiving BUP-NX. Because of the long duration of action of XR-NTX (full blockade out to 5 weeks after the last injection[17]), a grace period of 7-21 days can be expected during which the injection can be rescheduled, provided the participant has not relapsed and become re-dependent. If the participant misses a scheduled injection and does not otherwise meet the primary outcome of relapse, XR-NTX may then be continued following a negative naloxone challenge (if clinically indicated) up to 21 days after a missed dose (49 days post prior injection; see MOP).

8.5.2 BUP-NX Group

In keeping with the flexible randomization strategy, BUP-NX treatment is initiated as soon as practicable following consent, determination of eligibility, and randomization. Guidelines for induction at varying times from early in detoxification through early abstinence are provided in the study MOP. See also Section 8.5.2.2, titled “BUP-NX Induction”.

8.5.2.1 BUP-NX Medication

BUP-NX is provided as Suboxone® sublingual film, 4mg/1mg of buprenorphine/naloxone, or 8mg/2mg buprenorphine/naloxone to allow individualized medication plans. Medication is provided by NIDA or the NIDA contractor for distribution to the sites.

8.5.2.2 BUP-NX Induction

a) Participants randomized during a buprenorphine-based detoxification simply continue on buprenorphine (as BUP-NX). Doses may be escalated rapidly, and titrated to a maintenance dose of 8-24mg/day over 1-3 days. Lower doses and doses up to 32mg per day may be prescribed with the approval of the site PI and Study Physician. See guidelines in the study MOP.

b) Participants randomized during a methadone-based detoxification discontinue methadone, and are inducted onto BUP-NX no less than 24hours following the last methadone dose. See guidelines in the study MOP.

c) Participants randomized during a non-opioid-based detoxification or after completing a buprenorphine- or methadone-based detoxification, who are thus “drug-free”, are given an initial 4mg/1mg sublingual dose, followed by one hour of observation, and thereafter titrated up to a maximum dose of 16mg on day 1, and a maintenance dose of 8-24mg/day over days 2-7. See guidelines in the study MOP.

8.5.2.3 BUP-NX Maintenance

Maintenance doses of BUP-NX from 8mg-24mg are typical in community treatment. Lower dose and doses up to 32mg per day may be prescribed with the approval of the site PI and Study Physician. For all BUP-NX participants, from induction through week 24, daily doses may be titrated to minimize BUP-NX related AEs, minimize cravings, and in response to any intermittent illicit opioid use/lapse.

8.5.3 Dispensing of XR-NTX and BUP-NX

Study medications (XR-NTX and BUP-NX) are provided by the study at no cost to the participant. XR-NTX is administered in-clinic at induction and approximately every four weeks with the final injection occurring no later than week 22. BUP-NX is dispensed to participants at induction and at treatment weeks 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, and 20. Medication may be dispensed more frequently at the discretion of the study clinician. In addition, for participants receiving BUP-NX who are discontinued, who do not wish to continue, or for whom community resources to continue are not available, the study may dispense sufficient BUP-NX for up to a two-week taper beginning at any time during treatment or beginning at the week 24 visit. BUP-NX dose adjustments or emergency medication replacement between visits are allowed and will necessitate as-needed treatment and medication-dispensing visits. The clinical team may extend the window for medication administration or dispensing by up to three weeks if (a) the participant is abstinent (both self-report and urine are negative), (b) can restart the originally assigned medication, and (c) the treatment lapse is scheduled (i.e., the participant has provided a credible reason for the lapse and remains in contact with the study team).

8.5.3.1 Provisions for Access to Investigational Treatment After Study

Prior to the conclusion of the 24-week active treatment phase, the research team will make an effort to arrange for continued treatment with XR-NTX or BUP-NX as appropriate within the community context. Where this is not possible (due to insurance or availability of treatment resources, etc.), alternative treatment referrals (i.e., methadone maintenance, intensive

outpatient psychosocial aftercare) are made as appropriate. For participants receiving BUP-NX, who do not wish to continue, or for whom community resources are not available, the study provides a two-week BUP-NX taper.

8.6 Drug Packaging/Handling/Storage/Accountability

8.6.1 Study Medication Management

Each CTP is required to observe local, state, and federal regulations regarding receipt, custody, dispensing, and disposition of all study medications. Each CTP will maintain an adequate supply of unexpired study medications on site that is supplied by the NIDA contractor.

8.6.2 Drug Accountability Records and Dispensing of Study Medication

Appropriately qualified and trained study personnel maintain accurate and current accounting of all study medication by utilizing drug accountability records which are made available for review by study monitors and other appropriate research personnel.

Accurate drug accountability records:

- Demonstrate that the study drug was dispensed according to the protocol;
- Document receipt of the study medication, date, lot #, expiration date, quantity and dosage;
- Account for unopened, un-dispensed, unused, returned, waste or broken medication;
- Dosing logs should record participant ID #, date dispensed, drug name, lot # and amount dispensed;
- Temperature logs should show a daily record of medication storage temperature.

8.6.3 Study Medication Storage

Study medication should be stored in compliance with federal, state, and local laws and institutional policy. Study medication is stored in a secured location under the conditions specified by the package inserts (See Appendices C and D).

8.6.4 Used/Unused Medication

Study medication returned by a participant may not be re-issued for use. Unused study medication is returned and logged into a perpetual inventory of study medication returned. Damaged, returned, expired or unused study medication is accounted for by the NIDA contract monitor and sent to the central distributor or a reverse distributor for destruction. Expired XR-NTX may be destroyed on site per local institutional policies following a complete accounting by the NIDA contract monitor.

8.6.5 Lost Medication

At the discretion of the site study treatment team, very limited replacement of study medications is permitted.

8.6.6 Dispensing of Study Medications

All study medications shall be prepared and dispensed by a pharmacist or licensed medical practitioner appropriately trained and authorized to dispense study medications per local regulations.

8.6.7 Drug Packaging

XR-NTX is supplied in single use kits. Each kit will contain one 380 mg vial of Vivitrol® microspheres, one vial containing 4 mL (to deliver 3.4 mL) diluent for the suspension of Vivitrol®, one 5-mL prepackaged syringe, one 1-inch 20-gauge needle, two 1.5-inch 20-gauge needles and two 2-inch 20-gauge needles with needle protection devices. Lot number and medication expiration date is included on the kit labels as supplied by the manufacturer. The BUP-NX films are packaged individually for both the 4mg and 8mg films. Each package has the study drug information. The label has storage conditions as well as the manufacturer and distributor information.

8.7 Blinding

This study is a pragmatic, open-label, non-blinded clinical trial. Treatment assignment and active medication assignment is known to all staff and all participants.

8.8 Participant compensation

Study participants are provided with pharmacotherapy and medical management at no cost. In addition, participants are compensated with cash, or vouchers of equivalent value, to offset costs of time and travel and to provide modest incentives for attending study visits. This study does not employ contingency management targeting abstinence or specifically targeting medication adherence (in other words, compensation is earned for presenting to scheduled visits and completing assessments and medication management visits if applicable).

Participants receive $50 for completion of screening and baseline assessments and an additional $50 following induction onto study medication. Participants receive $20 for each weekly visit for weeks 1 through 23. Participants receive $50 for visit 24 and each of the 2 follow-up visits. Maximum compensation possible is $710. If a participant is found to be incarcerated at time of follow-up, the participant is compensated the agreed upon amount as approved by local IRB and/or collaborating prison facilities.

9.0 OUTCOME MEASURES

9.1 Primary Outcome

The primary goal of the study is to estimate the difference, if one exists, between XR-NTX and BUP-NX in the distribution of the time to relapse (i.e., loss of persistent abstinence) during the 6-month trial.

The primary outcome measure is the time to the event, with the event called relapse. By definition individuals are abstinent at the time of randomization. Relapse occurs if the participant is using any non-protocol prescribed opioids regularly starting at day 21 post-randomization or thereafter. Operationally, loss of persistent abstinence is defined as either: (a) four consecutive opioid use weeks, or (b) seven consecutive days of use by self-report. A use week is defined as any week during which a participant self-reports at least one day of use during that week, provides a urine sample positive for non-protocol opioids, or fails to provide a urine sample. Self-report of opioid (heroin or prescription opioids) and other substance use is ascertained at each weekly study visit using the Timeline Follow-Back for each day leading back to the previous visit. Urine is collected at each study visit and tested for opioids. In the event that a participant reports no use, but their urine test indicates use, then the week is considered a use week. Missing urine samples are classified as positive. The time of the event occurs at the start of the qualifying clinical event period (e.g., first of the 7 consecutive use days or start of the 4 consecutive weeks of use).

9.2 Secondary Outcomes

Table 2: Protocol Secondary Outcomes and Hypotheses

Outcomes	Hypotheses
Proportion successfully inducted onto assigned study medication (binary: did or did not receive first dose of XR-NTX, or achieve maintenance dose of BUP-NX)	BUP-NX will produce higher rate of successful induction than XR-NTX Significance/Rationale: XR-NTX induction requires completion of detoxification, whereas BUP-NX induction only requires onset of withdrawal symptoms. Thus XR-NTX may have more dropouts after randomization but prior to XR-NTX induction.
Adverse Events related to study medications	XR-NTX and BUP-NX will produce equivalent rates of SAEs, and equivalent rates of AEs, though AE pattern will differ somewhat (e.g. injection site reactions with XR-NTX) Significance/Rationale: Careful documentation of SAEs and AEs, including overdose episodes, would be considered essential safety data, and important component of a comparative effectiveness trial.
Opioid abstinence over time while on study medication (Weekly TLFB, confirmed by urine drug screens)	XR-NTX will produce greater opioid abstinence than BUP-NX Significance/Rationale: XR-NTX produces complete blockade of opioid effects, so that during treatment with monthly injections, opioid use can be expected to be minimal. In contrast BUP-NX may not produce complete blockade, or patients may reduce or stop doses for a few days and substitute other opioids (heroin, prescription opioids).

Outcomes	Hypotheses
Alcohol and other drug use, over time (TLFB and UDS)	XR-NTX will be superior to BUP-NX in producing abstinence from alcohol and other drugs Significance/Rationale: Clinical trials show XR-NTX is effective for treatment of alcohol dependence, and naltrexone has some evidence of efficacy for stimulant dependence.
Cigarette smoking (FTND, Tobacco Use Questionnaire, VAS nicotine craving)	XR-NTX will reduce cigarette smoking compared to BUP-NX Significance/Rationale: Naltrexone has been studied as a treatment for nicotine dependence, with some support from clinical trials, although inconsistent. Given high morbidity and mortality associated with nicotine dependence, a comparative advantage of one or the other of these treatments at reducing smoking would be valuable to examine.
Opioid Craving (VAS) over time	XR-NTX will be superior to BUP-NX in reducing opioid craving Significance/Rationale: Krupitsky et al. (Lancet 2011) pivotal XR-NTX trial showed, surprisingly, that XR-NTX reduced craving substantially compared to placebo.
Subacute withdrawal symptoms over time (HAM-D, SOWS)	XR-NTX will produce greater severity of subacute withdrawal symptoms than BUP-NX during the first month after randomization, but will be equivalent to BUP-NX in months 2 to 6 Significance/Rationale: Low-grade withdrawal-like symptoms (dubbed “naltrexone flu” by the Columbia group, and consisting typically of insomnia, fatigue, and anorexia, though not drug craving) have been observed in some patients in the 1 to 4 weeks after naltrexone initiation, resolving gradually. Further characterization of this syndrome would be important for developing treatment guidelines.
Problems related to drug abuse (ASI-Lite and EQ-5D)	XR-NTX will be superior to BUP-NX Significance/Rationale: Greater opioid and non-opioid abstinence on XR-NTX will result in fewer problems associated with active drug abuse.
HIV risk behavior over time (RAB and other HIV risk measures)	XR-NTX and BUP-NX will be equivalent Significance/Rationale: The opioid-dependent population is at high risk for HIV, both from injection drug use and from unsafe sexual practices. Effective treatment for the opioid dependence may reduce HIV risk behavior. Given the high morbidity and mortality associated with HIV, a comparative advantage of one or the other of these treatments would be valuable to examine.
Cognitive function (Trails Making Test Parts A and B, Stroop)	XR-NTX and BUP-NX will be equivalent Significance/Rationale: Some providers and policy-makers are concerned that patients maintained on BUP-NX will have opioid-agonist-related cognitive impairment.

10.0 PARTICIPANT DISCONTINUATION, FOLLOW-UP

10.1 Treatment Discontinuation

Study medication is discontinued in the event of intolerable side effects, safety concerns preventing further medication treatment (i.e., pregnancy), relapse, or the end of the 24-week active treatment phase (see MOP). Participants discontinuing medication, but not yet meeting relapse criteria, prior to week 24 continue within the same study assessment schedule. Participants meeting relapse criteria discontinue medication and research visits. All participants who end treatment early (prior to week 21) are encouraged to attend a visit at week 24 and are seen in long-term follow-up (weeks 28 and 36). In all cases of treatment discontinuation, the research team makes an effort to arrange for continued community treatment, as appropriate and available, including further XR-NTX and BUP-NX, or methadone maintenance and intensive outpatient psychosocial aftercare. For participants receiving BUP-NX, who do not wish to continue, or for whom community resources are not available, the study will provide a two-week BUP-NX taper, if clinically appropriate.

10.2 Follow-Up (Phase 4)

An effort will be made to assess all participants at weeks 28 and 36 post randomization. The goals for the follow-up assessments are as follows:

A. Assess safety in initial weeks and months following discontinuation of XR-NTX or BUP-NX. This would specifically address concerns about overdose deaths after XR-NTX and the criticism leveled at the FDA for approving XR-NTX indication without such data.

B. Determine 9-month outcome following randomization to up to six months of treatment with XR-NTX or BUP-NX, including rates of relapse after successful completion of 6 months of either XR-NTX or BUP-NX treatment. This would begin to address questions about how long it is necessary to maintain agonist or antagonist treatment and whether there are differences in long-term outcomes; it will address whether early gains are sustained across time; and it will provide descriptive data on the course of opioid use following six months of treatment.

C. Learn about what interventions are currently available and can be accessed in the community outside of a research study. This would address questions about what is current TAU for opioid dependence.

Aggressive outreach procedures will be implemented to locate and assess participants at the 28 and 36 week follow-up points and to minimize missing data. These procedures are detailed in the study MOP.

This study includes subjects who may be classified as prisoners per 45 CFR 46 Subpart C. If a subject becomes incarcerated during the study, treatment and follow-up procedures may be continued in accordance with local IRB approvals. Procedures must be compliant with 45 CFR 46 Subpart C. Data may be collected either in person, by phone, in writing, and/or by electronic means, provided that data collection follows the procedures approved by OHRP and the local IRB.

Details of the nature of the research will not be shared with staff at the jail/prison, and visits, whether in person or by phone, will only be conducted if the participant's confidentiality can be maintained and no audio-taping occurs.

11.0 STUDY FORMS, PROCEDURES AND ASSESSMENTS

Study assessments are intended to capture the outcomes of interest as efficiently as possible, minimizing the time and expense of research visits. Table 3 is a schedule of procedures and assessments (note that some study procedures are described in Section 8).

Table 3: Schedule of Forms, Procedures and Assessments

	Screening	Baseline	Randomization	Induction XR-NTX	Induction BUP-NX	Active Treatment																							Early end of Medication or Treatment (if not week 24)		Follow up		End of Study (if not wk 36)
Visit#	S	B	0	IND-X	IND-B	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	EOM[6]	EOT	28	36	EOS
Time	Day -10 to 0		0	Day 0-156	Day 0-156	6	13	20	27	34	41	48	55	62	69	76	83	90	97	104	111	118	125	132	139	146	153	160	167	varies	varies	195	251	varies
Informed consent	X																																	
Medical release form	X																																	
GENERAL																																		
Inclusion/exclusion checklist	X		X[1]																															
Locator form	X								X				X				X				X				X				X		X	X	X	X
Demographics form	X																																	
PhenX Tier 1 additional (QLP, TUH)		X																																
Motivations, attitudes & expectations form	X																																	
Treatment satisfaction survey																													X		X			
Relapse assessment									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X			
Continuing treatment forms																													X		X	X	X	X
Study termination form																																	X	X
SAFETY & MEDICAL																																		
Medical & psychiatric history	X																																	
Physical exam, incl vitals	X																												X[3]	X				
DSM-5 criteria	X																																	
CHRT-SR	X			X	X	X	X	X	X		X		X		X		X		X		X				X				X		X	X	X	X
Clinical labs: LFTs	X			X[7]	X[7]				X[3]								X[3]												X[3]	X				
Clinical labs: HepB, HepC, HIV	X																																	
Urine pregnancy/birth control assessment	X		X[2]	X[2]	X[2]				X[3]				X[3]				X[3]				X[3]				X[3]				X[3]	X				
AEs & SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Injection site examination						X[3]				X[3]				X[3]					X[3]						X[3]				X[3]	X				
TREATMENT SCHEDULE																																		
XR-NTX induction				X																														
BUP-NX induction					X																													
XR-NTX administration				X		approximately every 4 weeks with final injection occuring no later than week 22																													
BUP-NX dispensing					X	X	X	X	X		X		X		X		X		X		X				X									
BUP-NX taper																													X[4]	X[4]				
Medical management				X	X	X	X	X	X		X		X		X		X		X		X				X				X	X	X			
COMPLIANCE																																		
BUP-NX dose log					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X[4]		
Medical management log				X	X	X	X	X	X		X		X		X		X		X		X				X				X	X	X			
Psychosocial log						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X			
OUTCOME																																		
Time Line Follow-Back	X					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Urine drug screen	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
ASI-Lite		X																											X		X		X	X
VAS craving opioids	X					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
VAS non opioids, VNS	X								X				X				X				X				X				X		X	X	X	X
HAM-D (Hamilton depression scale)	X					X	X	X	X				X				X				X				X				X		X	X	X	X
SOWS (subjective opioid withdrawal scale)		X		3X	2X	X	X	X	X				X				X				X				X				X		X	X	X	X
Fagerstrom		X																																
Risk Assessment/HIV		X															X												X		X		X	X
Cognitive function (Trails, Stroop)		X							X				X								X								X		X			
Detoxification utilization	X																																	
EQ-5D		X							X				X				X				X				X				X		X	X	X	X
NMS		X							X				X				X				X				X				X		X	X	X	X
Genetics sample	X[5]								X[5]								X[5]												X[5]		X[5]			
Family Origin	X[5]								X[5]								X[5]												X[5]		X[5]			

X[1] = confirm just prior to randomization

X[2] = repeat only if more than seven days has elapsed since prior negative test

X[3] = only after successful induction onto study medication, see 11.2.5

X[4] = for those not able to transition to community-based BUP-NX treatment; may also occur if medication is discontinued in weeks 1-23

X[5]= genetics sample and Family Origin questionnaire are only completed once, ideally at screening, but may be collected at any visit requiring a blood draw

EOM[6] = at the visit where medication ends complete EOM assessments and corresponding week research assessments; if relapse concurrent also complete EOT

X[7] = Repeat if induction onto study medication occurs more than 2 weeks after randomization, see 11.2.5

11.1 General

11.1.1 Inclusion/Exclusion

This form lists each inclusion and exclusion criterion to document eligibility. Eligibility is assessed continually as appropriate. Only participants who continue to meet study eligibility criteria are allowed to continue with the screening process, and randomization.

11.1.2 Locator Form

A locator form is used to obtain information to assist in finding participants during treatment and at follow-up. This form collects the participant's current address, email address, and phone numbers. In order to facilitate locating participants if direct contact efforts are unsuccessful, addresses and phone numbers of family/friends who may know how to reach the participant are collected, as well as information such as social security number, driver's license number and other information to aid in searches of public records. This information is collected at screening, and is updated at least every month during the active treatment phase, at the end-of-treatment visit (EOT/week 24), and at the week 28 and week 36 (or EOS) post-treatment follow-up visits. No information from this form is used in data analyses nor is this information captured in the data capture system.

11.1.3 Demographics Form

The demographics form collects information about demographic characteristics of the participant, including gender, date of birth, ethnicity, race, education, employment status, and marital status. This form is completed at screening.

11.1.4 PhenX Tier 1

The Substance Abuse and Addiction Collection of the PhenX Toolkit (www.phenxtoolkit.org) includes measures that are being adopted across NIDA-funded research. The Core Tier 1 collection includes measures for demographics (age, ethnicity, gender, race, educational attainment, employment status, marital status), BMI, quality of life, and HIV risk and status; substance use measures include age of onset, past 30-day quantity and frequency, lifetime use for alcohol, tobacco and other substances. Where possible, answers to Core Tier 1 questions are populated from the answers to questions from other assessments, but some additional questions may be incorporated to accommodate this requirement. Quality of Life (QLP) and Tobacco Use History (TUH) are 2 such additions. Core Tier 1 assessments are completed at Baseline only.

Homelessness is of particular interest and concern with this population. Thus a question to determine whether the participant is currently homeless or living in a shelter is asked at baseline in conjunction with the PhenX Quality of Life assessment.

11.1.5 Motivations, Attitudes, and Expectations Form

Motivation for participating in the study and attitudes and expectations regarding study medication are collected once at screening.

11.1.6 Treatment Satisfaction Survey

Satisfaction with treatment is recorded on the Treatment Satisfaction Survey completed at the end-of-treatment visit (EOT/week 24).

11.1.7 Relapse

Relapse criteria is reviewed at each research visit beginning with visit 4 (since relapse by definition cannot occur before Day 21) and continuing through the end-of-treatment visit (EOT/week 24). This form documents the time to event.

11.1.8 Continuing Treatment Forms

At the conclusion of study treatment, participants are discharged to treatment in the community. These forms document the treatment plan identified for the participant at week 24 or at the end of treatment visit if treatment is stopped early. At the 2 follow up visits (weeks 28 and 36/EOS), participants are asked whether they are adhering to the treatment plan, have initiated other treatment or discontinued all treatment.

11.1.9 Study Termination Form

This form tracks the participant's status in the study. It is completed at the week 36/EOS visit or once the week 36 follow-up visit window lapses for participants who do not complete this final follow-up. This form is used in data analyses to address variables such as treatment retention and completion.

11.2 Safety and Medical

The study physician must review and approve all safety and eligibility assessments in order to confirm participant eligibility prior to randomization.

11.2.1 Medical and Psychiatric History

The study clinician obtains a medical and psychiatric history from the participant covering past and present health conditions to help determine eligibility and to provide baseline information. This is collected during screening. This information may be used in data analyses.

11.2.2 Physical Examination

The study clinician completes a physical examination, including blood pressure and heart rate, to ensure that there are no medical concerns regarding participation and to gather baseline information regarding the participant's physical health. During the screening physical exam, a description of the participant's body habitus is documented and the study clinician examines the planned injection sites to ensure adequacy for XR-NTX gluteal intramuscular injection of naltrexone with the supplied needle. The physical examination is performed at screening and is repeated at the end-of-medication visit (if medication is stopped early) or at the end-of-treatment visit (week 24). The physical exam, blood pressure and/or heart rate may be repeated at MM visits at the discretion of the medical clinician.

11.2.3 DSM-5 Criteria

The DSM-5 criteria is applied to determine a current diagnosis for substance use disorder. This is completed at screening to determine eligibility.

11.2.4 Concise Health Risk Tracking-Self Report (CHRT-SR)

The CHRT-SR[64] is a 16-item participant self-report assessment of suicidality and related thoughts and behaviors. The scale is designed to quickly and easily track suicidality in a manner consistent with the Columbia Classification Algorithm of Suicide Assessment (C-CASA).[65] The CHRT-SR is assessed at screening, induction, at subsequent MM visits and at the week 28 and

36/EOS visits. The CHRT-SR will assess high risk suicide ideation by a positive response (Agree or Strongly Agree) on any of the last three questions (thoughts of, thoughts of how and/or a specific plan to commit suicide) and prompt a clinician assessment for suicide risk before leaving the clinic.

11.2.5 Clinical Laboratory Tests

Liver function tests (LFTs, consisting of AST, ALT, albumin and bilirubin) and urine pregnancy test (for females) are performed to help determine eligibility at screening. Receipt and review of laboratory test results is necessary before confirming eligibility, conducting randomization and starting study medication. Results of LFTs conducted within four weeks prior to randomization (e.g., collected as part of routine detoxification admission) are acceptable. For participants whose induction onto their assigned study medication is delayed for longer than 2 weeks after randomization, LFTs and urine pregnancy should be repeated prior to start of study medication.

At screening, blood is collected for HIV antibody, hepatitis C virus (HCV) antibody and hepatitis B surface antigen (HBsAG) and hepatitis B surface antibody (HBsAB) tests. These tests do not determine eligibility and are only conducted on samples from participants who are randomized. Results of HIV antibody, hepatitis C virus (HCV) antibody and hepatitis B surface antigen (HBsAG) and hepatitis B surface antibody (HBsAB) tests conducted within four weeks prior to randomization (e.g., collected as part of routine detoxification admission) are acceptable.

For participants whose induction onto their assigned study medication occurs within 2 weeks of Day 0, LFTs are repeated at week 4, week 12, and at the end-of-medication visit (if medication is stopped early) or at the end-of-treatment visit (week 24). For participants whose induction onto their assigned study medication occurs more than 2 weeks after day 0, LFTs are repeated approximately 4 and 12 weeks following induction (a +/- 2 week window for post-induction LFTs is permitted), and at the end-of-medication visit (if medication is stopped early) or at the end-of-treatment visit (week 24). For participants who do not get inducted but continue on study, LFTs need not to be repeated at any of the planned visits with scheduled LFTs.

A laboratory that is accredited by the College of American Pathologists (CAP) or equivalent, and participates in the Clinical Laboratory Improvement Act of 1998 (CLIA) will perform these analyses. The laboratory will provide normal values and proof of lab certifications.

11.2.6 Pregnancy and Birth Control Assessment

This form documents that pregnancy tests were administered, test results, and breast feeding status. The pregnancy and birth control assessment, including on-site urine pregnancy tests, is conducted at screening and may be repeated prior to randomization and/or induction. Birth control assessment and urine pregnancy tests are repeated monthly and at the end-of-medication visit (if medication is stopped early) or at the end-of-treatment visit (week 24).

11.2.7 Adverse Events (AEs) and Serious Adverse Events (SAEs)

At each medical management visit the study clinician assesses for AEs and SAEs by asking the study participant, “How have you been feeling since your last visit?” AEs and SAEs may also be spontaneously reported to study staff at any visit following consent. AEs and SAEs suggesting medical or psychiatric deterioration will be brought to the attention of a study clinician for further evaluation and management. Medical management visits will emphasize overdose risk and risk-management; any reported overdose is recorded as an AE or SAE. AE and SAE reporting is according to the reporting definitions and procedures outlined in the protocol and in accordance with applicable regulatory requirements.

For the purpose of this study, the following AEs do not require reporting in the data system but is captured in the source documentation as medically indicated:

- Grade 1 (mild) unrelated adverse events

This would typically include mild physical events such as headache, cold, etc., that were considered not reasonably associated with the use of the study drug/intervention.

Events related to the injection of the study medication are recorded on the Injection Site Abnormality (INA) form and will not be duplicate-reported on an AE form. Events related to withdrawal symptoms are captured on the SOWS and HAM-D and will not be duplicate-reported on an AE form. Withdrawal symptoms not captured by the SOWS or HAM-D should be reported as an AE. Events captured on study specific forms (INA, SOWS, HAM-D) are not recorded separately as an AE, unless they meet the SAE definition. Any of these events that meet the definition of an SAE are reported on the AE/SAE form set. Any spontaneous reporting of withdrawal symptoms by the participant are captured on AE form in the following situations: withdrawal symptoms reported at visits without scheduled specific structured questionnaires (SOWS, HAM-D); and withdrawal symptoms not listed in the specific structured questionnaires (SOWS, HAM-D) reported at any visit.

11.2.8 Injection Site Examination

Appropriately qualified and trained medical personnel will examine the injection site on the next Medical Management visit following the XR-NTX administration. Participants are asked to immediately report any injection site reactions to study staff for evaluation, monitoring, and possible referral, as needed. Injection site reactions should be documented on the Injection Site Abnormality Log.

11.3 Compliance

11.3.1 Dose Logs

XR-NTX dosing is captured in the MM progress note and recorded in the appropriate CRF and dose log. A BUP-NX dose log documents the amount of medication dispensed for take-home dosing and reported as taken by the participant. These forms are completed at relevant clinic visits through the end of the active treatment phase.

11.3.2 Medical Management

A Medical Management attendance log is completed to document attendance or non-attendance at each Medical Management session during the active treatment phase. The Medical Management discontinuation form is completed when MM visits end (at week 24 post-randomization, when the primary outcome of opioid relapse is met, or for other reasons as determined by the study clinician).

11.3.3 Psychosocial Participation

At each weekly treatment visit, participants are asked to report on their participation in psychosocial TAU during the prior week.

11.4 Drug Use and Psychological

11.4.1 Timeline Follow-Back (TLFB)

The Timeline Follow-Back[66, 67] procedure is used to elicit the participant's self-reported use of substances before and during the entire study period. At screening, this form is used to assess substance use reported by the participant for the 30-day period prior to admission to detox. During detox, the TLFB is not captured in the data system until the date of discharge. The TLFB is administered at each study visit throughout the active treatment phase and through the end of the follow-up period to document the participant's self-reported use of substances for each day since the previous TLFB assessment.

11.4.2 Urine Drug Screen (UDS)

Urine drug screens are collected at screening, as part of XR-NTX induction, weekly from week 1 through week 24/EOT, and at follow-up visits at weeks 28 and 36/EOS. In most cases the UDS should be completed before assessing self-reported drug use or dispensing medications. All urine specimens are collected using FDA-approved one-step temperature-controlled urine drug test cups following all of the manufacturer's recommended procedures. The UDS tests for the presence of the following drugs: opioids, oxycodone, barbiturates, benzodiazepines, cocaine, amphetamine, methamphetamine, marijuana, methadone, buprenorphine, and ecstasy (MDMA). In the event urine specimen tampering is suspected, either based on the observation or the adulterant tests, study staff should request a second urine sample and may observe the urine collection process according to clinic standard operating procedures. A further validity check is performed using a commercially available adulterant test strip.

11.4.3 Addiction Severity Index Lite (ASI-Lite)

The ASI-Lite is derived from the Fifth Edition of the ASI[68], a structured clinical interview that yields scores for seven areas of functioning typically impacted by addiction, including medical status, employment status, drug use, alcohol use, family status, legal status, and psychiatric status. Opioid use questions, including the main type of opioid used by the participant, whether a prescription opioid or heroin, the onset of the use, the participant's perception of the substance that is most problematic, and their present treatment goal will also be assessed at screening as part of the ASI assessment. The ASI-Lite is completed at baseline, at the end-of-treatment visit (week 24/EOT), and at the week 36/EOS follow-up visit.

11.4.4 Visual Analog Scales (VAS)

Participants' cravings for opioids, alcohol, and other drugs are documented on visual analog scales (VAS) that range from 0 (no craving) to 100 (most intense craving possible). These scales are completed for opioid craving at screening and at each study visit throughout the active treatment phase, at the end-of-treatment visit (week 24/EOT), and at each follow-up. They are completed for alcohol, stimulants and tobacco craving at screening, weeks 4, 8, 12, 16, 20, 24/EOT, 28, and 36/EOS. VAS also documents responses to opioid use, in the event that participants use opioids during the study.

11.4.5 The Hamilton Depression Scale (17 item) (HAM-D)

The 17-item Hamilton Depression Scale (HAM-D) is a clinician-administered instrument, useful for following both depression and suicidal ideation, and also for following typical symptoms of subacute withdrawal (e.g., low appetite, fatigue, poor sleep). For the purpose of this study, adequately trained research staff conduct the Hamilton Depression Scale (HAM-D).

The HAM-D is completed at screening, at weeks 1, 2, 3, 4, 8, 12, 16 and 20, at the end-of-treatment visit (week 24/EOT), and at each follow-up. A score of 1 or more to item 3 (suicidality) prompts a clinician assessment for suicide risk before leaving the clinic.

11.4.6 The Subjective Opioid Withdrawal Scale (SOWS)

This scale is useful for following self-reported opioid withdrawal symptoms. It is administered at baseline, induction, weekly during the first month after randomization, and at weeks 8, 12, 16, and 20, at the end of treatment (EOT/week 24), and at each follow-up. At the induction visit for the XR-NTX group the SOWS is administered three times, the first time within the hour prior to the naloxone challenge, the second time 10-30 minutes following the naloxone challenge, and the third time 1-3 hours following the XR-NTX injection. At the induction visit for the BUP-NX group, the SOWS is administered twice, the first time within the hour prior to BUP-NX dosing and the second time 1-3 hours following dosing.

11.4.7 Fagerström Test for Nicotine Dependence (FTND)

The Fagerström Test for Nicotine Dependence (FTND) is used for assessing nicotine dependence [69, 70] and is administered at baseline.

11.4.8 Risk Assessment Battery (RAB)

The Risk Assessment Battery (RAB)[71] is a self-administered assessment of engagement in activities that increase the likelihood of contracting HIV. Several scores that measure drug risk, sex risk, and total risk are computed. This measure is completed at baseline, at week 12, and at the end-of-treatment visit (week 24/EOT), and at the week 36/EOS follow-up visit.

11.4.9 Cognitive Function Tests

Cognitive function is assessed using simple, brief, pen and paper tests (Trail Making Test, Parts A and B, and Stroop). These tests are completed at baseline, week 4, 8, 16, and at the end-of-treatment visit (EOT/week 24).

11.4.10 Detoxification Utilization Form

Data on detoxification, including number of days on the unit and medications received, is collected.

11.4.11 EuroQol (EQ-5D)

The EuroQol instrument is a standardized generalized (non disease-specific) system for describing and valuing health-related quality of life. The instrument consists of two components; the EuroQol classification instrument, which describes the respondent's health within 5 domains, and a visual analogue scale with which respondents rate their health. Responses to each component yield a preference weight that can be used to construct Quality-Adjusted Life Year estimates (QALYs). The EuroQol instrument is the recommended Health Quality Index for Economic Evaluations in the Substance Abuse and Addiction Collection of the PhenX Toolkit (www.phenxtoolkit.org). The EQ-5D is completed at baseline, week 4, 8, 12, 16, 20, and 24, at the 2 follow up visits, at the EOT visit if treatment ends early and at the EOS visit if not done at week 36.

11.4.12 Non-Study Medical and Other Services (NMS)

Medical services that are not part of the treatment intervention are recorded on the NMS form. The NMS form captures services received outside the study and CTP including therapy visits,

physician visits, subsequent residential or hospital detoxification, hospital visits and emergency room visits and medication use through participant self-report. The assessment also captures health insurance status, employment, criminal activities, and contact with the criminal justice system. Validity of self-reported health care utilization has been demonstrated.[72-74] The NMS is completed at baseline, week 4, 8, 12, 16, 20, and 24, at the 2 follow up visits, at the EOT visit if treatment ends early and at the EOS visit if not done at week 36.

11.5 Genetics Protocol Measures

Genetics protocol measures include one-time blood sample collection and completion of a Family Origin questionnaire. The blood sample should be collected at screening, but may be collected at any visit where there is a scheduled blood draw. The Family Origin questionnaire can be completed at any visit, ideally at the same time as the blood draw.

The Family Origin form is designed to be interviewer administered. It collects information about the participant and her/his biological family members' race/ethnicity, place of birth, and ancestry. If a participant does not know the information requested, the participant may answer "unknown".

12.0 STATISTICAL ANALYSIS

12.1 General Design

The primary goal of the study is to estimate the difference, if one exists, between XR-NTX and BUP-NX in the distribution of the time to relapse (i.e., loss of persistent abstinence) during the 6-month trial.

12.1.1 Primary and Secondary Outcomes (Endpoints)

Primary Endpoint: The primary outcome measure is the time to the event with the event called relapse. By definition individuals are abstinent at the time of randomization. Relapse occurs if the participant is using any non-protocol prescribed opioids regularly starting at day 21 post-randomization or thereafter. Operationally, loss of persistent abstinence is defined as either: (a) four consecutive opioid use weeks, or (b) seven consecutive days of use by self-report. A use week is defined as any week during which a participant self-reports at least one day of use during that week, provides a urine sample positive for non-protocol opioids, or fails to provide a urine sample. Self-report of opioid (heroin or prescription opioids) and other substance use is ascertained at each weekly study visit using the Timeline Follow-Back for each day leading back to the previous visit. Urine is collected at each study visit and tested for opioids. In the event that a participant reports no use, but their urine test indicates use, then the week is considered a use week. Missing urine samples are classified as positive. The time of the event occurs at the start of the qualifying clinical event period (e.g., first of the 7 consecutive use days or start of the 4 consecutive weeks of use).

Secondary Endpoints: Secondary endpoints include success of treatment initiation and selected opioid and other drug use measures as discussed in section 9.2. A set of additional secondary endpoints that describe adverse experiences and clinical states are detailed in that section.

12.1.2 Design

The therapeutic strategies defined above are evaluated and compared in a two-arm randomized open-label multi-center trial.

12.2 Rationale for Sample Size and Statistical Power

Original Projected Sample Size: 200 per treatment group. N = 400 total.

Data Analysis Modification Projected Sample Size: ~300 per treatment group. (N~600 total sufficient to enroll 350 late randomizers).

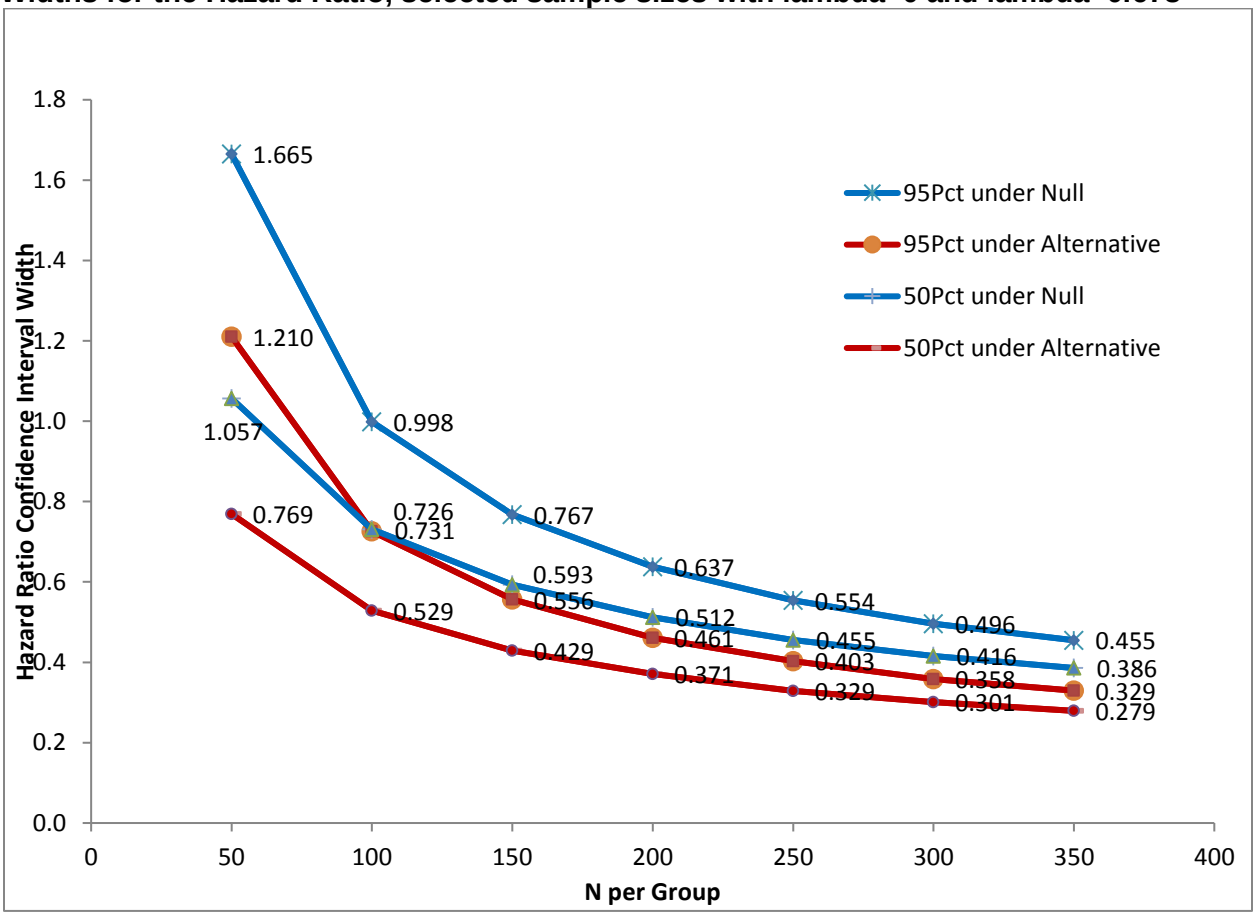
Rationale: The primary outcome is the time to relapse as defined above. Meta-analyses of randomized controlled trials of BUP-NX maintenance treatment for opioid dependence suggest that approximately 50% of patients are retained in BUP-NX treatment with good clinical outcome over 6 months.[2] Extended release naltrexone preparations have had few prior randomized comparisons but observations from a recent Russia-based trial evaluating the XR-NTX dose and formulation proposed for this trial had good results with 53% receiving all monthly injections and retained for 6 months. Direct randomized comparison of these approaches has not been performed.

We evaluate the anticipated variability of the primary terminal results by simulating under exponential distributional assumptions with event grouping over the first 21 days and using proportional hazards without censoring. Let one treatment have a 6-month success rate of 40% with exponential failure. We use a lower success target than indicated in the above paragraph because the use of the early randomization time point is expected to increase the percentage of

participants who are failures. There would be minimal impact on detectable alternatives if a higher 50% success rate was used. From the plot below, we observe that the 95% CI width for the hazard ratio for the 50th percentile of the simulation results under both the null and alternative hypotheses decreases by 31%, 19%, and 14% as the sample size increase by 50/arm from a base of 50/arm. CI width decreases by 11% when the sample size increases from 200/arm to 250/arm. We have selected 200/arm as subsequent precision improvements with this criteria are close to 10% per 100 sampling units.

Beyond a sample size of 150 to 200 patients per group, further increments in sample size (200 per group, 250 per group, 300 per group, etc.) yield diminishing returns in terms of only relatively small further narrowing of the 95% confidence interval. The rationale for increasing the total sample size to N ~600, in the event of a significant difference in induction success rate among early randomizers, is that given the current ratio of early to late randomizers, N ~600 total will yield approximately 250 early randomizers and 350 later randomizers. 350 late randomizers (N = 175 per treatment group) is close to the 400 (N = 200 per group) originally planned, and will yield a very similar (only slightly wider) 95% confidence interval. This will preserve the intent to achieve a relatively precise estimate of the difference in relapse rates among late randomizers.

Simulation results for the 50th and Upper 95th percentile of the 95% Confidence Interval Widths for the Hazard Ratio, selected sample sizes with lambda=0 and lambda=0.678



The decision theoretic properties of n=200/arm is evaluated further under a decision theoretic approach and using the logrank test. With two-sided alpha = 0.05, N = 400 total participants

provides 90% power to detect a hazard ratio of .63 for the second treatment. Table 4 provides additional characterization of power characteristics of the sample size.

Table 4. Detectable Alternatives and Power for 2-tailed 5% level logrank test without censoring Null distribution has a 40% 6 month success rate, N1=N2=200

Power (%)	Hazard Ratio	6 Month Survival Rate (%) under the Alternative
90.0	.633	56.0
80.0	.678	53.8

Note that inclusion of the baseline level of opioid dependence severity stratification variable in the statistical model as a covariate may increase power and narrow the confidence limits on treatment hazard ratios, should divergent success rates be present in the strata groupings.

Secondary analyses of moderators of treatment effect are important to trial sample size selection. With 200 XR-NTX cases evenly split between 2 levels of a classifying variable, we would have 79% power to detect, using a 2-tailed 5% level test of a binary endpoint, a 20 percentage point difference between the groups. Thus the selected sample size would be relatively robust in its ability to determine whether there are important differences in therapeutic success rates for major demographic or baseline clinical factors.

12.2.1 Projected Number of Sites, and Participants per Site

Number of Sites: We are targeting participation by 8 sites. Eligible sites will be programs that admit large numbers of actively using opioid-dependent patients per year to inpatient/residential treatment or partner with such detox facilities, where, presently, usual treatment consists of detoxification, followed by discharge to outpatient “drug free” counseling of some type, and few patients have access to medication (methadone, buprenorphine, or naltrexone) after discharge. This would support at least four randomizations per site per month, or up to 100 randomizations per site over the up to 24-month enrollment period.

Participants per Site: We expect 8 sites to randomize an average of approximately 78 participants per site.

12.3 Study modification for differential treatment initiation

To maximize generalizability, this study has been designed to permit entry of participants throughout the opiate detoxification process and early abstinence. At the time the study was designed it was understood that community-based practice of detoxification and medication induction would vary across sites and across patients within sites. It was further decided that the protocol would allow this variation in community based practice of detoxification-induction, consistent with the aims of an effectiveness trial to test the medications under real world conditions. It was also anticipated that induction onto BUP-NX would be easier than induction onto XR-NTX for patients who are randomized “early” while opioids are still in their system. This is because BUP-NX can be safely initiated while opioids are still in the system, as long as some signs of withdrawal begin to develop, while for XR-NTX one needs to wait until detoxification is completed and this delay is an opportunity for attrition. The concern is that a higher induction failure rate on XR-NTX, among those randomized early will contribute to differences in outcome (time-to-relapse) across the 6 month trial, with induction failure leading to relapse. If this is the case, then the interaction between early vs. late randomization and treatment assignment on the primary outcome (time to relapse) becomes germane.

Therefore, after the entry of 100 “early randomizers” (as defined in Section 8.3) we will compare the induction success rate in these early randomizers on XR-NTX vs. BUP-NX with a test of difference between proportions. The decision rule has >80% power (alpha=2.5% 1 tail) to identify differences of .25 or greater if the true initiation rate for the BUP-NX is in the expected range (>=.85). If the difference in induction failure rate is significant, then:

1. Increase the sample size to end enrollment at such time as 350 late randomizers have been enrolled to increase power to estimate the difference in primary outcome (time-to-relapse) in this late randomizer group. It is projected that at such time the total N will be approximately 600.
2. Amend the data analysis plan (Section 12.4 of the protocol).

12.4 Statistical Methods for Primary and Secondary Outcomes

Primary Outcome Analysis:

The initial analysis will be the construction of the asymptotic 95% CI for the hazard ratio of the difference between the treatment arms in the time to event distribution for the primary outcome. The study arm success rates with confidence intervals at week 24 and the difference in success rate at that time point and associated confidence intervals will be constructed.

If the data analysis modification is implemented, the binary baseline variable (early vs. later randomization as previously defined) is included in the primary outcome analysis (outcome = time-to-relapse) as a covariate, a priori. The early vs. late randomization covariate by treatment interaction is included in the primary outcome analysis. If the covariate (early vs. late randomization) by treatment interaction is significant at $P < .10$, then the interaction term is retained in the final model. To characterize the interaction, the effect of treatment assignment (i.e., the difference in time-to-relapse between treatments) is estimated separately in early vs. late randomizers, and these two separate estimates become the primary findings of the study. Induction success rate is a secondary outcome measure.

Subsequent analyses will explore the treatment effect as a function of time, stratification variables and other factors that may have differential impact on treatment success. The analyses will first model the time to event primary outcome measure as a function of treatment assignment (XR-NTX vs. BUP-NX), opioid dependence severity stratum and site in a proportional hazards regression model. The constancy of the relative hazard assumption will be examined via the interaction of treatment and time, and the interaction between treatment and baseline severity will be tested.

If the stratum by treatment interaction has a p-value<0.10, then this will be taken to indicate differences in strata-specific efficacy. We note that if this interaction is qualitative (i.e., reversal of treatment advantage in the subgroups[75]) this will have important consequences for future treatment and research decisions. We will test the pair-wise differences between XR-NTX and BUP-NX, separately in the low dependence vs. high dependence subgroups, and further examine the differences with an ordinal/continuous dependence covariate. Note that we are not powering the study to detect the interaction; however, given the likelihood that baseline predicts outcome, or may interact with treatment [76, 77], we are acknowledging that the coefficient of the main effect of treatment in the model is not meaningful in the presence of an interaction with baseline covariates, and that a significant interaction should prompt testing of the region(s) of the baseline covariate where the probability of treatment successes differ.[77, 78]

Secondary analyses of the 24 week successes will include screening baseline variables to identify potential subgroups in the XR-NTX group with differential results.

Secondary Outcome Analyses:

Successful initiation of protocol therapy is an important binary outcome that may also be useful to subsequently explain differences in the primary outcome. Most other secondary outcome analyses will follow a similar form and strategy to that above, with different linear models as appropriate for the form of the secondary outcome variable: dichotomous secondary outcomes will use logistic regression; time-to-event variables will use survival analysis with Cox models; continuous variables or count variables (e.g., bags per day of heroin use) will use mixed effect models depending on the distribution of the outcome (e.g., normal, Poisson, negative binomial, zero-inflated). Repeated measures will have time in the model in addition to treatment and baseline variates.

12.5 Significance Testing

The primary analysis focuses on estimation of the treatment difference and uses a criterion with 2.5% of the normal distribution mass in each tail. Levels of significance for additional tests and analyses are as identified.

12.6 Exploratory Analyses

Analysis of Predictors and Moderators of Treatment Effects:

Exploratory analyses will mainly involve exploring baseline demographic and clinical variables, and candidate genetic markers, as predictors of success, or as moderators of differences in success between XR-NTX and BUP-NX. This can be analyzed by entering each predictor as a covariate in the models outlined above for primary or secondary outcome measures, and testing for the main effect of the covariate, and covariate by treatment interactions. Alternatively, demographic, clinical, and genetic factors could be examined as predictors of outcome separately within the XR-NTX and BUP-NX groups.

Analysis of Mediators of Treatment Effects:

Some during-treatment variables will also be of interest to explore as potential mediators of outcome. For example, opioid use during treatment has been shown to predict relapse in naltrexone, mainly use after discontinuing naltrexone ("unblocked use"), but also repeated episodes of use while on naltrexone ("blocked use").[61, 79] Dysphoria, or subacute withdrawal symptoms during treatment would also be of interest as a mediator of outcome. For these analyses, the variables would be entered into the primary outcome model, or select secondary outcome models, as time-dependent covariates, examining the impact on the size of the coefficient of the treatment effect, or covariate by treatment interactions. Mediators could also be examined separately in the XR-NTX and BUP-NX groups.

12.7 Interim Analyses

The study will undergo safety monitoring by the designated DSMB. Both therapies are standard therapies with regulatory approval for treatment of opiate abuse. The treatment strategies have not been directly compared before and classic interim efficacy monitoring is not planned as both are considered acceptable therapies. An adaptive strategy for addressing substantial differential treatment acceptance is described above. Continuing the study until 350 late randomizers are included in the main analysis group will assist better understanding of personalized therapeutic strategies by making precise secondary assessments and identification of subgroups that differentially benefit possible.

12.8 Missing Data and Dropouts

Dropout from treatment is a typical failure mode for the treatment of opioid dependence with both XR-NTX and BUP-NX. A sensitivity analysis will be performed to examine the impact on the hazard ratio and its confidence limits of alternative endpoint definitions. In particular for the primary endpoint, individuals who withdraw will be considered events if they fail to provide weekly urine specimens. An alternative to the protocol definition which introduces these as censored observations will be examined. The analyses of these events can be complex as standard assumptions (missing at random) may not be plausible.

Other outcome variables (opioid and other substance use over time, craving, mood, etc.) will have missing data due to missed visits and dropout from treatment and from study participation. The generalized linear model, or mixed effects model frameworks that will be used for analyses, works with what data are gathered, and assumes missing data are missing at random. For selected secondary outcome analyses, sensitivity analyses will be considered to examine the stability of estimated treatment effects in the face of departures from the assumption of missing at random.

Aggressive tracking procedures are put into effect to attempt to locate participants and re-engage them, and to minimize missing data. These procedures are detailed in the study MOP. The greatest likelihood of violation of the assumption of missing at random derives from dropouts, since participants assigned to XR-NTX may dropout from the study for different reasons than participants assigned to BUP-NX, creating the potential for differential attrition. Differential study attrition, where outcome differs between the dropouts from the assigned treatments is a threat to the validity of the outcome analysis. Minimizing the rate of study dropout and loss to follow-up, through aggressive tracking and follow-up, serves to reduce this threat. At a minimum the data gathered on dropouts can be used to test the assumption of missing at random, by examining whether dropouts from the different treatment assignments have similar or different outcome.

12.9 Demographic and Baseline Characteristics

Demographic variables:

Gender, age, race, ethnicity, educational level, employment status, marital status.

Baseline clinical characteristics:

Opioid dependence severity, severity of other substance use, severity of mood/anxiety symptoms, severity of opioid withdrawal symptoms, current/past co-occurring psychiatric disorders, current medical disorders, select genetic markers (e.g., candidates will include the A118G variant of the mu-opioid receptor gene, the G36T variant of the kappa opioid receptor gene, and the 3'UTR haplotype of the prodynorphine gene), history of legal problems, currently under legal supervision (parole, probation, or mandated).

Baseline demographic and clinical variables will be summarized for each arm of the study. Descriptive summaries of the distribution of continuous baseline variables will be presented with percentiles (median, 25th and 75th percentiles), and with mean and standard deviation. Categorical variables will be summarized in terms of frequencies and percentages. Since randomization is expected to produce balance at baseline between the two arms of the trial, statistical comparisons of treatment groups with respect to baseline characteristics should be more informal. The updated CONSORT statement[80] no longer recommends formal testing of statistical significance of differences between baseline characteristics.

12.10 Safety Analysis

Adverse events (AEs), including serious adverse events (SAEs), will be summarized by body system and preferred term using MedDRA (The Medical Dictionary for Regulatory Activities). Adverse events will be presented in two ways: (1) the number and proportion of participants experiencing at least one incidence of each event will be presented overall and by treatment group; and (2) a table displaying the total number of each event will be given overall and by treatment group. Listings of serious adverse events will be given, sorted by treatment, body system, and preferred term. Detail in these listings will include severity, relationship to study drug, and action taken as available. Treatment arm differences will be monitored by the DSMB.

13.0 REGULATORY COMPLIANCE AND SAFETY MONITORING

13.1 Statement of Compliance

This trial will be conducted in compliance with the current version of the protocol, current Good Clinical Practice (GCP), the principles of the Declaration of Helsinki, and all other applicable regulatory requirements. Participating sites must obtain written approval of the study protocol, consent form, other supporting documents, and any advertising for participant recruitment from their local institutional review board (IRB) in order to participate in the study. Prior to study initiation, the protocol and the informed consent documents will be reviewed and approved by an appropriate Ethics Review Committee (ERC) or IRB. Any amendments to the protocol or consent materials must be approved before they are implemented. Annual progress reports and local Serious Adverse Event (SAE) reports will be submitted to each IRB, according to its usual procedures.

13.2 Institutional Review Board Approvals

Prior to initiating the study, site investigators will obtain written local IRB approval to conduct the study at their respective site. Should changes to the study protocol become necessary, protocol amendments will be submitted in writing by the investigators for IRB approval prior to implementation. In addition, IRBs will approve all consent forms, recruitment materials, social media use and any materials given to the participant. Annual reports and progress reports will be submitted to the IRBs annually or at a frequency requested by each IRB. Each site investigator is responsible for maintaining in his/her research files copies of all current IRB approval notice(s), IRB-approved consent document(s), including approval for all protocol modifications pertinent to his/her performance site(s). These materials must be received by the lead investigator prior to the initiation of research activities at a given site, and must be available at any time for audit.

13.3 Research Advisory Panel of California (California sites only)

Prior to initiating the study, the sponsor will obtain written approval from the Research Advisory Panel of California (RAP-C). Any planned research project to be conducted in California requiring the use of a Schedule I or Schedule II Controlled Substance as its main study drug as well as research for the treatment of controlled substance addiction or abuse utilizing any drug, scheduled or not (SAT) must be submitted to RAP-C for review and approval prior to study start-up. Study approval is based on review of the study protocol, consent form, and other pertinent study documents. Yearly reports will be provided to the RAP-C in order to obtain continuing study approval.

13.4 Confidentiality

By signing the protocol signature page the investigator affirms that information furnished to the investigator by NIDA will be maintained in confidence and such information will be divulged to the IRB, Ethical Review Committee, or similar expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. The Study lead investigator has obtained a federal Certificate of Confidentiality (CoC), protecting participants against disclosure of sensitive information (e.g., drug use), and will distribute it to all sites when received. The NIH office that issues the CoC will be advised of changes in the CoC application information. Participating CTP sites will be notified if CoC revision is necessary. Confidentiality will be maintained in

accordance with all applicable federal regulations and/or state/Commonwealth law and regulations.

Participant records will be kept confidential by the use of study codes for identifying participants on CRFs, secure separate storage of any documents that have participant identifiers, and secure computing procedures for entering and transferring electronic data.

13.4.1 Health Insurance Portability Accountability Act (HIPAA)

Study sites may be required by their institutions to obtain authorization from participants for use of protected health information. Releases of participant identifying information that are permitted by the HIPAA regulations, but which are prohibited by other applicable federal regulations and/or state/Commonwealth law and regulation, are prohibited. Sites will be responsible for communicating with their IRBs or Privacy Boards and obtaining the appropriate approvals or waivers to be in regulatory compliance.

13.4.2 Investigator Assurances

Each institution's IRB of record reviewing the study at the community treatment program (CTP) must file (or have previously filed) a Federal Wide Assurance (FWA) with the DHHS Office for Human Research Protection setting forth the commitment of the organization to establish appropriate policies and procedures for the protection of human research subjects, with documentation sent to NIDA or its designee. Research covered by these regulations cannot proceed in any manner prior to NIDA's receipt of certification that the research has been reviewed and approved by the IRB provided for in the assurance (45 CFR 46.103(b) and (f)). Prior to initiating the study, the principal investigator and sub-investigators at each study site will sign a protocol signature page, providing assurances that the study will be performed according to the standards stipulated therein.

13.4.3 Financial Disclosure

All investigators will comply with the requirements of 42 CFR Part 50, Subpart F to ensure that the design, conduct, and reporting of the research will not be biased by any conflicting financial interest. It is the responsibility of the investigator to maintain appropriate disclosure to their individual institution according to their requirements.

13.5 Drug Accountability

Upon receipt, the investigator, pharmacist, or authorized designee at each site is responsible for taking inventory of the investigational agents. A record of this inventory must be kept and usage must be documented. Any unused or expired investigational agent shall be accounted for.

13.5.1 DEA Registration

All DEA requirements must be met, including registration, inspection if required, and certification, as applicable. In order to receive shipments of study drug, sites must have a DEA registration (facility research registration or a practitioner registration) that has the address where study drug will be shipped on the registration. Additionally, dispensing any controlled substance requires a DEA registration unless exempt by federal or state law or pursuant to CFR Sections 1301.22-1301.26.

13.5.2 Inclusion of Women and Minorities

Unless specified in eligibility the study is open to any gender, race or ethnicity. A diverse group of study sites will be involved so that these sites can attract a diverse study population. If

difficulty is encountered in recruiting an adequate number of women and/or minorities, the difficulties involved in recruitment will be discussed in national conference calls and/or face-to-face meetings, encouraging such strategies as linkages with medical sites and or treatment programs that serve a large number of women or minorities, advertising in newspapers or radio stations with a high female or minority readership/listening audience, etc.

13.5.3 IND Requirements

Medications to be used in this study will be used in accordance with their approved labeling and therefore there is no plan to submit an IND application.

13.5.4 Regulatory Files

The regulatory files should contain all required regulatory documents, study-specific documents, and all important communications. Regulatory files will be available at each participating site for regulatory document inspection for compliance prior to study initiation, throughout the study, as well as at study closure.

13.5.5 Records Retention and Requirements

Research records for all study participants (e.g., case report forms, source documents, signed consent forms, and regulatory files) are to be maintained by the investigator in a secure location for a minimum of 3 years after the study is completed and closed. These records are also to be maintained in compliance with local IRB, state and federal requirements, whichever is longest. The sponsor and lead investigator must be notified in writing and acknowledgment must be received by the site prior to the destruction or relocation of research records.

13.5.6 Audits

The Sponsor has an obligation to ensure that this trial is conducted according to good research practice guidelines and may perform quality assurance audits for protocol compliance. The Lead Investigator and authorized staff from the National Lead Study Team; the National Institute on Drug Abuse Clinical Trials Network (NIDA CTN, the study sponsor); NIDA's contracted agents, monitors or auditors; and other agencies such as the Department of Health and Human Services (DHHS), the Office for Human Research Protection (OHRP) and the site's Institutional Review Board may inspect research records for verification of data, compliance with federal guidelines on human participant research, and to assess participant safety.

13.5.7 Reporting to Sponsor

The site principal investigator agrees to submit accurate, complete, legible and timely reports to the Sponsor, as required. These include, but are not limited to, reports of any changes that significantly affect the conduct or outcome of the trial or increase risk to study participants. Adverse Event reporting and Serious Adverse Event reporting will occur as described in Appendix A. At the completion of the trial, the national lead Investigator will provide a final report to the Sponsor.

13.5.8 Informed Consent

All potential candidates for the study will be given a current local IRB-approved copy of the Informed Consent Form to read. Appropriately qualified and trained study personnel will explain all aspects of the study in lay language and answer all of the study candidate's questions. Participants who remain interested after receiving an explanation of the study will be given a informed consent quiz to test his/her understanding of the project, the purpose and procedures

involved, and the voluntary nature of his/her participation. Those who cannot successfully answer quiz items will have the study re-explained by research staff with a focus on aspects they did not understand. Anyone who cannot demonstrate appropriate understanding of the study will be ineligible to participate and will be assisted in finding other treatment resources. Those who demonstrate understanding of the study and voluntarily agree to participate will be asked to sign the informed consent form. Participants will not be administered any assessments or study procedures prior to signing informed consent.

The informed consent process is a means of providing study information to each prospective participant and allows for an informed decision about participation in the study. The informed consent form must be updated or revised whenever important new safety information is available, or whenever the protocol is amended in a way that may affect a study participant's participation in the trial. Each study site must have the study informed consent approved by their local IRB(s). The site must maintain the original signed informed consent for every participant in a locked, secure location that is in compliance with their local IRB and institutional policies and that is accessible for quality assurance review and regulatory compliance. Every study participant should be given a copy of the signed consent form to keep for reference. Individuals who refuse to participate or who withdraw from the study will be treated without prejudice.

13.5.9 Clinical Monitoring

The monitoring of the study site will be conducted on a regular basis using a combination of NIDA-contracted monitors and RRTC (Regional Research and Training Center) site managers. Investigators will host periodic visits by NIDA contract monitors and local site managers. The purpose of these visits is to encourage and assess compliance with GCP requirements and to document the integrity of the trial progress.

NIDA contract monitors will monitor study compliance and study procedures to assess compliance with the protocol, GCP, and applicable regulations. NIDA contract monitors will assess accurate submission of data and that data are in agreement with source documentation and will also review regulatory/essential documents such as correspondence with the IRB. Areas of particular concern will be participant informed consent, protocol adherence, safety monitoring, IRB reviews and approvals, regulatory documents, participant records, study drug accountability, and principal investigator supervision and involvement in the trial. Reports will be prepared following the visit and forwarded to the site principal investigator, the lead investigator and NIDA.

Qualified RRTC site managers will provide site management for each site during the trial. This will take place as specified by the local protocol team, RRTC PI or lead team and will occur as often as needed to help prevent, detect, and correct problems at the study sites. RRTC staff will ensure site staff is trained and able to conduct the protocol appropriately and that study procedures are properly followed. If the RRTC staff's review of study documentation indicates that additional training of study personnel is needed, RRTC staff will undertake or arrange for that training. Details of the contract monitoring, RRTC site management, and data monitoring are found in the study Quality Assurance Monitoring plan.

13.5.10 Study Documentation

Study documentation includes all case report forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence, and signed protocol and amendments, Ethics Review Committee or Institutional Review Committee correspondence and approved current and previous consent forms and signed participant consent forms.

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. The original recording of an observation should be retained as the source document. If the original recording of an observation is the electronic record, that will be considered the source.

13.6 Safety Monitoring

13.6.1 Medical Monitor

A NIDA-assigned Medical/Safety Monitor will be responsible for overseeing safety and for evaluating all Adverse Events (AEs). He/She will review all Serious Adverse Events (SAEs) within five days of their occurrence and all other Adverse Events on a regular basis. It is the responsibility of the site principal investigator to provide this information to the medical safety monitor. It is also the site principal investigators' responsibility to inform the IRBs per local IRB guidelines.

13.6.2 Data and Safety Monitoring Board (DSMB)

This study will utilize the CTN DSMB to oversee ongoing trial progress. The purpose of this board is to determine whether risks emerge during the conduct of the trial that make continuation unethical (e.g., clear and significant superiority of one condition over another). This process is intended to assure the IRBs, the sponsor, and investigators that participants are provided with an accurate and ongoing risk evaluation when participating in CTN research trials. Safety monitoring begins with the initial review of the protocol during the study development process. The DSMB will meet at least annually. Recommendations from these reviews will be distributed to the site lead investigator for submission to their IRB.

13.6.3 Protocol Deviations Reporting and Management

Any departure from procedures and requirements outlined in the protocol will be classified as either a major or minor protocol deviation. The difference between a major and minor protocol deviation has to do with the seriousness of the event and the corrective action required. A minor protocol deviation is considered an action (or inaction) that by itself is not likely to affect the scientific soundness of the investigation or seriously affect the safety, rights, or welfare of a study participant. Major protocol deviations are departures that may compromise the participant safety, participant rights, inclusion/exclusion criteria or the integrity of study data and could be cause for corrective actions if not rectified or prevented from re-occurrence. Sites will be responsible for developing corrective action plans for both major and minor deviations as appropriate. Those corrective action plans may be reviewed/approved by the Lead Node and the CCC with overall approval by the site's IRB. All protocol deviations will be monitored at each site for (1) significance, (2) frequency, and (3) impact on the study objectives, to ensure that site performance does not compromise the integrity of the trial.

Sites will encourage all participants to attend visits in person, however visits by phone are allowed. In those cases, research staff should complete as many of the study procedures and assessments as possible. Missed assessments will be noted as a protocol deviation. The research team should also note that missed urine drug screens associated with phone visits will contribute towards meeting relapse criteria.

All protocol deviations will be recorded in the Electronic Data Capture (EDC) system via the Protocol Deviation CRF. The CCC, DSC and the Lead Investigator must be contacted immediately if an unqualified or ineligible participant is randomized into the study.

Additionally, each site is responsible for reviewing their local IRB's definition of a protocol deviation or violation and understanding which events need to be reported. Sites must recognize that the CTN and IRB definition of a reportable event may differ and act accordingly in following all reporting requirements for both entities.

13.6.4 Adverse Events (AEs)

The Lead Investigator (LI) may appoint a Study Clinician (e.g., MD, DO, PA, NP, or RN) for this study, who will review or provide consultation for each serious adverse event as needed. These reviews will include an assessment of the severity and causal relationship with the study drug or study procedures. The Study Clinician will also provide advice for decisions to exclude, refer, or withdraw participants as required. In addition, NIDA will assign a Medical Monitor to this protocol to independently review the safety data, and present it to the DSMB for periodic review. The medical monitor will determine which adverse events require expedited reporting to NIDA, the DSMB, pharmaceutical/distributors (Reckitt Benckiser Pharmaceuticals, Inc.) and regulatory authorities. This will include all suspected adverse reactions that are serious and unexpected. The study staff will be trained to monitor for and report adverse events and including serious adverse events.

Each of the participating CTPs has established practices for managing medical and psychiatric emergencies, and the study staff will continue to utilize these procedures. Study medical clinicians at each CTP will be responsible for monitoring participants for possible clinical deterioration or other problems, and for implementing appropriate courses of action.

Standard definitions for adverse events and serious adverse events, their identification, characterization regarding severity and relationship to therapy and processing are described in Appendix A.

For the purpose of this study, the following AE will not require reporting in the data system but will be captured in the source documentation as medically indicated:

- Grade 1 (mild) unrelated adverse events

This would typically include mild physical events such as headache, cold, etc., that were considered not reasonably associated with the use of the study drug/intervention.

Events related to the injection of the study medication will be recorded on the Injection Site Abnormality (INA) form and will not be duplicate-reported on an AE form. Events related to withdrawal symptoms will be captured on the SOWS and HAM-D and will not be duplicate-reported on an AE form. Withdrawal symptoms not captured by the SOWS or HAM-D should be reported as an AE. Events captured on study specific forms (INA, SOWS, HAM-D) will not be recorded separately as an AE, unless they meet the SAE definition. Any of these events that meet the definition of an SAE will be reported on the AE/SAE form set. Any spontaneous reporting of withdrawal symptoms by the participant will be captured on AE form in the following situations: withdrawal symptoms reported at visits without scheduled specific structured questionnaires (SOWS, HAM-D); and withdrawal symptoms not listed in the specific structured questionnaires (SOWS, HAM-D) reported at any visit.

13.6.5 Serious Adverse Events

For the purpose of this study, the following events will not be reported as an SAE. Detox admissions will be recorded on study specific forms in the data system. They would be reported to local IRBs per local IRB guidelines:

- Aspects of the index detox admission will be documented on the Detox Utilization Form while other detox admissions will be documented on the NMS form
- Admission for labor and delivery
- Admission for elective or pre-planned surgery

13.6.6 Known Potential Toxicities of Study Drug/Intervention

Refer to the package inserts for XR-NTX and BUP-NX in Appendices C and D.

14.0 DATA MANAGEMENT AND PROCEDURES

14.1 Design and Development

This protocol utilizes a centralized Data and Statistics Center (DSC). The DSC is responsible for the development of the electronic case report forms (eCRFs), development and validation of the clinical study database, ensuring data integrity, and training site and participating RRTC staff on applicable data management procedures. AdvantageEDC, a web-based distributed data entry system, has been implemented. This system has been developed to ensure that guidelines and regulations surrounding the use of computerized systems used in clinical trials are upheld. The remainder of this section provides an overview of the data management plan associated with this protocol.

14.2 Site Responsibilities

The data management responsibilities of each individual CTP is specified by the DSC and outlined in the AdvantageEDC User's Guide.

14.3 Data Center Responsibilities

The DSC 1) develops a data management plan and conducts data management activities in accordance with that plan, 2) provides final guided source documents and eCRFs for the collection of all data required by the study, 3) develops data dictionaries for each eCRF that comprehensively define each data element, 4) conducts ongoing data monitoring activities on study data from all participating CTPs, 5) monitors any preliminary analysis data cleaning activities as needed, and 6) rigorously monitors final study data cleaning.

14.4 Data Collection

Data is collected at the study sites either on source documents, which are to be entered at the site into eCRFs, or through direct electronic data capture. The eCRFs are supplied by the DSC. eCRFs are to be completed on an ongoing basis during the study. The medical chart and the source documents are the source of verification of data. Paper CRFs and eCRFs should be completed according to the CRF instruction manual and relevant instructions in the study operations manual. The investigator is responsible for maintaining accurate, complete and up-to-date records, and for ensuring the completion of the eCRFs for each research participant.

14.5 Data Acquisition and Entry

Completed forms and electronic data will be entered into the AdvantageEDC system in accordance with the AdvantageEDC User's Guide. Only authorized individuals shall have access to eCRFs.

14.6 Data Editing

Completed data is to be entered into AdvantageEDC. If incomplete or inaccurate data are found, a query will be generated to the sites for a response. Sites are to resolve data inconsistencies and errors and enter all corrections and changes into AdvantageEDC.

14.7 Data Lock and Transfer

Data will be transmitted by the DSC to the NIDA central data repository as requested by NIDA. The DSC will conduct final data quality assurance checks and "lock" the study database from further modification. The final analysis dataset will be returned to NIDA, as requested, for storage and archive.

14.8 Data Training

The training plan for CTP staff includes provisions for training on assessments, eCRF completion guidelines, data management procedures, and the use of AdvantageEDC.

14.9 Data QA

To address the issue of data entry quality, the DSC will follow a standard data monitoring plan. An acceptable quality level prior to study lock or closeout will be established as a part of the data management plan. Data quality summaries will be made available during the course of the protocol.

15.0 PUBLICATIONS AND OTHER RIGHTS

Per NIH policy, the results of the proposed trial are to be made available to the research community and to the public at large. The planning, preparation, and submission of publications will follow the policies of the Publications Committee of the CTN.

16.0 SIGNATURES

SPONSOR'S REPRESENTATIVE (CCTN DESIGNEE)

Printed Name	Signature	Date

ACKNOWLEDGEMENT BY INVESTIGATOR:

- I am in receipt of version 6.0 of the protocol and agree to conduct this clinical study in accordance with the design and provisions specified therein.
- I agree to follow the protocol as written except in cases where necessary to protect the safety, rights, or welfare of a participant, an alteration is required, and the sponsor and IRB have been notified prior to the action.
- I will ensure that the requirements relating to obtaining informed consent and institutional review board (IRB) review and approval in 45 CFR 46 are met.
- I agree to personally conduct or supervise this investigation at this site and to ensure that all site staff assisting in the conduct of this study are adequately and appropriately trained to implement this version of the protocol and that they are qualified to meet the responsibilities to which they have been assigned.
- I agree to comply with all the applicable federal, state, and local regulations regarding the obligations of clinical investigators as required by the Department of Health and Human Services (DHHS), the state, and the IRB.

SITE'S PRINCIPAL INVESTIGATOR

Printed Name	Signature	Date

Site Name _____

Node Affiliation _____

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18.0 APPENDICES

APPENDIX A – Adverse Event Reporting Definitions and Procedures
APPENDIX B – Data Safety and Monitoring Plan
APPENDIX C – XR-NTX
APPENDIX D – BUP-NX

APPENDIX A – Adverse Event Reporting Definitions and Procedures

Each participating site's principal investigator is responsible for study oversight, including ensuring human research subject protection by designating appropriately qualified and trained study personnel to assess, report and monitor adverse events.

Definition of Adverse Events and Serious Adverse Events

An **adverse event** (AE) is any untoward medical occurrence in humans, whether or not considered study drug/intervention related which occurs during the conduct of a clinical trial. Any change from baseline in clinical status or any findings from ECGs, lab results, x-rays, physical examinations, etc., that are considered clinically significant by the study clinician are considered AEs.

Suspected adverse reaction is any adverse event for which there is a reasonable possibility that the study drug/intervention caused the adverse event. A reasonable possibility implies that there is evidence that the study drug/intervention caused the event.

Adverse reaction is any adverse event caused by the study drug/intervention.

An **adverse event, suspected adverse reaction,** or **adverse reaction** is considered "**serious**" (i.e., a serious adverse event, serious suspected adverse reaction or serious adverse reaction) if, in the view of either the study clinician or sponsor, it:

1. Results in death: A death occurring during the study or which comes to the attention of the study staff during the protocol-defined follow-up period, whether or not considered caused by the study drug/intervention, must be reported.
2. Is life-threatening: Life-threatening means that the study participant was, in the opinion of the medical clinician or sponsor, at immediate risk of death from the reaction as it occurred and required immediate intervention.
3. Requires inpatient hospitalization or prolongation of existing hospitalization.
4. Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5. Is a congenital abnormality or birth defect.
6. Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event.

Definition of Expectedness

Any adverse event is considered "unexpected" if it is not listed in the investigator brochure or the package insert or is not listed at the specificity or severity that has been observed. If neither is available then the protocol and informed consent form are used to determine an unexpected adverse event.

Pregnancy

Any pregnancies that occur while a participant is enrolled in the study will be captured on a pregnancy CRF and not separately reported as an AE or SAE. Women who become pregnant during the active treatment period will be discontinued from further medication administration, referred for medical care, and the pregnancy followed until an outcome is known.

Medical and Psychiatric History

A thorough medical and psychiatric history during the screening phase should record any chronic, acute, or intermittent preexisting or current illnesses, diseases, symptoms, or laboratory signs of the participant, to avoid reporting pre-existing conditions as new AEs and to assist in the assessment of worsening in intensity or severity of these conditions that would indicate an AE. Stable chronic conditions, such as arthritis, which are present prior to clinical trial entry and do not worsen are not considered AEs.

Site Staff's Role in Eliciting and Reporting Adverse Events

Appropriately qualified and trained study personnel will elicit participant reporting of AEs and SAEs at each study visit designated to collect AEs. Adverse events (medical and/or psychiatric) assessment and collection will begin when the participant signs the informed consent form and follow-up will continue through 30 days after the last study visit. Study personnel will obtain as much information as possible about the reported AE/SAE to complete the AE/SAE forms and will consult as warranted.

Standard reporting, within 7 calendar days of the site becoming aware of the event, is required for reportable AEs. Expedited reporting (within 24 hours of their occurrence and/or site staff's knowledge of the event) is required for reportable SAEs (including death and life-threatening events). Local sites are responsible for reporting SAEs to their IRB, per their IRB's guidelines.

Site staff is required to enter reportable AEs and SAEs in the AdvantageEDC system. The AE form is used to capture reportable AEs (as defined in the protocol). Additional information may need to be gathered to evaluate serious adverse events and to complete the appropriate CRFs and the summary. This process may include obtaining hospital discharge reports, medical records, autopsy records or any other type records or information necessary to provide a complete and clear picture of the serious event and events preceding and following the event. If the SAE is not resolved or stable at the time of the initial report or if new information becomes available after the initial report, follow-up information must be submitted as soon as possible.

Reportable adverse events will be followed until resolution, stabilization or study end. Any serious adverse reactions will be followed until resolution or stabilization even beyond the end of the study.

For the purpose of this study, the following AE classification will not require reporting in the data system but will be captured in the source documentation as medically indicated:

- Grade 1 (mild) unrelated adverse events

This would typically include mild physical events such as headache, cold, etc., that were considered not reasonably associated with the use of the study drug/intervention.

Events related to the injection of the study medication will be recorded on the Injection Site Abnormality (INA) form and will not be duplicate-reported on an AE form. Events related to withdrawal symptoms will be captured on the SOWS and HAM-D and will not be duplicate-reported on an AE form. Withdrawal symptoms not captured by the SOWS or HAM-D should be reported as an AE. Events captured on study specific forms (INA, SOWS, HAM-D) will not be recorded separately as an AE, unless they meet the SAE definition. Any of these events that

meet the definition of an SAE will be reported on the AE/SAE form set. Any spontaneous reporting of withdrawal symptoms by the participant will be captured on AE form in the following situations: withdrawal symptoms reported at visits without scheduled specific structured questionnaires (SOWS, HAM-D); and withdrawal symptoms not listed in the specific structured questionnaires (SOWS, HAM-D) reported at any visit.

Site Staff's Role in Assessing Severity and Causality of Adverse Events

Appropriately qualified and trained study personnel will conduct an initial assessment of seriousness, severity, and causality when eliciting participant reporting of adverse events. A study clinician will be expected to review all reportable AEs for seriousness, severity, and causality on at least a weekly basis.

Guidelines for Assessing Severity

The severity of an adverse event refers to the intensity of the event.

Grade 1	Mild	Transient or mild discomfort (< 48 hours), no or minimal medical intervention/therapy required, hospitalization not necessary (non-prescription or single-use prescription therapy may be employed to relieve symptoms, e.g., aspirin for simple headache, acetaminophen for post-surgical pain)
Grade 2	Moderate	Mild to moderate limitation in activity some assistance may be needed; no or minimal intervention/therapy required, hospitalization possible.
Grade 3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/ therapy required hospitalization possible.

Guidelines for Determining Causality

The study clinician will use the following question when assessing causal relationship of an adverse event with study drug/intervention where an affirmative answer designates the event as a suspected adverse reaction:

Is there a reasonable possibility that the study drug/intervention caused the event?

Site Staff's Role in Monitoring Adverse Events

Site designated quality assurance personnel will review study sites and respective study data on a regular basis and will promptly advise sites to report any previously unreported safety issues and ensure that the reportable safety-related events are being followed to resolution and reported appropriately. Staff education, re-training or appropriate corrective action plan will be implemented at the participating site when unreported or unidentified reportable AEs or serious events are discovered, to ensure future identification and timely reporting by the site.

Sponsor's Role in Safety Management Procedures of AEs/SAEs

A NIDA CCTN assigned Medical Monitor is responsible for reviewing all serious adverse event reports. All reported SAEs will generate an e-mail notification to the Medical Monitor, pharmaceutical distributor (Reckitt Benckiser Pharmaceuticals) lead investigator, and designees. All SAEs will be reviewed by the Medical Monitor in AdvantageEDC and, if needed, additional information will be requested. The medical monitor will also report events to the sponsor, pharmaceutical distributor (Reckitt Benckiser Pharmaceuticals) and the Data and Safety Monitoring Board (DSMB). The DSMB will receive summary reports of all adverse events annually, at a minimum. The DSMB or the NIDA CCTN assigned Medical Monitor may also

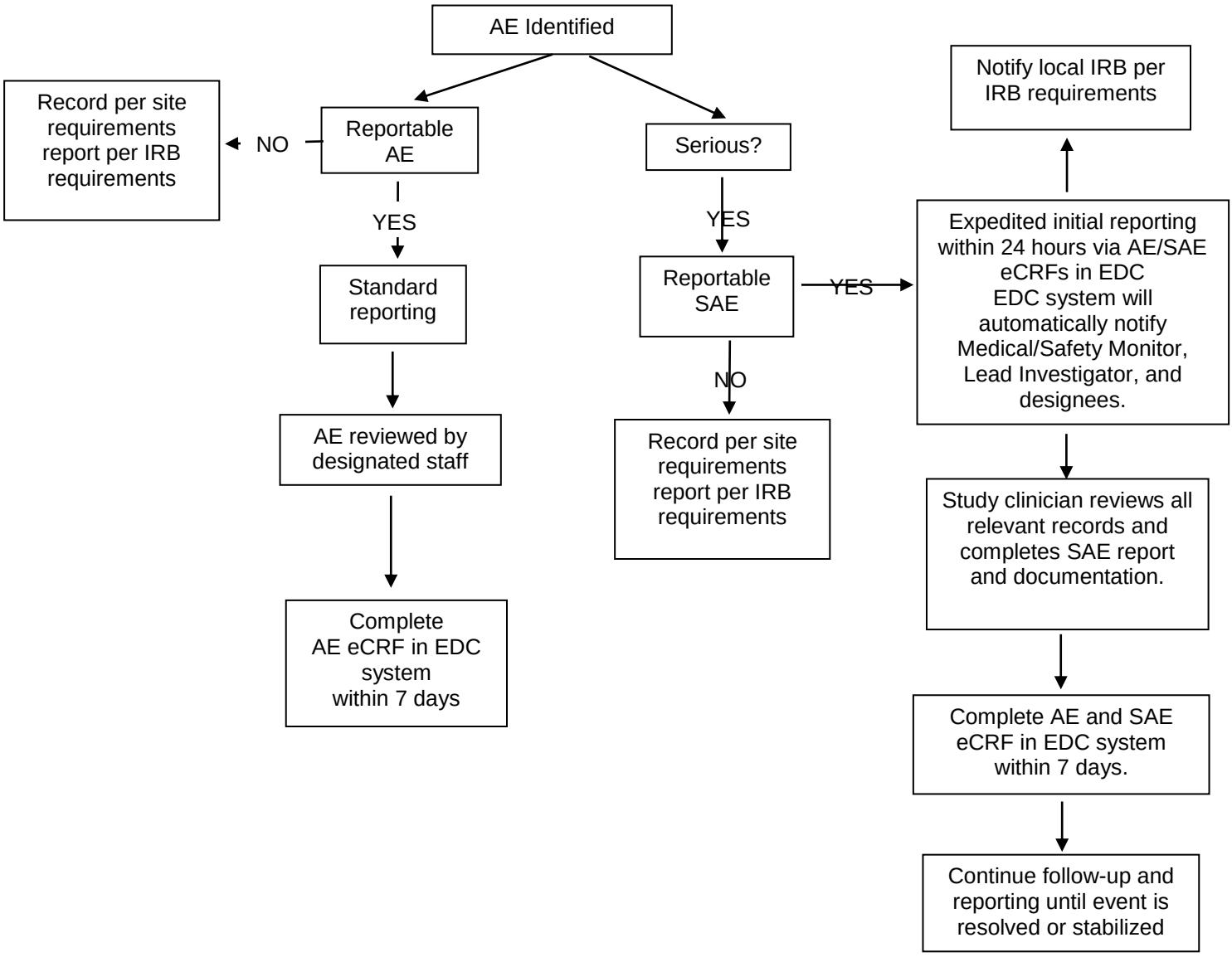
request additional and updated information. Details regarding specific adverse events, their treatment and resolution, will be summarized by the medical monitor in writing for review by the sponsor and DSMB. Subsequent review by the Medical Monitor, DSMB, and ethics review committee or IRB, the sponsor, or relevant local regulatory authorities may also suspend further trial treatment at a site. The study sponsor and DSMB retain the authority to suspend additional enrollment and treatments for the entire study as applicable.

Reporting to the Data and Safety Monitoring Board

The DSMB will receive listing of AEs and summary reports of all SAEs at a frequency requested by the DSMB, but at least annually. Furthermore, the DSMB will be informed of any SAE that is a serious unexpected suspected adverse reaction within 15 days of being reported by site.

Participant Withdrawal

The study clinician must apply his/her clinical judgment to determine whether or not an adverse event is of sufficient severity to require that the participant be withdrawn from further study medication administration. The study clinician should consult with the site principal investigator, the lead investigator and/or Medical Monitor as needed. If necessary, a study clinician may suspend any trial treatments and institute the necessary medical therapy to protect a participant from any immediate danger. A participant may also voluntarily withdraw from treatment due to what he/she perceives as an intolerable adverse event or for any other reason. If voluntary withdrawal is requested, the participant will be asked to complete an end-of-medication visit to assure safety and to document end-of-medication outcomes and will be given recommendations for medical care and/or referrals to treatment, as necessary.


AE Identified
Reportable AE
NO
Record per site requirements report per IRB requirements
YES
Standard reporting
AE reviewed by designated staff
Complete AE eCRF in EDC system within 7 days
Serious?
YES
Reportable SAE
YES
NO
Record per site requirements report per IRB requirements
Notify local IRB per IRB requirements
Expedited initial reporting within 24 hours via AE/SAE eCRFs in EDC
EDC system will automatically notify Medical/Safety Monitor, Lead Investigator, and designees.
Study clinician reviews all relevant records and completes SAE report and documentation.
Complete AE and SAE eCRF in EDC system within 7 days.
Continue follow-up and reporting until event is resolved or stabilized

APPENDIX B – Data Safety and Monitoring Plan

1.0 BRIEF STUDY OVERVIEW

The primary goal of the CTN-0051 study is to estimate the difference, if one exists, between XR-NTX and BUP-NX in the distribution of the time to loss of persistent abstinence during the 6-month trial. As part of secondary outcomes, the study will evaluate and compare XR-NTX versus BUP-NX in regards to safety events, opioid dependence, relapse, and retention. The misuse of alcohol, tobacco, and other drugs of abuse will be compared, in addition to the craving for opioids and other drugs. Depression, anxiety, and sub-acute withdrawal symptoms will also be compared between the two treatments. Details for the definitions and reporting of safety events are found in the protocol (Appendix A).

2.0 OVERSIGHT OF CLINICAL RESPONSIBILITIES

A. Site Principal Investigator

Each participating site's Principal Investigator (PI) is responsible for study oversight, including ensuring human research subject protection by designating appropriately qualified, trained research staff and medical clinicians to assess, report, and monitor adverse events.

Regarding safety and in accordance with FDA reporting requirements, all Adverse Events (AEs) occurring during the course of the clinical trial will be collected, documented, and reported by the investigator or sub-investigators according to the Protocol. The assessment of Adverse Events (medical and/or psychiatric) will commence at the time of participant consent and will continue through 30 days post last active treatment visit.

The occurrence of AEs and Serious Adverse Events (SAEs) will be assessed at each clinic visit during the study. Serious adverse events will be followed until resolved or considered stable, with reporting to the CCC Safety Monitor/Medical Monitor through the follow-up period.

Standard reporting, within 7 days of the site becoming aware of the event, is required for reportable AEs. Expedited reporting (within 24 hours of their occurrence and/or site's knowledge of the event) is required for reportable SAEs (including death and life-threatening events).

B. Medical Monitor/Safety Monitor

The NIDA CCTN Clinical Coordinating Center (CCC) Safety Monitor/Medical Monitor is responsible for reviewing all adverse events and serious adverse events reported. All SAEs will be reviewed at the time they are reported in the EDC. The Medical Monitor will also indicate concurrence or not with the details of the report provided by the site PI. Where further information is needed the Safety monitor/Medical monitor will discuss the event with the site. Reviews of SAEs will be conducted in AdvantageEDC data system and will be a part of the safety database. All AEs are reviewed on a weekly basis to observe trends or unusual events.

Reports will be generated and presented for Data Safety Monitoring Board (DSMB) meetings. The DSMB will receive listings of AEs and summary reports of all SAEs at a frequency requested by the DSMB, but at least annually. Furthermore, the DSMB will be informed of expedited reports of SAEs

C. Data And Safety Monitoring Board (DSMB)

The NIDA CTN DSMB affiliated with this trial will be responsible for conducting periodic reviews of accumulating safety, trial performance, and outcome data. The DSMB will make recommendations to NIDA CCTN as to whether there is sufficient support for continuation of the trial, evidence that study procedures should be changed, or evidence that the trial (or a specific

site) should be halted for reasons relating to safety of the study participants or inadequate trial performance (e.g., poor recruitment).

Following each DSMB meeting, the NIDA CCTN will communicate the outcomes of the meeting, based on DSMB recommendations, in writing to the study Lead Investigator. This communication detailing study safety information will be submitted to participating IRBs.

D. Quality Assurance (QA) Monitoring

The monitoring of the study site will be conducted on a regular basis using a combination of NIDA CCTN CCC contract monitors and the RRTC site managers. Investigators will host periodic visits for the NIDA CCTN CCC contract monitors and RRTC site managers. The purpose of these visits is to assess compliance with GCP requirements and to document the integrity of the trial progress. Areas of particular concern will be the review of Inclusion/Exclusion criteria, participant Informed Consent Forms, protocol adherence, safety monitoring, IRB reviews and approvals, regulatory documents, participant records, study drug accountability, and Principal Investigator supervision and involvement in the trial. The monitors will interact with the site staff to identify issues and re-train the site as needed to enhance research quality.

QA Site Visit Reports will be prepared by the NIDA CCC contract monitors following each site visit. These reports will be and forwarded to the site Principal Investigator, the study Lead Investigator and NIDA CCTN.

E. Management Of Risks To Participants

Confidentiality

Confidentiality of participant records will be secured by the use of study codes for identifying participants on CRFs, secure storage of any documents that have participant identifiers, and secure computing procedures for entering and transferring electronic data. No identifying information will be disclosed in reports, publications or presentations.

Information Meeting Reporting Requirements

The consent form will specifically state the types of information that are required to be reported and the fact that the information will be reported as required. These include suspected or known sexual or physical abuse of a child or elders, or threatened violence to self and/or others.

Subject Protection

The study clinician will evaluate all pertinent screening and baseline assessments prior to participant randomization to ensure that the participant is eligible and safe to enter the study. Adverse events (AEs) will be assessed and documented at each clinic visit. Concomitant medications will be assessed at each medical management visit. Individuals who experience an AE that compromises safe participation will be discontinued from further medication administration and provided referrals for other treatment or to specialized care. Study personnel will request that the participant complete an end-of medication visit to assure safety and to document end-of-medication outcomes.

Pregnancy

Pregnancy is an exclusion criterion for study participation. A positive pregnancy test post-randomization will result in the cessation of study medication. Participants who discontinue medications will be expected to continue with study visits. Pregnancy test results will be recorded on the Pregnancy and Birth Control Assessment CRF (PBC). Related outcome information will be recorded on the Pregnancy Outcome CRF (PO1, PO2, etc.). The site staff will follow the participant until an outcome of the pregnancy is known.

Study Specific Risks

Vivitrol® and Suboxone® block the effects of exogenous opioids after administration. After treatment, participants are likely to have reduced tolerance to opioids. Following Vivitrol® treatment, opioid use at the end of a dosing interval or after missing a dose could result in potentially life-threatening opioid intoxication (involving respiratory compromise or arrest, circulatory collapse, etc.). Attempting to overcome the blockade effects of Vivitrol® by administering large amounts of exogenous opioids is associated with potential risk of overdose. Participants in this study will receive an information card that will notify clinicians that they are receiving Vivitrol® or Suboxone® as part of a research study.

3.0 DATA MANAGEMENT PROCEDURES

This protocol will utilize a centralized Data and Statistics Center (DSC). A web-based distributed data entry model will be implemented. This electronic data capture system (AdvantageEDC) will be developed to ensure that guidelines and regulations surrounding the use of computerized systems in clinical trials are upheld.

4.0 DATA AND STATISTICS CENTER RESPONSIBILITIES

The DSC will: 1) develop and apply data management procedures to ensure the collection of accurate and good-quality data, 2) provide source documents and electronic Case Report Forms (eCRFs) for the collection of all data required by the study, 3) develop data dictionaries for each eCRF that will comprehensively define each data element, 4) prepare instructions for the use of AdvantageEDC and for the completion of eCRFs, 5) conduct ongoing monitoring activities on study data collected from all participating sites, 6) perform data cleaning activities prior to any interim analyses and prior to the final study database lock.

5.0 DATA COLLECTION AND ENTRY

Data will be collected at the study sites on source documents and entered by the site into eCRFs in AdvantageEDC, or will be collected via direct entry into the eCRF. In the event that AdvantageEDC is not available, the DSC will provide the sites with paper source documents and completion instructions. Data will be entered into AdvantageEDC in accordance with the instructions provided during project-specific training and guidelines established by the DSC. Data entry into the eCRFs shall be performed by authorized individuals. Selected eCRFs may also require the investigator's electronic signature.

The investigator at the site is responsible for maintaining accurate, complete and up-to-date research records. In addition, the investigator is responsible for ensuring the timely completion of eCRFs for each research participant.

6.0 DATA MONITORING, CLEANING AND EDITING

eCRFs will be monitored for completeness and accuracy throughout the study. Dynamic reports listing missing values and forms are available to sites at all times in AdvantageEDC. These reports will be monitored regularly by the DSC. In addition, the DSC will identify inconsistencies within eCRFs and between eCRFs and post queries in AdvantageEDC on a scheduled basis. Sites will resolve data inconsistencies and errors by entering all corrections and changes directly into AdvantageEDC.

As described above, the CCC will conduct regular visits to sites, during which, audits comparing source documents to the data entered on the eCRF will be performed. Any discrepancies identified between the source document and the eCRF will be corrected by the site.

Trial progress and data status reports, which provide information on recruitment, availability of primary outcome, treatment exposure, attendance at long term follow-up visits, regulatory status, and data quality, will be generated daily and posted to a secure website. These reports are available to the site, the corresponding RRTC, the lead investigator, the coordinating centers, and NIDA CCTN, to monitor the sites' progress on the study.

7.0 DATA LOCK AND TRANSFER

At the conclusion of data collection for the study, the DSC will perform final data cleaning activities and will "lock" the study database from further modification. The final analysis dataset will be returned to NIDA CCTN, as requested, for storage and archive.

APPENDIX C – XR-NTX

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VIVITROL® safely and effectively. See full prescribing information for VIVITROL.

VIVITROL® (naltrexone for extended-release injectable suspension)
Intramuscular
Initial U.S. Approval: 1984

RECENT MAJOR CHANGES

Boxed Warning	Removed 7/2013
Dosage and Administration,	
Switching from Buprenorphine and Methadone (2.3)	7/2013
Contraindications—Acute Hepatitis or Liver Failure	Removed 7/2013
Warnings and Precautions	
Vulnerability to Opioid Overdose (5.1)	7/2013
Injection Site Reaction (5.2)	7/2013
Precipitation of Opioid Withdrawal (5.3)	7/2013
Hepatotoxicity (5.4)	7/2013

INDICATIONS AND USAGE

- VIVITROL is indicated for the treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment with VIVITROL. Patients should not be actively drinking at the time of initial VIVITROL administration (1.1).
- VIVITROL is indicated for the prevention of relapse to opioid dependence, following opioid detoxification (1.2).
- VIVITROL should be part of a comprehensive management program that includes psychosocial support (1).

DOSAGE AND ADMINISTRATION

The recommended dose of VIVITROL is 380 mg delivered intramuscularly every 4 weeks or once a month. The injection should be administered by a healthcare provider as an intramuscular (IM) gluteal injection, alternating buttocks for each subsequent injection, using the carton components provided (2 and 16.1).

Prior to initiating VIVITROL, an opioid-free duration of a minimum of 7–10 days is recommended for patients, to avoid precipitation of opioid withdrawal that may be severe enough to require hospitalization (5.3).

VIVITROL must not be administered intravenously or subcutaneously.
The entire dose pack should be stored in the refrigerator (2-8°C, 36-46°F) (2.3 and 16.1).
Do not expose the product to temperatures above 25°C (77°F). VIVITROL should not be frozen (2.4).

DOSAGE FORMS AND STRENGTHS

VIVITROL is an injectable suspension containing 380 mg of naltrexone in a microsphere formulation and 4 mL diluent (3).

CONTRAINDICATIONS

VIVITROL is contraindicated in:

- Patients receiving opioid analgesics (5.3).
- Patients with current physiologic opioid dependence (5.3).
- Patients in acute opioid withdrawal (5.3).
- Any individual who has failed the naloxone challenge test or has a positive urine screen for opioids (4).
- Patients who have previously exhibited hypersensitivity to naltrexone, polylactide-co-glycolide (PLG), carboxymethylcellulose, or any other components of the diluent (4).

WARNINGS AND PRECAUTIONS

- **Vulnerability to Opioid Overdose:** Following VIVITROL treatment opioid tolerance is reduced from pretreatment baseline, and patients are vulnerable to potentially fatal overdose at the end of a dosing interval, after missing a dose, or after discontinuing VIVITROL treatment. Attempts to overcome blockade may also lead to fatal overdose (5.1).
- **Injection Site Reactions:** In some cases, injection site reactions may be very severe. Some cases of injection site reactions required surgical intervention (5.2).
- **Precipitation of Opioid Withdrawal:** Opioid-dependent and opioid-using patients, including those being treated for alcohol dependence, should be opioid-free before starting VIVITROL treatment, and should notify healthcare providers of any recent opioid use. An opioid-free duration of a minimum of 7-10 days is recommended for patients to avoid precipitation of opioid withdrawal that may be severe enough to require hospitalization. (5.3).
- **Hepatotoxicity:** Cases of hepatitis and clinically significant liver dysfunction were observed in association with VIVITROL treatment during the clinical development program and in the postmarketing period. Discontinue use of VIVITROL in the event of symptoms or signs of acute hepatitis (5.4).
- **Depression and Suicidality:** Monitor patients for the development of depression or suicidal thinking (5.5).
- **When Reversal of VIVITROL Blockade Is Required for Pain Management:** In an emergency situation in patients receiving VIVITROL, suggestions for pain management include regional analgesia or use of non-opioid analgesics (5.6).

ADVERSE REACTIONS

The adverse events seen most frequently in association with VIVITROL therapy for alcohol dependence (i.e, those occurring in ≥5% and at least twice as frequently with VIVITROL than placebo) include nausea, vomiting, injection site reactions (including induration, pruritus, nodules and swelling), muscle cramps, dizziness or syncope, somnolence or sedation, anorexia, decreased appetite or other appetite disorders (6).

The adverse events seen most frequently in association with VIVITROL therapy in opioid-dependent patients (i.e., those occurring in ≥2% of patients treated with VIVITROL and at least twice as frequently with VIVITROL than placebo) were hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache (6).
To report SUSPECTED ADVERSE REACTIONS, contact Alkermes, Inc. at 1-800-VIVITROL (1-800-848-4876) and/or email: usmedinfo@alkermes.com or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

Naltrexone antagonizes the effects of opioid-containing medicines, such as cough and cold remedies, antidiarrheal preparations, and opioid analgesics (7).

USE IN SPECIFIC POPULATIONS

- VIVITROL pharmacokinetics have not been evaluated in subjects with severe hepatic impairment (8.7).
- Caution is recommended in administering VIVITROL to patients with moderate to severe renal impairment (8.6).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide

Revised: July 2013

FULL PRESCRIBING INFORMATION: CONTENTS*

Reference ID: 3348450

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

Reference ID: 3348450

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Treatment with VIVITROL should be part of a comprehensive management program that includes psychosocial support.

1.1 Alcohol Dependence

VIVITROL is indicated for the treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment with VIVITROL. Patients should not be actively drinking at the time of initial VIVITROL administration.

1.2 Opioid Dependence

VIVITROL is indicated for the prevention of relapse to opioid dependence, following opioid detoxification.

2 DOSAGE AND ADMINISTRATION

VIVITROL must be prepared and administered by a healthcare provider.

Prior to initiating VIVITROL, an opioid-free duration of a minimum of 7–10 days is recommended for patients, to avoid precipitation of opioid withdrawal that may be severe enough to require hospitalization [*see Warnings and Precautions (5.3)*].

The recommended dose of VIVITROL is 380 mg delivered intramuscularly every 4 weeks or once a month. The injection should be administered by a healthcare provider as an intramuscular (IM) gluteal injection, alternating buttocks for each subsequent injection, using the carton components provided *[see How Supplied/Storage and Handling (16)]*. The needles provided in the carton are customized needles. VIVITROL must not be injected using any other needle. The needle lengths (either 1.5 or 2 inches) may not be adequate in every patient because of body habitus. Body habitus should be assessed prior to each injection for each patient to assure that needle length is adequate for intramuscular administration. For patients with a larger amount of subcutaneous tissue overlying the gluteal muscle, the administering healthcare provider may utilize the supplied 2-inch needle with needle protection device to help ensure that the injectate reaches the intramuscular mass. For very lean patients, the 1.5-inch needle may be appropriate to prevent the needle contacting the periosteum. Either needle may be used for patients with average body habitus. Healthcare providers should ensure that the VIVITROL injection is given correctly, and should consider alternate treatment for those patients whose body habitus precludes an intramuscular gluteal injection with one of the provided needles.

VIVITROL must not be administered intravenously or subcutaneously.

If a patient misses a dose, he/she should be instructed to receive the next dose as soon as possible.

Pretreatment with oral naltrexone is not required before using VIVITROL.

2.1 Reinitiation of Treatment in Patients Previously Discontinued

There are no data to specifically address reinitiation of treatment. Patients reinitiating treatment with VIVITROL should be opioid-free at the time of dose administration *[see Indications and Usage (1), Contraindications (4), and Warnings and Precautions (5.3)]*.

2.2 Switching From Oral Naltrexone

There are no systematically collected data that specifically address the switch from oral naltrexone to VIVITROL.

2.3 Switching from Buprenorphine, Buprenorphine/Naloxone, or Methadone

There are no systematically collected data that specifically address the switch from buprenorphine or methadone to VIVITROL; however, review of postmarketing case reports have indicated that some patients may experience severe manifestations of precipitated withdrawal when being switched from opioid agonist therapy to opioid antagonist therapy *[see Warnings and Precautions (5.3)]*. Patients transitioning from buprenorphine or methadone may be vulnerable to precipitation of withdrawal symptoms for as long as 2 weeks. Healthcare providers should be prepared to manage withdrawal symptomatically with non-opioid medications.

2.4 Directions for Use

To ensure proper dosing, it is important that you follow the preparation and administration instructions outlined in this document.

VIVITROL must be suspended **only** in the diluent supplied in the carton and must be administered **only** with one of the administration needles supplied in the carton. The microspheres, diluent, preparation needle, and an administration needle with needle protection device are required for preparation and administration. Two thin-walled 1.5-inch needles with needle protection device and two 2-inch thin-walled needles with needle protection device have been provided to accommodate varying patient body habitus. For patients with a larger amount of subcutaneous tissue overlying the gluteal muscle, the administering healthcare provider may utilize the supplied 2-inch needle with needle protection device to help ensure that the injectate reaches the intramuscular mass. For very lean patients, the 1.5-inch needle may be appropriate to prevent the needle contacting the periosteum. Either needle may be used for patients with average body habitus. A spare administration needle of each size is provided in case of clogging *[see How Supplied/Storage and Handling (16)]*. Do not substitute any other components for the components of the carton.

Prior to preparation, allow drug to reach room temperature (approximately 45 minutes).

Parenteral products should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit. A properly mixed suspension will be milky white, will not contain clumps, and will move freely down the wall of the vial *[see Directions for Use, illustration below]*.

Product to be prepared and administered by a healthcare provider.

Keep out of reach of children.

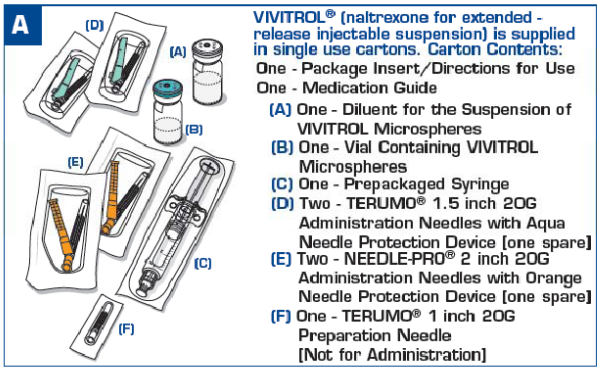
Prepare and administer the VIVITROL suspension using aseptic technique.

WARNING: To reduce the risk of a needlestick:

- Do not intentionally disengage the needle protection device.
- Discard bent or damaged needle into a sharps container and use the spare needle provided. Do not attempt to straighten the needle or engage needle protection device if the needle is bent or damaged.
- Do not mishandle the needle protection device in a way that could lead to protrusion of the needle.
- Do not use free hand to press sheath over needle.

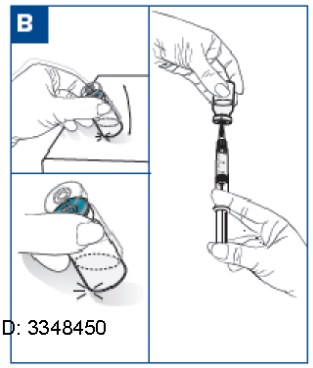
THE CARTON SHOULD NOT BE EXPOSED TO TEMPERATURES EXCEEDING 25 °C (77 °F).

The entire carton should be stored in the refrigerator (2-8°C, 36-46°F). Unrefrigerated, VIVITROL microspheres can be stored at temperatures not exceeding 25°C (77°F) for no more than 7 days prior to administration. Do not expose unrefrigerated product to temperatures above 25°C (77°F). VIVITROL should not be frozen.



Parenteral products should be visually inspected for particulate matter and discoloration prior to administration.

NEEDLE-PRO® and the color orange applied to the needle protection device are trademarks of the Smiths Medical family of companies.



1. Remove the carton from refrigeration. Prior to preparation, allow drug to reach room temperature (approximately 45 minutes).

2. To ease mixing, firmly tap the VIVITROL microspheres vial on a hard surface, ensuring the powder moves freely. (see Figure B)

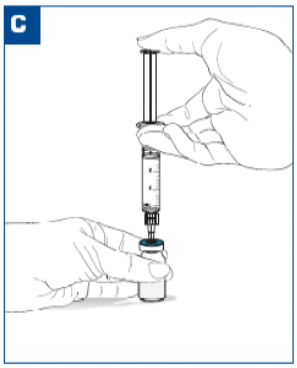
3

Reference ID: 3348450

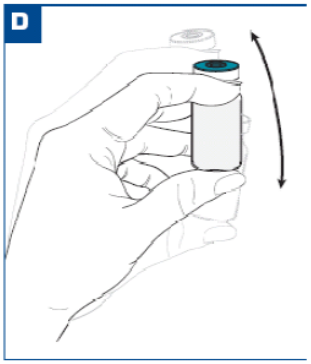
3. Remove flip-off caps from both vials. DO NOT USE IF FLIP-OFF CAPS ARE BROKEN OR MISSING.

4. Wipe the vial tops with an alcohol swab.

5. Place the 1-inch preparation needle on the syringe and withdraw 3.4 mL of the diluent from the diluent vial. Some diluent will remain in the diluent vial. (see Figure B)



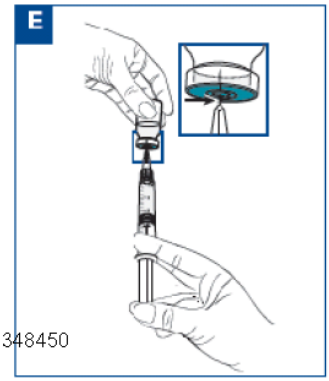
Inject the 3.4 mL of diluent into the VIVITROL microsphere vial. (see Figure C)



Mix the powder and diluent by vigorously shaking the vial for approximately 1 minute. (see Figure D)

Ensure that the dose is thoroughly suspended prior to proceeding to Step E.

A PROPERLY MIXED SUSPENSION WILL BE MILKY WHITE, WILL NOT CONTAIN CLUMPS, AND WILL MOVE FREELY DOWN THE WALLS OF THE VIAL.



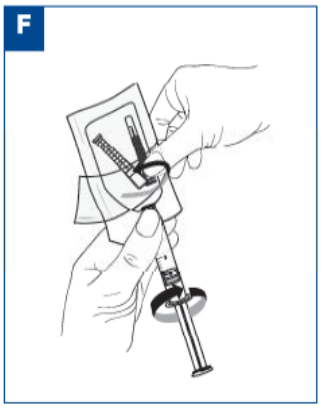
1. Immediately after suspension, withdraw 4.2 mL of the suspension into the syringe using the same preparation needle. (see Figure E)

2. Select the appropriate needle for an intramuscular injection based on patient's body habitus:

4

Reference ID: 3348450

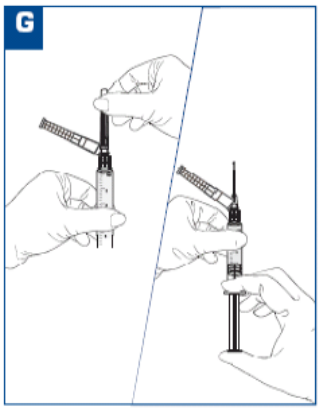
a. 1.5-inch TERUMO® Needle
b. 2-inch NEEDLE-PRO® Needle



1. Remove the preparation needle and replace with appropriately selected administration needle for immediate use.

2. Peel the blister pouch of the selected administration needle open halfway. Grasp sheath using the plastic pouch. Attach the luer connection to the syringe with an easy clockwise twisting motion. (see Figure F)

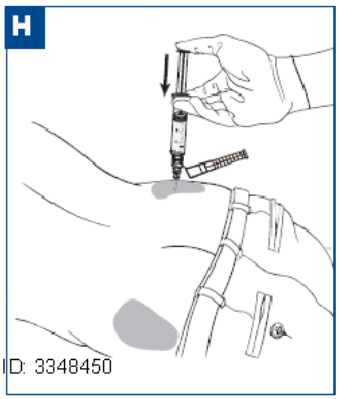
3. Seat the needle firmly on the needle protection device with a push and clockwise twist.



1. Pull the sheath away from the needle -do not twist the sheath because it could result in loosening the needle.

2. Prior to injecting, tap the syringe to release any air bubbles, then push gently on the plunger until 4 mL of the suspension remains in the syringe. (see Figure G)

THE SUSPENSION IS NOW READY FOR IMMEDIATE ADMINISTRATION.



1. Using a circular motion, clean the injection site with the alcohol swab. Let the site dry before injecting. Do not touch the site again before giving injections.

2. Administer the suspension by deep intramuscular (IM) injection into a gluteal muscle, alternating buttocks per monthly injection. **Remember to aspirate for blood before injection.** (see Figure H)

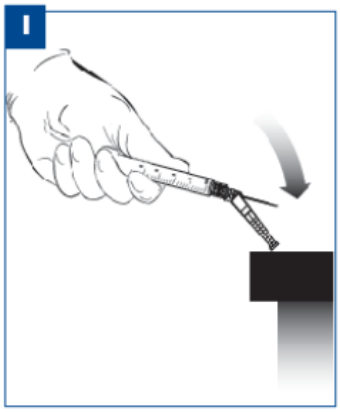
5

Reference ID: 3348450

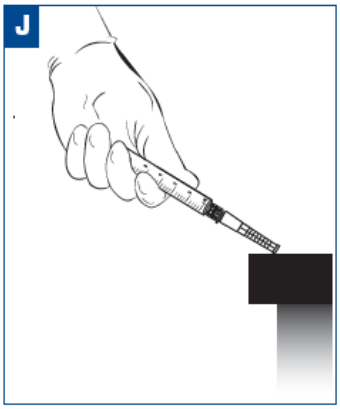
3. If blood aspirates or the needle clogs, do not inject. Change to the spare needle provided in the carton and administer into an adjacent site in the same gluteal region, again aspirating for blood before injection.

4. Inject the suspension in a smooth and continuous motion.

VIVITROL must NOT be given intravenously or subcutaneously.



After the injection is administered, cover the needle by pressing the needle protection device against a flat surface using a one-handed motion away from self and others. (see Figure I)



Visually confirm needle is fully engaged into the needle protection device. (see Figure J)

DISPOSE OF USED AND UNUSED ITEMS IN PROPER WASTE CONTAINERS.

3 DOSAGE FORMS AND STRENGTHS

VIVITROL is an injectable suspension for single use. VIVITROL contains 380 mg of naltrexone in a microsphere formulation per vial (337 mg of naltrexone per gram of microspheres) and 4 mL diluent.

4. CONTRAINDICATIONS

VIVITROL is contraindicated in:

- Patients receiving opioid analgesics *[see Warnings and Precautions (5.3)]*.
- Patients with current physiologic opioid dependence *[see Warnings and Precautions (5.3)]*.
- Patients in acute opioid withdrawal *[see Warnings and Precautions (5.3)]*.
- Any individual who has failed the naloxone challenge test or has a positive urine screen for opioids *[see Warnings and Precautions (5.3)]*.
- Patients who have previously exhibited hypersensitivity to naltrexone, PLG, carboxymethylcellulose, or any other components of the diluent *[see Warnings and Precautions (5.8)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Vulnerability to Opioid Overdose

After opioid detoxification, patients are likely to have reduced tolerance to opioids. VIVITROL blocks the effects of exogenous opioids for approximately 28 days after administration. However, as the blockade wanes and eventually dissipates completely, patients who have been treated with VIVITROL may respond to lower doses of opioids than previously used, just as they would have shortly after completing detoxification. This could result in potentially life-threatening opioid intoxication (respiratory compromise or arrest, circulatory collapse, etc.) if the patient uses previously tolerated doses of opioids. Cases of opioid overdose with fatal outcomes have been reported in patients who used opioids at the end of a dosing interval, after missing a scheduled dose, or after discontinuing treatment.

Patients should be alerted that they may be more sensitive to opioids, even at lower doses, after VIVITROL treatment is discontinued, especially at the end of a dosing interval (i.e., near the end of the month that VIVITROL was administered), or after a dose of VIVITROL is missed. It is important that patients inform family members and the people closest to the patient of this increased sensitivity to opioids and the risk of overdose *[see Patient Counseling Information (17)]*.

There is also the possibility that a patient who is treated with VIVITROL could overcome the opioid blockade effect of VIVITROL. Although VIVITROL is a potent antagonist with a prolonged pharmacological effect, the blockade produced by VIVITROL is surmountable. The

plasma concentration of exogenous opioids attained immediately following their acute administration may be sufficient to overcome the competitive receptor blockade. This poses a potential risk to individuals who attempt, on their own, to overcome the blockade by administering large amounts of exogenous opioids. Any attempt by a patient to overcome the antagonism by taking opioids is especially dangerous and may lead to life-threatening opioid intoxication or fatal overdose. Patients should be told of the serious consequences of trying to overcome the opioid blockade *[see Patient Counseling Information (17)]*.

5.2 Injection Site Reactions

VIVITROL injections may be followed by pain, tenderness, induration, swelling, erythema, bruising, or pruritus; however, in some cases injection site reactions may be very severe. In the clinical trials, one patient developed an area of induration that continued to enlarge after 4 weeks, with subsequent development of necrotic tissue that required surgical excision. In the postmarketing period, additional cases of injection site reaction with features including induration, cellulitis, hematoma, abscess, sterile abscess, and necrosis, have been reported. Some cases required surgical intervention, including debridement of necrotic tissue. Some cases resulted in significant scarring. The reported cases occurred primarily in female patients.

VIVITROL is administered as an intramuscular gluteal injection, and inadvertent subcutaneous injection of VIVITROL may increase the likelihood of severe injection site reactions. The needles provided in the carton are customized needles. VIVITROL must not be injected using any other needle. The needle lengths (either 1.5 inches or 2 inches) may not be adequate in every patient because of body habitus. Body habitus should be assessed prior to each injection for each patient to assure that the proper needle is selected and that the needle length is adequate for intramuscular administration. For patients with a larger amount of subcutaneous tissue overlying the gluteal muscle, the administering healthcare provider may utilize the supplied 2-inch needle with needle protection device to help ensure that the injectate reaches the intramuscular mass. For very lean patients, the 1.5-inch needle may be appropriate to prevent the needle contacting the periosteum. Either needle may be used for patients with average body habitus. Healthcare providers should ensure that the VIVITROL injection is given correctly, and should consider alternate treatment for those patients whose body habitus precludes an intramuscular gluteal injection with one of the provided needles.

Patients should be informed that any concerning injection site reactions should be brought to the attention of the healthcare provider *[see Patient Counseling Information (17)]*. Patients exhibiting signs of abscess, cellulitis, necrosis, or extensive swelling should be evaluated by a physician to determine if referral to a surgeon is warranted.

5.3 Precipitation of Opioid Withdrawal

The symptoms of spontaneous opioid withdrawal (which are associated with the discontinuation of opioid in a dependent individual) are uncomfortable, but they are not generally believed to be severe or necessitate hospitalization. However, when withdrawal is precipitated abruptly by the administration of an opioid antagonist to an opioid-dependent patient, the resulting withdrawal syndrome can be severe enough to require hospitalization. Review of postmarketing cases of

precipitated opioid withdrawal in association with naltrexone treatment has identified cases with symptoms of withdrawal severe enough to require hospital admission, and in some cases, management in the intensive care unit.

To prevent occurrence of precipitated withdrawal in patients dependent on opioids, or exacerbation of a pre-existing subclinical withdrawal syndrome, opioid-dependent patients, including those being treated for alcohol dependence, should be opioid-free (including tramadol) before starting VIVITROL treatment. An opioid-free interval of a minimum of 7–10 days is recommended for patients previously dependent on short-acting opioids. Patients transitioning from buprenorphine or methadone may be vulnerable to precipitation of withdrawal symptoms for as long as two weeks.

If a more rapid transition from agonist to antagonist therapy is deemed necessary and appropriate by the healthcare provider, monitor the patient closely in an appropriate medical setting where precipitated withdrawal can be managed.

In every case, healthcare providers should always be prepared to manage withdrawal symptomatically with non-opioid medications because there is no completely reliable method for determining whether a patient has had an adequate opioid-free period. A naloxone challenge test may be helpful; however, a few case reports have indicated that patients may experience precipitated withdrawal despite having a negative urine toxicology screen or tolerating a naloxone challenge test (usually in the setting of transitioning from buprenorphine treatment). Patients should be made aware of the risks associated with precipitated withdrawal and encouraged to give an accurate account of last opioid use. Patients treated for alcohol dependence with VIVITROL should also be assessed for underlying opioid dependence and for any recent use of opioids prior to initiation of treatment with VIVITROL. Precipitated opioid withdrawal has been observed in alcohol-dependent patients in circumstances where the prescriber had been unaware of the additional use of opioids or co-dependence on opioids.

5.4 Hepatotoxicity

Cases of hepatitis and clinically significant liver dysfunction were observed in association with VIVITROL exposure during the clinical development program and in the postmarketing period. Transient, asymptomatic hepatic transaminase elevations were also observed in the clinical trials and postmarketing period. Although patients with clinically significant liver disease were not systematically studied, clinical trials did include patients with asymptomatic viral hepatitis infections. When patients presented with elevated transaminases, there were often other potential causative or contributory etiologies identified, including pre-existing alcoholic liver disease, hepatitis B and/or C infection, and concomitant usage of other potentially hepatotoxic drugs. Although clinically significant liver dysfunction is not typically recognized as a manifestation of opioid withdrawal, opioid withdrawal that is precipitated abruptly may lead to systemic sequelae including acute liver injury.

Patients should be warned of the risk of hepatic injury and advised to seek medical attention if they experience symptoms of acute hepatitis. Use of VIVITROL should be discontinued in the event of symptoms and/or signs of acute hepatitis.

5.5 Depression and Suicidality

Alcohol- and opioid-dependent patients, including those taking VIVITROL, should be monitored for the development of depression or suicidal thinking. Families and caregivers of patients being treated with VIVITROL should be alerted to the need to monitor patients for the emergence of symptoms of depression or suicidality, and to report such symptoms to the patient's healthcare provider.

Alcohol Dependence

In controlled clinical trials of VIVITROL administered to adults with alcohol dependence, adverse events of a suicidal nature (suicidal ideation, suicide attempts, completed suicides) were infrequent overall, but were more common in patients treated with VIVITROL than in patients treated with placebo (1% vs 0). In some cases, the suicidal thoughts or behavior occurred after study discontinuation, but were in the context of an episode of depression that began while the patient was on study drug. Two completed suicides occurred, both involving patients treated with VIVITROL.

Depression-related events associated with premature discontinuation of study drug were also more common in patients treated with VIVITROL (~1%) than in placebo-treated patients (0).

In the 24-week, placebo-controlled pivotal trial in 624 alcohol-dependent patients, adverse events involving depressed mood were reported by 10% of patients treated with VIVITROL 380 mg, as compared to 5% of patients treated with placebo injections.

Opioid Dependence

In an open-label, long-term safety study conducted in the US, adverse events of a suicidal nature (depressed mood, suicidal ideation, suicide attempt) were reported by 5% of opioid-dependent patients treated with VIVITROL 380 mg (n=101) and 10% of opioid-dependent patients treated with oral naltrexone (n=20). In the 24-week, placebo-controlled pivotal trial that was conducted in Russia in 250 opioid-dependent patients, adverse events involving depressed mood or suicidal thinking were not reported by any patient in either treatment group (VIVITROL 380 mg or placebo).

5.6 When Reversal of VIVITROL Blockade Is Required for Pain Management

In an emergency situation in patients receiving VIVITROL, suggestions for pain management include regional analgesia or use of non-opioid analgesics. If opioid therapy is required as part of anesthesia or analgesia, patients should be continuously monitored in an anesthesia care setting by persons not involved in the conduct of the surgical or diagnostic procedure. The opioid therapy must be provided by individuals specifically trained in the use of anesthetic drugs and the management of the respiratory effects of potent opioids, specifically the establishment and maintenance of a patent airway and assisted ventilation.

Irrespective of the drug chosen to reverse VIVITROL blockade, the patient should be monitored closely by appropriately trained personnel in a setting equipped and staffed for cardiopulmonary resuscitation.

5.7 Eosinophilic Pneumonia

In clinical trials with VIVITROL, there was one diagnosed case and one suspected case of eosinophilic pneumonia. Both cases required hospitalization, and resolved after treatment with antibiotics and corticosteroids. Similar cases have been reported in postmarketing use. Should a person receiving VIVITROL develop progressive dyspnea and hypoxemia, the diagnosis of eosinophilic pneumonia should be considered *[see Adverse Reactions (6)]*. Patients should be warned of the risk of eosinophilic pneumonia, and advised to seek medical attention should they develop symptoms of pneumonia. Clinicians should consider the possibility of eosinophilic pneumonia in patients who do not respond to antibiotics.

5.8 Hypersensitivity Reactions Including Anaphylaxis

Cases of urticaria, angioedema, and anaphylaxis have been observed with use of VIVITROL in the clinical trial setting and in postmarketing use. Patients should be warned of the risk of hypersensitivity reactions, including anaphylaxis. In the event of a hypersensitivity reaction, patients should be advised to seek immediate medical attention in a healthcare setting prepared to treat anaphylaxis. The patient should not receive any further treatment with VIVITROL.

5.9 Intramuscular Injections

As with any intramuscular injection, VIVITROL should be administered with caution to patients with thrombocytopenia or any coagulation disorder (eg, hemophilia and severe hepatic failure).

5.10 Alcohol Withdrawal

Use of VIVITROL does not eliminate nor diminish alcohol withdrawal symptoms.

5.11 Interference with Laboratory Tests

VIVITROL may be cross-reactive with certain immunoassay methods for the detection of drugs of abuse (specifically opioids) in urine. For further information, reference to the specific immunoassay instructions is recommended.

6 ADVERSE REACTIONS

Serious adverse reactions that may be associated with VIVITROL therapy in clinical use include: severe injection site reactions, eosinophilic pneumonia, serious allergic reactions, unintended precipitation of opioid withdrawal, accidental opioid overdose and depression and suicidality.

The adverse events seen most frequently in association with VIVITROL therapy for alcohol dependence (ie, those occurring in ≥ 5% and at least twice as frequently with VIVITROL than placebo) include nausea, vomiting, injection site reactions (including induration, pruritus, nodules and swelling), muscle cramps, dizziness or syncope, somnolence or sedation, anorexia, decreased appetite or other appetite disorders.

The adverse events seen most frequently in association with VIVITROL therapy in opioid-dependent patients (ie, those occurring in ≥ 2% and at least twice as frequently with VIVITROL

than placebo) were hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache.

6.1 Clinical Studies Experience

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 practice.

In all controlled and uncontrolled trials during the premarketing development of VIVITROL, more than 1100 patients with alcohol and/or opioid dependence have been treated with VIVITROL. Approximately 700 patients have been treated for 6 months or more, and more than 400 for 1 year or longer.

Adverse Events Leading to Discontinuation of Treatment

Alcohol Dependence

In controlled trials of 6 months or less in alcohol-dependent patients, 9% of alcohol-dependent patients treated with VIVITROL discontinued treatment due to an adverse event, as compared to 7% of the alcohol-dependent patients treated with placebo. Adverse events in the VIVITROL 380-mg group that led to more dropouts than in the placebo-treated group were injection site reactions (3%), nausea (2%), pregnancy (1%), headache (1%), and suicide-related events (0.3%). In the placebo group, 1% of patients withdrew due to injection site reactions, and 0% of patients withdrew due to the other adverse events.

Opioid Dependence

In a controlled trial of 6 months, 2% of opioid-dependent patients treated with VIVITROL discontinued treatment due to an adverse event, as compared to 2% of the opioid-dependent patients treated with placebo.

Common Adverse Reactions

Alcohol Dependence

Table 1 lists all treatment-emergent clinical adverse reactions, regardless of causality, occurring in ≥5% of patients with alcohol dependence, for which the incidence was greater in the combined VIVITROL group than in the placebo group. A majority of patients treated with VIVITROL in clinical studies had adverse reactions with a maximum intensity of "mild" or "moderate".

Table 1: Treatment-emergent Adverse Reactions (Reactions in ≥5% of patients with alcohol dependence treated with VIVITROL and occurring more frequently in the combined VIVITROL group than in the placebo group)

Body System	Adverse Reaction / Preferred Term	Placebo		Naltrexone for extended-release injectable suspension							
		N=214		400 mg N=25		380 mg N=205		190 mg N=210		All N=440	
		N	%	N	%	N	%	N	%	N	%
Gastrointestinal	Nausea	24	11	8	32	68	33	53	25	129	29

Body System	Adverse Reaction / Preferred Term	Placebo		Naltrexone for extended-release injectable suspension							
		N=214		400 mg N=25		380 mg N=205		190 mg N=210		All N=440	
		N	%	N	%	N	%	N	%	N	%
Disorders	Vomiting NOS	12	6	3	12	28	14	22	10	53	12
	Diarrhea[a)]	21	10	3	12	27	13	27	13	57	13
	Abdominal pain[b)]	17	8	4	16	23	11	23	11	50	11
	Dry Mouth	9	4	6	24	10	5	8	4	24	5
Infections & Infestations	Pharyngitis[c)]	23	11	0	0	22	11	35	17	57	13
Psychiatric Disorders	Insomnia, sleep disorder	25	12	2	8	29	14	27	13	58	13
	Anxiety[d)]	17	8	2	8	24	12	16	8	42	10
	Depression	9	4	0	0	17	8	7	3	24	5
General Disorders & Administration Site Conditions	Any ISR	106	50	22	88	142	69	121	58	285	65
	Injection site tenderness	83	39	18	72	92	45	89	42	199	45
	Injection site induration	18	8	7	28	71	35	52	25	130	30
	Injection site pain	16	7	0	0	34	17	22	10	56	13
	Other ISR (primarily nodules, swelling)	8	4	8	32	30	15	16	8	54	12
	Injection site pruritus	0	0	0	0	21	10	13	6	34	8
	Injection site ecchymosis	11	5	0	0	14	7	9	4	23	5
	Asthenic conditions[e)]	26	12	3	12	47	23	40	19	90	20
Musculoskeletal & Connective Tissue Disorders	Arthralgia, arthritis, joint stiffness	11	5	1	4	24	12	12	6	37	9
	Back pain, back stiffness	10	5	1	4	12	6	14	7	27	6
	Muscle cramps[f)]	3	1	0	0	16	8	5	2	21	5
Skin & Subcutaneous Tissue Disorders	Rash[g)]	8	4	3	12	12	6	10	5	25	6
Nervous System Disorders	Headache[h)]	39	18	9	36	51	25	34	16	94	21
	Dizziness, syncope	9	4	4	16	27	13	27	13	58	13
	Somnolence, sedation	2	1	3	12	8	4	9	4	20	5
Metabolism & Nutrition Disorders	Anorexia, appetite decreased NOS, appetite disorder NOS	6	3	5	20	30	14	13	6	48	11

a) Includes the preferred terms: diarrhea NOS; frequent bowel movements; gastrointestinal upset; loose stools

b) Includes the preferred terms: abdominal pain NOS; abdominal pain upper; stomach discomfort; abdominal pain lower
c) Includes the preferred terms: nasopharyngitis; pharyngitis streptococcal; pharyngitis NOS
d) Includes the preferred terms: anxiety NEC; anxiety aggravated; agitation; obsessive compulsive disorder; panic attack; nervousness; posttraumatic stress
e) Includes the preferred terms: malaise; fatigue (these two comprise the majority of cases); lethargy; sluggishness
f) Includes the preferred terms: muscle cramps; spasms; tightness; twitching; stiffness; rigidity
g) Includes the preferred terms: rash NOS; rash papular; heat rash
h) Includes the preferred terms: headache NOS; sinus headache; migraine; frequent headaches

Opioid Dependence

In the open-label, long-term safety study conducted in the US, the commonly reported adverse reactions among the opioid-dependent patients in the study were similar to those commonly observed events in the alcohol-dependent populations in VIVITROL clinical trials as displayed in Table 1, above. For example, injection site reactions of all types, nausea and diarrhea occurred in more than 5% of patients on VIVITROL in the open-label study. In contrast, 48% percent, of the opioid-dependent patients had at least one adverse event in the "Infections and Infestations" Body System. Adverse Reactions/Preferred Terms of nasopharyngitis, upper respiratory tract infection, urinary tract infection, and sinusitis were most commonly reported.

In the placebo-controlled study in opioid-dependent patients conducted in Russia, the overall frequency of adverse events was lower than in the U.S. population described above. Table 2 lists treatment-emergent clinical adverse events, regardless of causality, occurring in ≥2% of patients with opioid dependence, for which the incidence was greater in the VIVITROL group than in the placebo group. All adverse events were assessed as having a maximum intensity of "mild" or "moderate."

Table 2: Treatment-emergent Clinical Adverse Events (Events in ≥2% of patients with opioid dependence treated with VIVITROL and occurring more frequently in the VIVITROL group than in the placebo group)

Body System	Adverse Event / Preferred Term	Placebo N=124		VIVITROL 380 mg N=126	
		n	%	n	%
Investigations	Alanine aminotransferase increased	7	6	16	13
	Aspartate aminotransferase increased	3	2	13	10
	Gamma-glutamyltransferase increased	4	3	9	7
Infections and Infestations	Nasopharyngitis	3	2	9	7
	Influenza	5	4	6	5
Psychiatric Disorders	Insomnia	1	1	8	6
Vascular Disorders	Hypertension	4	3	6	5
General Disorders and Administration Site Conditions	Injection site pain	1	1	6	5
Gastrointestinal Disorders	Toothache	2	2	5	4
Nervous System Disorders	Headache	3	2	4	3

Laboratory Tests

Eosinophil Count:

In clinical trials, subjects on VIVITROL had increases in eosinophil counts relative to subjects on placebo. With continued use of VIVITROL, eosinophil counts returned to normal over a period of several months.

Platelet Count:

VIVITROL 380 mg was associated with a decrease in platelet count. In clinical trials, alcohol-dependent patients treated with VIVITROL experienced a mean maximal decrease in platelet count of 17.8 x 10^3/μL, compared to 2.6 x 10^3/μL in placebo patients.

After 24 weeks of treatment, opioid-dependent patients treated with VIVITROL experienced a mean maximal decrease in platelet count of 62.8 x 10^3/μL, compared to 39.9 x 10^3/μL in placebo patients. In randomized controlled trials, VIVITROL was not associated with an increase in bleeding-related adverse events.

Hepatic Enzyme Elevations:

In short-term, controlled trials, in alcohol-dependent patients, the incidence of AST elevations associated with VIVITROL treatment was similar to that observed with oral naltrexone treatment (1.5% each) and slightly higher than observed with placebo treatment (0.9%).

In the 6-month controlled trial conducted in opioid-dependent subjects, 89% had a baseline diagnosis of hepatitis C infection, and 41% had a baseline diagnosis of HIV infection. There were frequently observed elevated liver enzyme levels (ALT, AST, and GGT); these were more commonly reported as adverse events in the VIVITROL 380-mg group than in the placebo group. Patients could not enroll in this trial if they had a baseline ALT or AST value that was more than three times the upper limit of normal. More patients treated with VIVITROL in this study experienced treatment-emergent elevations in transaminases to more than three times the upper limit of normal than patients treated with placebo. Shifts to more than three times the upper limit of normal occurred in 20% of patients treated with VIVITROL as compared with 13% of placebo patients. Shifts in values of AST to more than three times the upper limit were also more common in the VIVITROL (14%) arm compared with the placebo (11%) arm. Opioid-dependent patients treated with VIVITROL experienced a mean maximal increase from baseline ALT levels of 61 IU/L compared with 48 IU/L in placebo patients. Similarly for AST, opioid-dependent patients treated with VIVITROL experienced a mean maximal increase from baseline AST levels of 40 IU/L compared with 31 IU/L in placebo patients.

Creatinine Phosphokinase:

In short-term controlled trials in alcohol-dependent patients, more patients treated with VIVITROL 380 mg (11%) and oral naltrexone (17%) shifted from normal creatinine phosphokinase (CPK) levels before treatment to abnormal CPK levels at the end of the trials, compared to placebo patients (8%). In open-label trials, 16% of patients dosed for more than 6 months had increases in CPK. For both the oral naltrexone and VIVITROL 380-mg groups, CPK abnormalities were most frequently in the range of 1–2 x ULN. However, there were

reports of CPK abnormalities as high as 4x ULN for the oral naltrexone group, and 35 x ULN for the VIVITROL 380-mg group. Overall, there were no differences between the placebo and naltrexone (oral or injectable) groups with respect to the proportions of patients with a CPK value at least three times the upper limit of normal. No factors other than naltrexone exposure were associated with the CPK elevations.

More opioid-dependent patients treated with VIVITROL 380-mg (39%) shifted from normal creatinine phosphokinase (CPK) levels before treatment to abnormal CPK levels during the study as compared to patients treated with placebo (32%). There were reports of CPK abnormalities as high as 41.8 x ULN for the placebo group, and 22.1 x ULN for the VIVITROL 380-mg group.

Other Events Observed During the VIVITROL Clinical Studies

The following is a list of treatment-emergent adverse reactions reported by alcohol- and/or opioid-dependent subjects treated with VIVITROL in all clinical trials. The listing does not include those events already listed in the previous tables or elsewhere in labeling, those events for which a drug cause was remote, those events that were so general as to be uninformative, and those events reported only once that did not have a substantial probability of being acutely life-threatening.

Blood and Lymphatic System Disorders – lymphadenopathy (including cervical adenitis), white blood cell count increased

Cardiac Disorders – angina pectoris, angina unstable, atrial fibrillation, cardiac failure congestive, coronary artery atherosclerosis, myocardial infarction, palpitations

Eye Disorders – conjunctivitis, vision blurred

Gastrointestinal Disorders – abdominal discomfort, colitis, constipation, flatulence, gastroesophageal reflux disease, gastrointestinal hemorrhage, hemorrhoids, pancreatitis acute, paralytic ileus, perirectal abscess

General Disorders and Administration Site Conditions – chest pain, chest tightness, chills, face edema, irritability, lethargy, pyrexia, rigors

Hepatobiliary Disorders – cholecystitis acute, cholelithiasis

Immune System Disorders – seasonal allergy, hypersensitivity reaction (including angioneurotic edema and urticaria)

Infections and Infestations – bronchitis, gastroenteritis, laryngitis, pneumonia, sinusitis, tooth abscess, upper respiratory tract infection, urinary tract infection, advanced HIV disease in HIV-infected patients

Investigations – weight decreased, weight increased

Metabolism and Nutrition Disorders – appetite increased, dehydration, heat exhaustion, hypercholesterolemia

Musculoskeletal and Connective Tissue Disorders –joint stiffness, muscle spasms, myalgia, pain in limb

Nervous System Disorders – cerebral arterial aneurysm, convulsions, disturbance in attention, dysgeusia, mental impairment, migraine, ischemic stroke, paresthesia

Pregnancy, Puerperium, and Perinatal Conditions – abortion missed

Psychiatric Disorders – abnormal dreams, agitation, alcohol withdrawal syndrome, euphoric mood, delirium, libido decreased

Respiratory, Thoracic, and Mediastinal Disorders – chronic obstructive pulmonary disease, dyspnea, pharyngolaryngeal pain, sinus congestion

Skin and Subcutaneous Tissue Disorders –night sweats, pruritus, sweating increased

Vascular Disorders –deep venous thrombosis, hot flushes, pulmonary embolism

6.2 Postmarketing Reports

Hypersensitivity Reactions including Anaphylaxis

Hypersensitivity reactions including anaphylaxis have been reported during postmarketing surveillance.

Reports From Other Intramuscular Drug Products Containing Polylactide-co-glycolide (PLG) Microspheres

Retinal Artery Occlusion

Retinal artery occlusion after injection with another drug product containing polylactide-co-glycolide (PLG) microspheres has been reported very rarely during postmarketing surveillance. This event has been reported in the presence of abnormal arteriovenous anastomosis. No cases of retinal artery occlusion have been reported during VIVITROL clinical trials or postmarketing surveillance. VIVITROL should be administered by intramuscular (IM) injection into the gluteal muscle, and care must be taken to avoid inadvertent injection into a blood vessel *[see Dosage and Administration (2)]*.

7 DRUG INTERACTIONS

Patients taking VIVITROL may not benefit from opioid-containing medicines. Naltrexone antagonizes the effects of opioid-containing medicines, such as cough and cold remedies, antidiarrheal preparations and opioid analgesics.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

There are no adequate and well-controlled studies of either naltrexone or VIVITROL in pregnant women. VIVITROL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnancy Category C: Reproduction and developmental studies have not been conducted for VIVITROL. Studies with naltrexone administered via the oral route have been conducted in pregnant rats and rabbits.

Teratogenic Effects: Naltrexone has been shown to increase the incidence of early fetal loss when given to rats at doses ≥30 mg/kg/day (11 times the human exposure based on an $AUC_{(0\text{-}28d)}$ comparison) and to rabbits at oral doses ≥60 mg/kg/day (2 times the human exposure based on an $AUC_{(0\text{-}28d)}$ comparison).

There was no evidence of teratogenicity when naltrexone was administered orally to rats and rabbits during the period of major organogenesis at doses up to 200 mg/kg/day (175- and 14-times the human exposure based on an $AUC_{(0\text{-}28d)}$ comparison, respectively).

8.2 Labor and Delivery

The potential effect of VIVITROL on duration of labor and delivery in humans is unknown.

8.3 Nursing Mothers

Transfer of naltrexone and 6β-naltrexol into human milk has been reported with oral naltrexone. Because of the potential for tumorigenicity shown for naltrexone in animal studies, and because of the potential for serious adverse reactions in nursing infants from VIVITROL, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and efficacy of VIVITROL have not been established in the pediatric population. The pharmacokinetics of VIVITROL have not been evaluated in a pediatric population.

8.5 Geriatric Use

In trials of alcohol-dependent subjects, 2.6% (n=26) of subjects were >65 years of age, and one patient was >75 years of age. Clinical studies of VIVITROL did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects. No subjects over age 65 were included in studies of opioid-dependent subjects. The pharmacokinetics of VIVITROL have not been evaluated in the geriatric population.

8.6 Renal Impairment

Pharmacokinetics of VIVITROL are not altered in subjects with mild renal insufficiency (creatinine clearance of 50-80 mL/min). Dose adjustment is not required in patients with mild renal impairment. VIVITROL pharmacokinetics have not been evaluated in subjects with moderate and severe renal insufficiency. Because naltrexone and its primary metabolite are excreted primarily in the urine, caution is recommended in administering VIVITROL to patients with moderate to severe renal impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

The pharmacokinetics of VIVITROL are not altered in subjects with mild to moderate hepatic impairment (Groups A and B of the Child-Pugh classification). Dose adjustment is not required in subjects with mild or moderate hepatic impairment. VIVITROL pharmacokinetics were not evaluated in subjects with severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

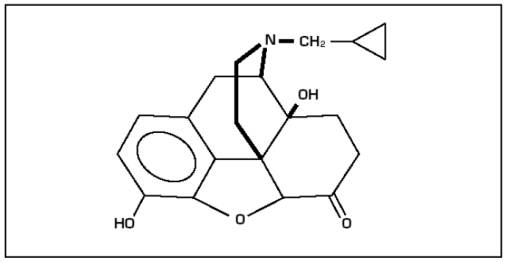
There is limited experience with overdose of VIVITROL. Single doses up to 784 mg were administered to 5 healthy subjects. There were no serious or severe adverse events. The most common effects were injection site reactions, nausea, abdominal pain, somnolence, and dizziness. There were no significant increases in hepatic enzymes.

In the event of an overdose, appropriate supportive treatment should be initiated.

11 DESCRIPTION

VIVITROL® (naltrexone for extended-release injectable suspension) is supplied as a microsphere formulation of naltrexone for suspension, to be administered by intramuscular injection. Naltrexone is an opioid antagonist with little, if any, opioid agonist activity.

Naltrexone is designated chemically as morphinan-6-one, 17 (cyclopropylmethyl) 4,5-epoxy-3,14-dihydroxy-(5α) (CAS Registry # 16590-41-3). The molecular formula is $C_{20}H_{23}NO_4$ and its molecular weight is 341.41 in the anhydrous form (ie, < 1% maximum water content). The structural formula is:



Naltrexone base anhydrous is an off-white to a light tan powder with a melting point of 168-170ºC (334-338ºF). It is insoluble in water and is soluble in ethanol.

VIVITROL is provided as a carton containing a vial each of VIVITROL microspheres and diluent, one 5-mL syringe, one 1-inch 20-gauge preparation needle, two 1.5-inch 20-gauge and two 2-inch 20-gauge administration needles with needle protection device.

VIVITROL microspheres consist of a sterile, off-white to light tan powder that is available in a dosage strength of 380 mg of naltrexone per vial. Naltrexone is incorporated in 75:25

polylactide-co-glycolide (PLG) at a concentration of 337 mg of naltrexone per gram of microspheres.

The diluent is a clear, colorless solution. The composition of the diluent includes carboxymethylcellulose sodium salt, polysorbate 20, sodium chloride, and water for injection. The microspheres must be suspended in the diluent prior to injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of action

Naltrexone is an opioid antagonist with highest affinity for the mu opioid receptor. Naltrexone has little or no opioid agonist activity.

Naltrexone has few, if any, intrinsic actions besides its opioid blocking properties. However, it does produce some pupillary constriction, by an unknown mechanism.

12.2 Pharmacodynamics

The administration of VIVITROL is not associated with the development of tolerance or dependence. In subjects physically dependent on opioids, VIVITROL will precipitate withdrawal symptomatology.

Occupation of opioid receptors by naltrexone may block the effects of endogenous opioid peptides. It markedly attenuates or completely blocks, reversibly, the subjective effects of exogenous opioids. The neurobiological mechanisms responsible for the reduction in alcohol consumption observed in alcohol-dependent patients treated with naltrexone are not entirely understood. However, involvement of the endogenous opioid system is suggested by preclinical data.

Naltrexone blocks the effects of opioids by competitive binding at opioid receptors. This makes the blockade produced potentially surmountable, but overcoming full naltrexone blockade by administration of opioids may result in non-opioid receptor-mediated symptoms such as histamine release.

VIVITROL is not aversive therapy and does not cause a disulfiram-like reaction either as a result of opiate use or ethanol ingestion.

12.3 Pharmacokinetics

Absorption

VIVITROL is an extended-release, microsphere formulation of naltrexone designed to be administered by intramuscular (IM) gluteal injection every 4 weeks or once a month. After IM injection, the naltrexone plasma concentration time profile is characterized by a transient initial peak, which occurs approximately 2 hours after injection, followed by a second peak observed approximately 2-3 days later. Beginning approximately 14 days after dosing, concentrations slowly decline, with measurable levels for greater than 1 month.

Maximum plasma concentration (C_{max}) and area under the curve (AUC) for naltrexone and 6β-naltrexol (the major metabolite) following VIVITROL administration are dose proportional. Compared to daily oral dosing with naltrexone 50 mg over 28 days, total naltrexone exposure is 3 to 4-fold higher following administration of a single dose of VIVITROL 380 mg. Steady state is reached at the end of the dosing interval following the first injection. There is minimal accumulation (<15%) of naltrexone or 6β-naltrexol upon repeat administration of VIVITROL.

Distribution

In vitro data demonstrate that naltrexone plasma protein binding is low (21%).

Metabolism

Naltrexone is extensively metabolized in humans. Production of the primary metabolite, 6β-naltrexol, is mediated by dihydrodiol dehydrogenase, a cytosolic family of enzymes. The cytochrome P450 system is not involved in naltrexone metabolism. Two other minor metabolites are 2-hydroxy-3-methoxy-6β-naltrexol and 2-hydroxy-3-methoxy-naltrexone. Naltrexone and its metabolites are also conjugated to form glucuronide products.

Significantly less 6β-naltrexol is generated following IM administration of VIVITROL compared to administration of oral naltrexone due to a reduction in first-pass hepatic metabolism.

Elimination

Elimination of naltrexone and its metabolites occurs primarily via urine, with minimal excretion of unchanged naltrexone.

The elimination half life of naltrexone following VIVITROL administration is 5-10 days and is dependent on the erosion of the polymer. The elimination half life of 6β-naltrexol following VIVITROL administration is 5-10 days.

Special Populations

Pediatric: Pharmacokinetics of VIVITROL have not been evaluated in a pediatric population.

Geriatric: Pharmacokinetics of VIVITROL have not been evaluated in the geriatric population *[see Use in Specific Populations (8.5)]*.

Race: Effect of race on the pharmacokinetics of VIVITROL has not been studied.

Gender: In a study in healthy subjects (n=18 females and 18 males), gender did not influence the pharmacokinetics of VIVITROL.

Renal Insufficiency: A population pharmacokinetic analysis indicated mild renal insufficiency (creatinine clearance of 50-80 mL/min) had little or no influence on VIVITROL pharmacokinetics and that no dosage adjustment is necessary. VIVITROL pharmacokinetics have not been evaluated in subjects with moderate and severe renal insufficiency *[see Use in Specific Populations (8.6)]*.

Hepatic Insufficiency: The pharmacokinetics of VIVITROL are not altered in subjects with mild to moderate hepatic impairment (Groups A and B of the Child-Pugh classification). VIVITROL pharmacokinetics were not evaluated in subjects with severe hepatic impairment *[see Use in Specific Populations (8.7)]*.

Drug Interactions

In vitro Studies: Because naltrexone is not a substrate for CYP drug metabolizing enzymes, inducers or inhibitors of these enzymes are unlikely to change the clearance of VIVITROL. An in vitro CYP inhibition study demonstrated that naltrexone is not an inhibitor of major CYP enzymes (CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4). An in vitro CYP induction study demonstrated that naltrexone is not an inducer of CYP3A4 and CYP1A2.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Carcinogenicity studies have not been conducted with VIVITROL.

Carcinogenicity studies of oral naltrexone hydrochloride (administered via the diet) have been conducted in rats and mice.

In a two-year carcinogenicity study in rats, there were small increases in the numbers of testicular mesotheliomas in males and tumors of vascular origin in males and females. The incidence of testicular mesothelioma in males given naltrexone at a dietary dose of 100 mg/kg/day (3-times the human exposure based on an $AUC_{(0\text{-}28d)}$ comparison) was 6%, compared with a maximum historical incidence of 4%. The incidence of vascular tumors in males and females given dietary doses of 100 mg/kg/day was 4% but only the incidence in females was increased compared with a maximum historical control incidence of 2% (3 and 32 times the human exposure based on an $AUC_{(0\text{-}28d)}$ comparison in males and females, respectively). There was no evidence of carcinogenicity in a 2-year dietary study with naltrexone in male and female mice (12 and 3 times the human exposure based on an $AUC_{(0\text{-}28d)}$ comparison, respectively). The clinical significance of these findings is not known.

Mutagenesis: Naltrexone was negative in the following in vitro genotoxicity studies: bacterial reverse mutation assay (Ames test), the heritable translocation assay, CHO cell sister chromatid exchange assay, and the mouse lymphoma gene mutation assay. Naltrexone was also negative in an in vivo mouse micronucleus assay. In contrast, naltrexone tested positive in the following assays: Drosophila recessive lethal frequency assay, non-specific DNA damage in repair tests with E. coli and WI-38 cells, and urinalysis for methylated histidine residues.

Impairment of Fertility: Naltrexone given via oral gavage caused a significant increase in pseudopregnancy and a decrease in pregnancy rates in rats at 100 mg/kg/day (75 times the human exposure based on an $AUC_{(0\text{-}28d)}$ comparison). There was no effect on male fertility at this dose level (6 times the human exposure based on an $AUC_{(0\text{-}28d)}$ comparison). The relevance of these observations to human fertility is not known.

14 CLINICAL STUDIES

Alcohol Dependence

The efficacy of VIVITROL in the treatment of alcohol dependence was evaluated in a 24-week, placebo-controlled, multi-center, double-blind, randomized trial of alcohol-dependent (DSM-IV

criteria) outpatients. Subjects were treated with an injection every 4 weeks of VIVITROL 190 mg, VIVITROL 380 mg or placebo. Oral naltrexone was not administered prior to the initial or subsequent injections of study medication. Psychosocial support was provided to all subjects in addition to medication.

Subjects treated with VIVITROL 380 mg demonstrated a greater reduction in days of heavy drinking than those treated with placebo. Heavy drinking was defined as self-report of 5 or more standard drinks consumed on a given day for male patients and 4 or more drinks for female patients. Among the subset of patients (n=53, 8% of the total study population) who abstained completely from drinking during the week prior to the first dose of medication, compared with placebo-treated patients, those treated with VIVITROL 380 mg had greater reductions in the number of drinking days and the number of heavy drinking days. In this subset, patients treated with VIVITROL were also more likely than placebo-treated patients to maintain complete abstinence throughout treatment. The same treatment effects were not evident among the subset of patients (n=571, 92% of the total study population) who were actively drinking at the time of treatment initiation.

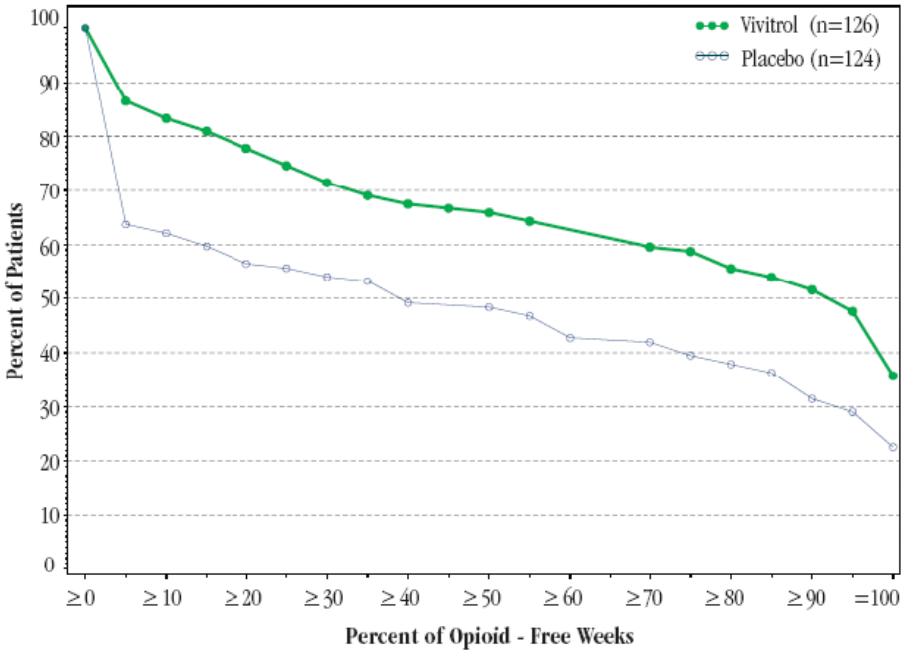
Opioid Dependence

The efficacy of VIVITROL in the treatment of opioid dependence was evaluated in a 24-week, placebo-controlled, multi-center, double-blind, randomized trial of opioid-dependent (DSM-IV) outpatients, who were completing or had recently completed detoxification. Subjects were treated with an injection every 4 weeks of VIVITROL 380 mg or placebo. Oral naltrexone was not administered prior to the initial or subsequent injections of study medication. Standardized, manual-based psychosocial support was provided on a biweekly basis to all subjects in addition to medication.

Figure 1, below, displays the cumulative percentage of subjects with opioid-free weeks ranging from no visits (0%) to all visits (100%). An opioid-free week was one in which urine drug test results were negative for opioids and self-reported opioid use was also zero. An initial period of engagement in treatment was permitted during which opiate use, if it occurred, was not considered in the analysis. Subjects discontinuing from the trial were assumed to have had opioid-use weeks for the weeks after dropout.

The cumulative percentage of subjects achieving each observed percentage of opioid-free weeks was greater in the VIVITROL group compared to the placebo group. Complete abstinence (opioid-free at all weekly visits) was sustained by 23% of subjects in the placebo group compared with 36% of subjects in the VIVITROL group from Week 5 to Week 24.

Figure 1: Subjects Sustaining Varying Percentages of Opioid-Free Weeks



A greater percentage of subjects in the VIVITROL group remained in the study compared to the placebo group.

16 HOW SUPPLIED/STORAGE AND HANDLING

VIVITROL (naltrexone for extended-release injectable suspension) is supplied in single-use cartons. Each carton contains one 380-mg vial of VIVITROL microspheres, one vial containing 4 mL (to deliver 3.4 mL) of diluent for the suspension of VIVITROL, one 5-mL prepackaged syringe, one 1-inch 20-gauge needle, two 1.5-inch 20-gauge needles and two 2-inch 20-gauge needles with needle protection devices: NDC 65757-300-01.

16.1 Storage and Handling

The entire dose pack should be stored in the refrigerator (2 - 8°C, 36 - 46°F). Unrefrigerated, VIVITROL can be stored at temperatures not exceeding 25°C (77°F) for no more than 7 days prior to administration. Do not expose the product to temperatures above 25°C (77°F). VIVITROL should not be frozen.

Parenteral products should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit. A properly mixed suspension will be

milky white, will not contain clumps, and will move freely down the wall of the vial *[see Dosage and Administration (2.3)]*.

Keep out of Reach of Children.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Medication Guide.

17.1 Patient Information

Physicians should include the following issues in discussions with patients for whom they prescribe VIVITROL:

- Advise patients that if they previously used opioids, they may be more sensitive to lower doses of opioids and at risk of accidental overdose should they use opioids when their next dose is due, if they miss a dose, or after VIVITROL treatment is discontinued. It is important that patients inform family members and the people closest to the patient of this increased sensitivity to opioids and the risk of overdose.
- Advise patients that because VIVITROL can block the effects of opioids, patients will not perceive any effect if they attempt to self-administer heroin or any other opioid drug in small doses while on VIVITROL. Further, emphasize that administration of large doses of heroin or any other opioid to try to bypass the blockade and get high while on VIVITROL may lead to serious injury, coma, or death.
- Patients on VIVITROL may not experience the expected effects from opioid-containing analgesic, antidiarrheal, or antitussive medications.
- Advise patients that a reaction at the site of VIVITROL injection may occur. Reactions include pain, tenderness, induration, swelling, erythema, bruising, or pruritus. Serious injection site reactions including necrosis may occur. Some of these injection site reactions have required surgery. Patients should receive their injection from a healthcare provider qualified to administer the injection. Patients should be advised to seek medical attention for worsening skin reactions.
- Advise patients that they should be off all opioids, including opioid-containing medicines, for a minimum of 7 – 10 days before starting VIVITROL in order to avoid precipitation of opioid withdrawal. Patients transitioning from buprenorphine or methadone may be vulnerable to precipitation of withdrawal symptoms for as long as two weeks. Ensure that patients understand that withdrawal precipitated by administration of an opioid antagonist may be severe enough to require hospitalization if they have not been opioid-free for an adequate period of time, and is different from the experience of spontaneous withdrawal that occurs with discontinuation of opioid in a dependent individual. Advise patients that they should not take VIVITROL if they have any symptoms of opioid withdrawal. Advise all patients, including those with alcohol dependence, that it is imperative to notify

healthcare providers of any recent use of opioids or any history of opioid dependence before starting VIVITROL to avoid precipitation of opioid withdrawal.

- Advise patients that VIVITROL may cause liver injury. Patients should immediately notify their physician if they develop symptoms and/or signs of liver disease.
- Advise patients that they may experience depression while taking VIVITROL. It is important that patients inform family members and the people closest to the patient that they are taking VIVITROL and that they should call a doctor right away should they become depressed or experience symptoms of depression.
- Advise patients to carry documentation to alert medical personnel to the fact that they are taking VIVITROL (naltrexone for extended-release injectable suspension). This will help to ensure that patients obtain adequate medical treatment in an emergency.
- Advise patients that VIVITROL may cause an allergic pneumonia. Patients should immediately notify their physician if they develop signs and symptoms of pneumonia, including dyspnea, coughing, or wheezing.
- Advise patients that they should not take VIVITROL if they are allergic to VIVITROL or any of the microsphere or diluent components.
- Advise patients that they may experience nausea following the initial injection of VIVITROL. These episodes of nausea tend to be mild and subside within a few days post-injection. Patients are less likely to experience nausea in subsequent injections. Patients should be advised that they may also experience tiredness, headache, vomiting, decreased appetite, painful joints and muscle cramps.
- Advise patients that because VIVITROL is an intramuscular injection and not an implanted device, once VIVITROL is injected, it is not possible to remove it from the body.
- Advise patients that VIVITROL has been shown to treat alcohol and opioid dependence only when used as part of a treatment program that includes counseling and support.
- Advise patients that dizziness may occur with VIVITROL treatment, and they should avoid driving or operating heavy machinery until they have determined how VIVITROL affects them.
- Advise patients to notify their physician if they:
  - become pregnant or intend to become pregnant during treatment with VIVITROL.
  - are breast-feeding.
  - experience respiratory symptoms such as dyspnea, coughing, or wheezing when taking VIVITROL.
  - experience any allergic reactions when taking VIVITROL.
  - experience other unusual or significant side effects while on VIVITROL therapy.

27

Reference ID: 3348450

- Patients should be advised of any other risks and information based on the clinical judgment of their physician.

US Patent Nos. 5,792,477; 5,916,598; 6,194,006; 6,264,987; 6,331,317; 6,379,703; 6,379,704; 6,395,304; 6,403,114; 6,495,166; 6,534,092; 6,537,586; 6,596,316; 6,713,090; 6,667,061; 6,495,164; 6,939,033;5,650,173; 5,654,008; 6,540,393; 6,705,757; 6,861,016

17.2 Frequently Asked Questions About Administering VIVITROL:

1. **Can I prepare the suspension prior to my patient's arrival?**

   No. You may remove the carton from the refrigerator prior to the patient's arrival, but once the diluent is added to the VIVITROL microspheres, the dose should be mixed and the suspension administered immediately. It is very important to use proper aseptic technique when preparing the suspension *[see Dosage and Administration (2.4)]*.

2. **How much time do I have between preparing and administering the dose?**

   It is recommended that the suspension be administered *immediately* once the product has been suspended and transferred into the syringe. If a few minutes' delay occurs after suspension but before transfer into the syringe *[see Dosage and Administration (2.4; Figure D)]*, the vial can be inverted a few times to resuspend and then transferred into the syringe for immediate use *[see Dosage and Administration (2.4)]*.

3. **Can I use needles other than those provided in the carton?**

   No. The needles in the carton are specially designed for administration of VIVITROL. Do not make any substitutions for components of the carton *[see Dosage and Administration (2.4)]*.

4. **The suspension is milky white upon mixing with the diluent. Is this normal?**

   Yes. VIVITROL microspheres will form a milky suspension when mixed with the provided diluent *[see Dosage and Administration (2.4)]*.

5. **What if a needle clog occurs during administration of the product?**

   If a clog occurs during administration, the needle should be withdrawn from the patient, capped with the attached needle protection device, and replaced with the spare administration needle. Gently push on the plunger until a bead of the suspension appears at the tip of the needle. The remainder of the suspension should then be administered into an adjacent site in the same gluteal region *[see Dosage and Administration (2.4)]*.

For additional information, visit www.vivitrol.com or call 1-800-848-4876

Manufactured and marketed by:

Alkermes, Inc.

852 Winter Street

Waltham, MA 02451-1420

Printed in U.S.A.

REV: July 2013

29

Reference ID: 3348450

APPENDIX D – BUP-NX

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SUBOXONE safely and effectively. See full prescribing information for SUBOXONE.
SUBOXONE® (buprenorphine and naloxone) sublingual film for sublingual administration CIII
Initial U.S. Approval: 2002

----------RECENT MAJOR CHANGES----------

Dosage and Administration, Induction (2.1)	04/2014
Dosage and Administration, Patients With Hepatic Impairment (2.5)	04/2014
Warnings and Precautions, Use in Patients With Impaired Hepatic Function (5.11)	04/2014

----------INDICATIONS AND USAGE----------

SUBOXONE sublingual film is a partial-opioid agonist indicated for treatment of opioid dependence. Prescription use of this product is limited under the Drug Addiction Treatment Act. (1)

----------DOSAGE AND ADMINISTRATION----------

- For patients dependent on short-acting opioid products who are in opioid withdrawal; on Day 1, administer up to 8 mg/ 2 mg SUBOXONE sublingual film (in divided doses). On Day 2, administer up to 16 mg/4 mg of SUBOXONE sublingual film as a single dose. (2.1)
- For patients dependent on methadone or long-acting opioid products, induction onto sublingual buprenorphine monotherapy is recommended on Days 1 and 2 of treatment. (2.1)
- For maintenance treatment, the target dosage of SUBOXONE sublingual film is usually 16 mg/4 mg as a single daily dose. (2.2)
- Place the SUBOXONE sublingual film under the tongue, close to the base on the left or right side and allow to completely dissolve. Film should not be chewed, swallowed, or moved after placement. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Sublingual film: 2 mg buprenorphine with 0.5 mg naloxone, 4 mg buprenorphine with 1 mg naloxone, 8 mg buprenorphine with 2 mg naloxone and 12 mg buprenorphine with 3 mg naloxone. (3)

----------CONTRAINDICATIONS----------

Hypersensitivity to buprenorphine or naloxone. (4)

----------WARNINGS AND PRECAUTIONS----------

- Buprenorphine can be abused in a similar manner to other opioids. Clinical monitoring appropriate to the patient's level of stability is essential. Multiple refills should not be prescribed early in treatment or without appropriate patient follow-up visits. (5.1)
- Significant respiratory depression and death have occurred in association with buprenorphine, particularly when taken by the intravenous (IV) route in combination with benzodiazepines or other CNS depressants (including alcohol). (5.2)
- Consider dose reduction of CNS depressants, SUBOXONE sublingual film, or both in situations of concomitant prescription. (5.3)
- Store SUBOXONE sublingual film safely out of the sight and reach of children. Buprenorphine can cause severe, possibly fatal, respiratory depression in children. (5.4)
- Chronic administration produces opioid-type physical dependence. Abrupt discontinuation or rapid dose taper may result in opioid withdrawal syndrome. (5.5)
- Monitor liver function tests prior to initiation and during treatment and evaluate suspected hepatic events. (5.6)
- Do not administer SUBOXONE sublingual film to patients with known hypersensitivity to buprenorphine or naloxone. (5.7)
- An opioid withdrawal syndrome is likely to occur with parenteral misuse of SUBOXONE sublingual film by individuals physically dependent on full opioid agonists or by sublingual administration before the agonist effects of other opioids have subsided. (5.8)
- Neonatal withdrawal has been reported following use of buprenorphine by the mother during pregnancy. (5.9)
- SUBOXONE sublingual film is not appropriate as an analgesic. There have been reported deaths of opioid naïve individuals who received a 2 mg sublingual dose. (5.10)
- Buprenorphine/naloxone products are not recommended in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment (5.11)
- Caution patients about the risk of driving or operating hazardous machinery. (5.12)

----------ADVERSE REACTIONS----------

Adverse events commonly observed with the sublingual administration of the SUBOXONE sublingual film were oral hypoesthesia, glossodynia, oral mucosal erythema, headache, nausea, vomiting, hyperhidrosis, constipation, signs and symptoms of withdrawal, insomnia, pain, and peripheral edema. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Reckitt Benckiser Pharmaceuticals Inc. at 1-877-782-6966 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Monitor patients starting or ending CYP3A4 inhibitors or inducers for potential over or under dosing. (7.1)
- Use caution in prescribing SUBOXONE sublingual film for patients receiving benzodiazepines or other CNS depressants and warn patients against concomitant self-administration/misuse. (7.3)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Nursing mothers: Caution should be exercised when administered to a nursing woman. (8.3)
- Safety and effectiveness of SUBOXONE sublingual film in patients below the age of 16 has not been established. (8.4)
- Administer SUBOXONE sublingual film with caution to elderly or debilitated patients. (8.5)
- Buprenorphine/naloxone products are not recommended in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: April 2014

Reference ID: 3496928

FULL PRESCRIBING INFORMATION: CONTENTS*

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

Reference ID: 3496928

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SUBOXONE sublingual film is indicated for treatment of opioid dependence and should be used as part of a complete treatment plan to include counseling and psychosocial support.

Under the Drug Addiction Treatment Act (DATA) codified at 21 U.S.C. 823(g), prescription use of this product in the treatment of opioid dependence is limited to physicians who meet certain qualifying requirements, and who have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence and have been assigned a unique identification number that must be included on every prescription.

2 DOSAGE AND ADMINISTRATION

2.1 Induction

Prior to induction, consideration should be given to the type of opioid dependence (i.e., long- or short-acting opioid products), the time since last opioid use, and the degree or level of opioid dependence. To avoid precipitating an opioid withdrawal syndrome, the first dose of buprenorphine/naloxone should be started only when objective signs of moderate withdrawal appear.

On Day 1, an induction dosage of up to 8 mg /2 mg SUBOXONE sublingual film is recommended. Clinicians should start with an initial dose of 2 mg/ 0.5 mg or 4 mg/1 mg buprenorphine/naloxone and may titrate upwards in 2 or 4 mg increments of buprenorphine, at approximately 2-hour intervals, under supervision, to 8 mg/2 mg buprenorphine/naloxone based on the control of acute withdrawal symptoms.

On Day 2, a single daily dose of up to 16 mg/4 mg SUBOXONE sublingual film is recommended.

Medication should be prescribed in consideration of the frequency of visits. Provision of multiple refills is not advised early in treatment or without appropriate patient follow-up visits.

Patients dependent on methadone or long-acting opioid products

Patients dependent upon methadone or long-acting opioid products may be more susceptible to precipitated and prolonged withdrawal during induction than those on short-acting opioid products. Buprenorphine/naloxone combination products have not been evaluated in adequate and well-controlled studies for induction in patients on long-acting opioid products, and contain naloxone, which is absorbed in small amounts by the sublingual route and could cause worse precipitated and prolonged withdrawal. For this reason, **buprenorphine monotherapy is recommended in patients taking long-acting opioids when used according to approved administration instructions.** Following induction, the patient may then be transitioned to once-daily SUBOXONE sublingual film.

Patients dependent on heroin or other short-acting opioid products

Patients dependent on heroin or short-acting opioid products may be inducted with either SUBOXONE sublingual film or with sublingual buprenorphine monotherapy. The first dose of SUBOXONE sublingual film or buprenorphine should be administered when objective signs of moderate opioid withdrawal appear, and not less than 6 hours after the patient last used an opioid.

It is recommended that an adequate maintenance dose, titrated to clinical effectiveness, be achieved as rapidly as possible. In some studies, a too-gradual induction over several days led to a high rate of drop-out of buprenorphine patients during the induction period.

Reference ID: 3496928

2.2 Maintenance

The dosage of SUBOXONE sublingual film from Day 3 onwards should be progressively adjusted in increments/decrements of 2 mg/0.5 mg or 4 mg/1 mg buprenorphine/naloxone to a level that holds the patient in treatment and suppresses opioid withdrawal signs and symptoms.

After treatment induction and stabilization, the maintenance dose of SUBOXONE sublingual film is generally in the range of 4 mg/1 mg buprenorphine/naloxone to 24 mg/6 mg buprenorphine/naloxone per day depending on the individual patient and clinical response. The recommended target dosage of SUBOXONE sublingual film during maintenance is 16 mg/4 mg buprenorphine/naloxone/day as a single daily dose. Dosages higher than 24 mg/6 mg daily have not been demonstrated to provide a clinical advantage.

2.3 Method of Administration

Do not cut, chew, or swallow SUBOXONE sublingual film. Place the SUBOXONE sublingual film under the tongue, close to the base on the left or right side. If an additional sublingual film is necessary to achieve the prescribed dose, place the additional sublingual film sublingually on the opposite side from the first film. Place the sublingual film in a manner to minimize overlapping as much as possible. The sublingual film must be kept under the tongue until the film is completely dissolved. **SUBOXONE sublingual film should NOT be moved after placement. Proper administration technique should be demonstrated to the patient.**

2.4 Clinical Supervision

Treatment should be initiated with supervised administration, progressing to unsupervised administration as the patient's clinical stability permits. SUBOXONE sublingual film is subject to diversion and abuse. When determining the prescription quantity for unsupervised administration, consider the patient's level of stability, the security of his or her home situation, and other factors likely to affect the ability to manage supplies of take-home medication.

Ideally patients should be seen at reasonable intervals (e.g., at least weekly during the first month of treatment) based upon the individual circumstances of the patient. Medication should be prescribed in consideration of the frequency of visits. Provision of multiple refills is not advised early in treatment or without appropriate patient follow-up visits. Periodic assessment is necessary to determine compliance with the dosing regimen, effectiveness of the treatment plan, and overall patient progress.

Once a stable dosage has been achieved and patient assessment (e.g., urine drug screening) does not indicate illicit drug use, less frequent follow-up visits may be appropriate. A once-monthly visit schedule may be reasonable for patients on a stable dosage of medication who are making progress toward their treatment objectives. Continuation or modification of pharmacotherapy should be based on the physician's evaluation of treatment outcomes and objectives such as:

1. Absence of medication toxicity.
2. Absence of medical or behavioral adverse effects.
3. Responsible handling of medications by the patient.
4. Patient's compliance with all elements of the treatment plan (including recovery-oriented activities, psychotherapy, and/or other psychosocial modalities).
5. Abstinence from illicit drug use (including problematic alcohol and/or benzodiazepine use).

Reference ID: 3496928

If treatment goals are not being achieved, the physician should re-evaluate the appropriateness of continuing the current treatment.

2.5 Patients With Hepatic Impairment

Because the doses of this fixed combination product cannot be individually titrated, severe hepatic impairment results in a reduced clearance of naloxone to a much greater extent than buprenorphine, and moderate hepatic impairment also results in a reduced clearance of naloxone to a greater extent than buprenorphine, the combination product should generally be avoided in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment *[see Warnings and Precautions (5.11)]*.

2.6 Unstable Patients

Physicians will need to decide when they cannot appropriately provide further management for particular patients. For example, some patients may be abusing or dependent on various drugs, or unresponsive to psychosocial intervention such that the physician does not feel that he/she has the expertise to manage the patient. In such cases, the physician may want to assess whether to refer the patient to a specialist or more intensive behavioral treatment environment. Decisions should be based on a treatment plan established and agreed upon with the patient at the beginning of treatment.

Patients who continue to misuse, abuse, or divert buprenorphine products or other opioids should be provided with, or referred to, more intensive and structured treatment.

2.7 Stopping Treatment

The decision to discontinue therapy with SUBOXONE sublingual film after a period of maintenance should be made as part of a comprehensive treatment plan. Taper patients to avoid opioid withdrawal signs and symptoms.

2.8 Switching Between Buprenorphine or Buprenorphine and Naloxone Sublingual Tablets and SUBOXONE Sublingual Film

Patients being switched between buprenorphine and naloxone or buprenorphine only sublingual tablets and SUBOXONE sublingual film should be started on the corresponding dosage of the previously administered product. However, dosage adjustments may be necessary when switching between products. Not all strengths and combinations of the SUBOXONE sublingual films are bioequivalent to the SUBOXONE (buprenorphine and naloxone) sublingual tablets as observed in pharmacokinetic studies *[see Clinical Pharmacology (12.3)]*. Therefore, systemic exposures of buprenorphine and naloxone may be different when patients are switched from tablets to film or vice-versa. Patients should be monitored for symptoms related to over-dosing or under-dosing.

2.9 Switching Between SUBOXONE Sublingual Film Strengths

As indicated in Table 1, the sizes and the compositions of the four units of SUBOXONE sublingual films, i.e., 2 mg/0.5 mg, 4 mg/1 mg, 8 mg/2 mg and the 12 mg/3 mg units, are different from one another. If patients switch between various combinations of lower and higher strength units of SUBOXONE sublingual films to obtain the same total dose, (e.g., from three 4 mg/1 mg units to a single 12 mg/3 mg unit, or vice-versa), systemic exposures of buprenorphine and naloxone may be different and patients should be monitored for over-dosing or under-dosing. For this reason, pharmacist should not substitute one or more film strengths for another without approval of the prescriber.

Table 1. Comparison of Available SUBOXONE Sublingual Film Strengths by Dimensions and Drug Concentrations.

Reference ID: 3496928

SUBOXONE sublingual film unit strength (buprenorphine/naloxone)	SUBOXONE sublingual film unit dimensions	Buprenorphine Concentration % (w/w)	Naloxone Concentration % (w/w)
2 mg/0.5 mg	22.0 mm x 12.8 mm	5.4	1.53
4 mg/1 mg (2 times the length of the 2 mg/0.5 mg unit)	22.0 mm x 25.6 mm	5.4	1.53
8 mg/2 mg	22.0 mm x 12.8 mm	17.2	4.88
12 mg/3 mg (1.5 times the length of the 8 mg/2 mg unit)	22 mm X 19.2 mm	17.2	4.88

3 DOSAGE FORMS AND STRENGTHS

SUBOXONE sublingual film is supplied as an orange rectangular sublingual film with a white printed logo in four dosage strengths:

- buprenorphine/naloxone 2 mg/0.5 mg,
- buprenorphine/naloxone 4 mg/1 mg,
- buprenorphine/naloxone 8 mg/2 mg and
- buprenorphine/naloxone 12 mg/3 mg

4 CONTRAINDICATIONS

SUBOXONE sublingual film should not be administered to patients who have been shown to be hypersensitive to buprenorphine or naloxone as serious adverse reactions, including anaphylactic shock, have been reported *[see Warnings and Precautions (5.7)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Abuse Potential

Buprenorphine can be abused in a manner similar to other opioids, legal or illicit. Prescribe and dispense buprenorphine with appropriate precautions to minimize risk of misuse, abuse, or diversion, and ensure appropriate protection from theft, including in the home. Clinical monitoring appropriate to the patient's level of stability is essential. Multiple refills should not be prescribed early in treatment or without appropriate patient follow-up visits *[see Drug Abuse and Dependence (9.2)]*.

5.2 Respiratory Depression

Buprenorphine, particularly when taken by the IV route, in combination with benzodiazepines or other CNS depressants (including alcohol), has been associated with significant respiratory depression and death. Many, but not all, post-marketing reports regarding coma and death associated with the concomitant use of buprenorphine and benzodiazepines involved misuse by self-injection. Deaths have also been reported in association with concomitant administration of buprenorphine with other depressants such as alcohol or other CNS depressant drugs. Patients should be warned of the potential danger of self-administration of benzodiazepines or other depressants while under treatment with SUBOXONE sublingual film *[see Drug Interactions (7.3)]*.

Reference ID: 3496928

In the case of overdose, the primary management should be the re-establishment of adequate ventilation with mechanical assistance of respiration, if required. Naloxone may be of value for the management of buprenorphine overdose. Higher than normal doses and repeated administration may be necessary.

SUBOXONE sublingual film should be used with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression).

5.3 CNS Depression

Patients receiving buprenorphine in the presence of opioid analgesics, general anesthetics, benzodiazepines, phenothiazines, other tranquilizers, sedative/hypnotics, or other CNS depressants (including alcohol) may exhibit increased CNS depression. Consider dose reduction of CNS depressants, SUBOXONE sublingual film, or both in situations of concomitant prescription *[see Drug Interactions (7.3)]*.

5.4 Unintentional Pediatric Exposure

Buprenorphine can cause severe, possibly fatal, respiratory depression in children who are accidentally exposed to it. Store buprenorphine-containing medications safely out of the sight and reach of children.

5.5 Dependence

Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces physical dependence of the opioid type, characterized by withdrawal signs and symptoms upon abrupt discontinuation or rapid taper. The withdrawal syndrome is typically milder than seen with full agonists and may be delayed in onset. Buprenorphine can be abused in a manner similar to other opioids. This should be considered when prescribing or dispensing buprenorphine in situations when the clinician is concerned about an increased risk of misuse, abuse, or diversion *[see Drug Abuse and Dependence (9.3)]*.

5.6 Hepatitis, Hepatic Events

Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in individuals receiving buprenorphine in clinical trials and through post-marketing adverse event reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of death, hepatic failure, hepatic necrosis, hepatorenal syndrome, and hepatic encephalopathy. In many cases, the presence of pre-existing liver enzyme abnormalities, infection with hepatitis B or hepatitis C virus, concomitant usage of other potentially hepatotoxic drugs, and ongoing injecting drug use may have played a causative or contributory role. In other cases, insufficient data were available to determine the etiology of the abnormality. Withdrawal of buprenorphine has resulted in amelioration of acute hepatitis in some cases; however, in other cases no dose reduction was necessary. The possibility exists that buprenorphine had a causative or contributory role in the development of the hepatic abnormality in some cases. Liver function tests, prior to initiation of treatment are recommended to establish a baseline. Periodic monitoring of liver function during treatment is also recommended. A biological and etiological evaluation is recommended when a hepatic event is suspected. Depending on the case, SUBOXONE sublingual film may need to be carefully discontinued to prevent withdrawal signs and symptoms and a return by the patient to illicit drug use, and strict monitoring of the patient should be initiated.

5.7 Allergic Reactions

Cases of hypersensitivity to buprenorphine and naloxone containing products have been reported both in clinical trials and in the post-marketing experience. Cases of bronchospasm, angioneurotic edema, and anaphylactic shock have been reported. The most common signs and symptoms include rashes, hives, and pruritus. A history of hypersensitivity to buprenorphine or naloxone is a contraindication to the use of SUBOXONE sublingual film.

Reference ID: 3496928

5.8 Precipitation of Opioid Withdrawal Signs and Symptoms

Because it contains naloxone, SUBOXONE sublingual film is likely to produce withdrawal signs and symptoms if misused parenterally by individuals dependent on full opioid agonists such as heroin, morphine, or methadone. Because of the partial agonist properties of buprenorphine, SUBOXONE sublingual film may precipitate opioid withdrawal signs and symptoms in such persons if administered sublingually before the agonist effects of the opioid have subsided.

5.9 Neonatal Withdrawal

Neonatal withdrawal has been reported in the infants of women treated with buprenorphine during pregnancy. From post-marketing reports, the time to onset of neonatal withdrawal signs ranged from Day 1 to Day 8 of life with most cases occurring on Day 1. Adverse events associated with the neonatal withdrawal syndrome included hypertonia, neonatal tremor, neonatal agitation, and myoclonus, and there have been reports of convulsions, apnea, respiratory depression, and bradycardia.

5.10 Use in Opioid Naïve Patients

There have been reported deaths of opioid naive individuals who received a 2 mg dose of buprenorphine as a sublingual tablet for analgesia. SUBOXONE sublingual film is not appropriate as an analgesic.

5.11 Use in Patients With Impaired Hepatic Function

Buprenorphine/naloxone products are not recommended in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment. Because hepatic impairment results in a reduced clearance of naloxone to a much greater extent than buprenorphine, the doses of buprenorphine and naloxone in this fixed-dose combination product cannot be individually titrated. Therefore, patients with severe hepatic impairment will be exposed to substantially higher levels of naloxone than patients with normal hepatic function. This may result in an increased risk of precipitated withdrawal at the beginning of treatment (induction) and may interfere with buprenorphine's efficacy throughout treatment. In patients with moderate hepatic impairment, the differential reduction of naloxone clearance compared to buprenorphine clearance is not as great as in subjects with severe hepatic impairment. Therefore, buprenorphine/naloxone products are not recommended for initiation of treatment (induction) in patients with moderate hepatic impairment due to the increased risk of precipitated withdrawal. However, buprenorphine/naloxone products may be used with caution for maintenance treatment in patients with moderate hepatic impairment who have initiated treatment on a buprenorphine product without naloxone. However, patients should be carefully monitored and consideration given to the possibility of naloxone interfering with buprenorphine's efficacy *[see Use in Specific Populations (8.6)]*.

5.12 Impairment of Ability to Drive or Operate Machinery

SUBOXONE sublingual film may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery, especially during treatment induction and dose adjustment. Patients should be cautioned about driving or operating hazardous machinery until they are reasonably certain that SUBOXONE sublingual film therapy does not adversely affect his or her ability to engage in such activities.

5.13 Orthostatic Hypotension

Like other opioids, SUBOXONE sublingual film may produce orthostatic hypotension in ambulatory patients.

5.14 Elevation of Cerebrospinal Fluid Pressure

Buprenorphine, like other opioids, may elevate cerebrospinal fluid pressure and should be used with caution in patients with head injury, intracranial lesions, and other circumstances when cerebrospinal pressure may be

Reference ID: 3496928

increased. Buprenorphine can produce miosis and changes in the level of consciousness that may interfere with patient evaluation.

5.15 Elevation of Intracholedochal Pressure

Buprenorphine has been shown to increase intracholedochal pressure, as do other opioids, and thus should be administered with caution to patients with dysfunction of the biliary tract.

5.16 Effects in Acute Abdominal Conditions

As with other opioids, buprenorphine may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

5.17 General Precautions

SUBOXONE sublingual film should be administered with caution in debilitated patients and those with myxedema or hypothyroidism, adrenal cortical insufficiency (e.g., Addison's disease); CNS depression or coma; toxic psychoses; prostatic hypertrophy or urethral stricture; acute alcoholism; delirium tremens; or kyphoscoliosis.

6 ADVERSE REACTIONS

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 practice.

6.1 Clinical Trials Experience

The safety of SUBOXONE sublingual film is supported by clinical trials using SUBUTEX (buprenorphine) sublingual tablets and SUBOXONE (buprenorphine and naloxone) sublingual tablets, and other trials using buprenorphine sublingual solutions, as well as an open-label study in 194 patients treated with SUBOXONE sublingual film. In total, safety data from clinical studies are available from over 3000 opioid-dependent subjects exposed to buprenorphine at doses in the range used in the treatment of opioid dependence. Few differences in the adverse event profile were noted among SUBOXONE sublingual film, SUBOXONE (buprenorphine and naloxone) sublingual tablets, SUBUTEX (buprenorphine) sublingual tablets and a buprenorphine ethanolic sublingual solution.

The most common adverse event (>1%) associated with the sublingual administration of the SUBOXONE sublingual film was oral hypoesthesia. Other adverse events were constipation, glossodynia, oral mucosal erythema, vomiting, intoxication, disturbance in attention, palpitations, insomnia, withdrawal syndrome, hyperhidrosis, and blurred vision.

Other adverse event data were derived from larger, controlled studies of SUBOXONE (buprenorphine and naloxone) and SUBUTEX (buprenorphine) tablets and of buprenorphine sublingual solution. In a comparative study of SUBOXONE (buprenorphine and naloxone) and SUBUTEX (buprenorphine) sublingual tablets, adverse event profiles were similar for subjects treated with 16 mg/4 mg SUBOXONE (buprenorphine and naloxone) sublingual tablets or 16 mg SUBUTEX (buprenorphine) sublingual tablets. The following adverse events were reported to occur by at least 5% of patients in a 4 week study of SUBOXONE (buprenorphine and naloxone) sublingual tablets and SUBUTEX (buprenorphine) sublingual tablets.

Reference ID: 3496928

Table 2. Adverse Events (≥ 5%) by Body System and Treatment Group in a 4 Week Study

Body System/ Adverse Event (COSTART Terminology)	SUBOXONE (buprenorphine and naloxone) sublingual tablets 16 mg/4 mg/day N=107 n (%)	SUBUTEX (buprenorphine) sublingual tablets 16 mg/day N=103 n (%)	Placebo N=107 n (%)
Body as a Whole			
Asthenia	7 (6.5%)	5 (4.9%)	7 (6.5%)
Chills	8 (7.5%)	8 (7.8%)	8 (7.5%)
Headache	39 (36.4%)	30 (29.1%)	24 (22.4%)
Infection	6 (5.6%)	12 (11.7%)	7 (6.5%)
Pain	24 (22.4%)	19 (18.4%)	20 (18.7%)
Pain abdomen	12 (11.2%)	12 (11.7%)	7 (6.5%)
Pain back	4 (3.7%)	8 (7.8%)	12 (11.2%)
Withdrawal syndrome	27 (25.2%)	19 (18.4%)	40 (37.4%)
Cardiovascular System			
Vasodilation	10 (9.3%)	4 (3.9%)	7 (6.5%)
Digestive System			
Constipation	13 (12.1%)	8 (7.8%)	3 (2.8%)
Diarrhea	4 (3.7%)	5 (4.9%)	16 (15.0%)
Nausea	16 (15.0%)	14 (13.6%)	12 (11.2%)
Vomiting	8 (7.5%)	8 (7.8%)	5 (4.7%)
Nervous System			
Insomnia	15 (14.0%)	22 (21.4%)	17 (15.9%)
Respiratory System			
Rhinitis	5 (4.7%)	10 (9.7%)	14 (13.1%)
Skin And Appendages			
Sweating	15 (14.0%)	13 (12.6%)	11 (10.3%)

Abbreviations: COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms.

The adverse event profile of buprenorphine was also characterized in the dose-controlled study of a buprenorphine ethanolic solution, over a range of doses in four months of treatment. Table 3 shows adverse events reported by at least 5% of subjects in any dose group in the dose-controlled trial.

Table 3. Adverse Events (≥5%) by Body System and Treatment Group in a 16 Week Study

Body System/ Adverse Event (COSTART Terminology)	Buprenorphine Dose				
	Very Low* N=184 n (%)	Low* N=180 n (%)	Moderate* N=186 n (%)	High* N=181 n (%)	Total* N=731 n (%)
Body as a Whole					
Abscess	9 (5%)	2 (1%)	3 (2%)	2 (1%)	16 (2%)
Asthenia	26 (14%)	28 (16%)	26 (14%)	24 (13%)	104 (14%)
Chills	11 (6%)	12 (7%)	9 (5%)	10 (6%)	42 (6%)
Fever	7 (4%)	2 (1%)	2 (1%)	10 (6%)	21 (3%)
Flu syndrome	4 (2%)	13 (7%)	19 (10%)	8 (4%)	44 (6%)
Headache	51 (28%)	62 (34%)	54 (29%)	53 (29%)	220 (30%)
Infection	32 (17%)	39 (22%)	38 (20%)	40 (22%)	149 (20%)
Injury accidental	5 (3%)	10 (6%)	5 (3%)	5 (3%)	25 (3%)
Pain	47 (26%)	37 (21%)	49 (26%)	44 (24%)	177 (24%)
Pain back	18 (10%)	29 (16%)	28 (15%)	27 (15%)	102 (14%)
Withdrawal syndrome	45 (24%)	40 (22%)	41 (22%)	36 (20%)	162 (22%)
Digestive System					
Constipation	10 (5%)	23 (13%)	23 (12%)	26 (14%)	82 (11%)
Diarrhea	19 (10%)	8 (4%)	9 (5%)	4 (2%)	40 (5%)
Dyspepsia	6 (3%)	10 (6%)	4 (2%)	4 (2%)	24 (3%)
Nausea	12 (7%)	22 (12%)	23 (12%)	18 (10%)	75 (10%)
Vomiting	8 (4%)	6 (3%)	10 (5%)	14 (8%)	38 (5%)
Nervous System					
Anxiety	22 (12%)	24 (13%)	20 (11%)	25 (14%)	91 (12%)
Depression	24 (13%)	16 (9%)	25 (13%)	18 (10%)	83 (11%)
Dizziness	4 (2%)	9 (5%)	7 (4%)	11 (6%)	31 (4%)
Insomnia	42 (23%)	50 (28%)	43 (23%)	51 (28%)	186 (25%)

Reference ID: 3496928

Nervousness	12 (7%)	11 (6%)	10 (5%)	13 (7%)	46 (6%)
Somnolence	5 (3%)	13 (7%)	9 (5%)	11 (6%)	38 (5%)
Respiratory System					
Cough increase	5 (3%)	11 (6%)	6 (3%)	4 (2%)	26 (4%)
Pharyngitis	6 (3%)	7 (4%)	6 (3%)	9 (5%)	28 (4%)
Rhinitis	27 (15%)	16 (9%)	15 (8%)	21 (12%)	79 (11%)
Skin and Appendages					
Sweat	23 (13%)	21 (12%)	20 (11%)	23 (13%)	87 (12%)
Special Senses					
Runny eyes	13 (7%)	9 (5%)	6 (3%)	6 (3%)	34 (5%)

*Sublingual solution. Doses in this table cannot necessarily be delivered in tablet form, but for comparison purposes:
1 mg solution would be less than a tablet dose of 2 mg
4 mg solution approximates a 6 mg tablet dose
8 mg solution approximates a 12 mg tablet dose
16 mg solution approximates a 24 mg tablet dose

The safety of SUBOXONE sublingual film during treatment induction is supported by a clinical trial using 16 patients treated with SUBOXONE sublingual film and 18 treated with a buprenorphine-only sublingual film. Few differences in the adverse event profiles were noted between SUBOXONE sublingual film and the buprenorphine-only sublingual film.

The most common adverse event occurring during treatment induction and the 3 days following induction using SUBOXONE sublingual film was restlessness. Other adverse events were anxiety, piloerection, stomach discomfort, irritability, headache, rhinorrhea, cold sweat, arthralgia, and lacrimation increased.

Four subjects left the study early on the first day of sublingual film administration. However, there was not evidence to suggest that any of the four subjects experienced precipitated withdrawal secondary to the administration of buprenorphine or buprenorphine/naloxone sublingual films.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of SUBOXONE sublingual film. Because 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.

The most frequently reported postmarketing adverse events were peripheral edema, stomatitis, glossitis, and tongue disorder.

7 DRUG INTERACTIONS

7.1 Cytochrome P-450 3A4 (CYP3A4) Inhibitors and Inducers

Buprenorphine is metabolized to norbuprenorphine primarily by cytochrome CYP3A4; therefore, potential interactions may occur when SUBOXONE sublingual film is given concurrently with agents that affect CYP3A4 activity. The concomitant use of SUBOXONE sublingual film with CYP3A4 inhibitors (e.g., azole antifungals such

as ketoconazole, macrolide antibiotics such as erythromycin, and HIV protease inhibitors) should be monitored and may require dose-reduction of one or both agents.

The interaction of buprenorphine with CYP3A4 inducers has not been studied; therefore, it is recommended that patients receiving SUBOXONE sublingual film be monitored for signs and symptoms of opioid withdrawal if inducers of CYP3A4 (e.g., efavirenz, phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered *[see Clinical Pharmacology (12.3)]*.

7.2 Antiretrovirals

Three classes of antiretroviral agents have been evaluated for CYP3A4 interactions with buprenorphine. Nucleoside reverse transcriptase inhibitors (NRTIs) do not appear to induce or inhibit the P450 enzyme pathway, thus no interactions with buprenorphine are expected. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are metabolized principally by CYP3A4. Efavirenz, nevirapine and etravirine are known CYP3A inducers whereas delaviridine is a CYP3A inhibitor. Significant pharmacokinetic interactions between NNRTIs (e.g., efavirenz and delavirdine) and buprenorphine have been shown in clinical studies, but these pharmacokinetic interactions did not result in any significant pharmacodynamic effects. It is recommended that patients who are on chronic buprenorphine treatment have their dose monitored if NNRTIs are added to their treatment regimen. Studies have shown some antiretroviral protease inhibitors (PIs) with CYP3A4 inhibitory activity (nelfinavir, lopinavir/ritonavir, ritonavir) have little effect on buprenorphine pharmacokinetic and no significant pharmacodynamic effects. Other PIs with CYP3A4 inhibitory activity (atazanavir and atazanavir/ritonavir) resulted in elevated levels of buprenorphine and norbuprenorphine and patients in one study reported increased sedation. Symptoms of opioid excess have been found in post-marketing reports of patients receiving buprenorphine and atazanavir with and without ritonavir concomitantly. Monitoring of patients taking buprenorphine and atazanavir with and without ritonavir is recommended, and dose reduction of buprenorphine may be warranted.

7.3 Benzodiazepines

There have been a number of post-marketing reports regarding coma and death associated with the concomitant use of buprenorphine and benzodiazepines. In many, but not all, of these cases, buprenorphine was misused by self-injection. Preclinical studies have shown that the combination of benzodiazepines and buprenorphine altered the usual ceiling effect on buprenorphine-induced respiratory depression, making the respiratory effects of buprenorphine appear similar to those of full opioid agonists. SUBOXONE sublingual film should be prescribed with caution to patients taking benzodiazepines or other drugs that act on the CNS, regardless of whether these drugs are taken on the advice of a physician or are being abused/misused. Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines while taking SUBOXONE sublingual film, and should also be cautioned to use benzodiazepines concurrently with SUBOXONE sublingual film only as directed by their physician.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

Risk Summary

There are no adequate and well-controlled studies of SUBOXONE sublingual film or buprenorphine/naloxone in pregnant women. Limited published data on use of buprenorphine, the active ingredient in SUBOXONE, in pregnancy, have not shown an increased risk of major malformations. All pregnancies, regardless of drug exposure, have a background risk of 2-4% for major birth defects, and 15-20% for pregnancy loss. Reproductive and developmental studies in rats and rabbits identified adverse events at clinically relevant doses. Pre-and postnatal development studies in rats demonstrated dystocia, increased neonatal deaths, and developmental delays. No clear teratogenic effects were seen with a range of doses equivalent to or greater than the human

dose. However, in a few studies, some events such as acephalus, omphalocele, and skeletal abnormalities were observed but these findings were not clearly treatment-related. Embryofetal death was also observed in both rats and rabbits.

SUBOXONE sublingual film should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Disease-associated maternal and embryo-fetal risk

Opioid dependence in pregnancy is associated with adverse obstetrical outcomes such as low birth weight, preterm birth, and fetal death.

Fetal/neonatal adverse reactions

Neonatal abstinence syndrome may occur in newborn infants of mothers who were on buprenorphine maintenance treatment. Observe newborns for poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly *[see Warnings and Precautions (5.9)]*.

Labor or Delivery

As with all opioids, use of buprenorphine prior to delivery may result in respiratory depression in the newborn. Closely monitor neonates for signs of respiratory depression. An opioid antagonist such as naloxone should be available for reversal of opioid induced respiratory depression in the neonate.

Data

Human Data

Studies have been conducted to evaluate neonatal outcomes in women exposed to buprenorphine during pregnancy. Limited published data on malformations from trials, observational studies, case series, and case reports on buprenorphine use in pregnancy have not shown an increased risk of major malformations. Based on these studies the incidence of neonatal abstinence syndrome is not clear and there does not appear to be a dose-response relationship.

Animal Data

Effects on embryo-fetal development were studied in Sprague-Dawley rats and Russian white rabbits following oral (1:1) and intramuscular (IM) (3:2) administration of mixtures of buprenorphine and naloxone. Following oral administration to rats and rabbits, no teratogenic effects were observed at buprenorphine doses up to 250 mg/kg/day and 40 mg/kg/day, respectively (estimated exposure approximately 150 times and 50 times, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis). No definitive drug-related teratogenic effects were observed in rats and rabbits at IM doses up to 30 mg/kg/day (estimated exposure approximately 20 times and 35 times, respectively, the recommended human daily dose of 16 mg on a mg/m^2 basis). Acephalus was observed in one rabbit fetus from the low-dose group and omphalocele was observed in two rabbit fetuses from the same litter in the mid-dose group; no findings were observed in fetuses from the high-dose group. Following oral administration of buprenorphine to rats, dose-related post-implantation losses, evidenced by increases in the numbers of early resorptions with consequent reductions in the numbers of fetuses, were observed at doses of 10 mg/kg/day or greater (estimated exposure approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis). In the rabbit, increased post-implantation losses occurred at an oral dose of 40 mg/kg/day. Following IM administration in the rat and the rabbit, post-implantation losses, as evidenced by decreases in live fetuses and increases in resorptions, occurred at 30 mg/kg/day.

Buprenorphine was not teratogenic in rats or rabbits after IM or subcutaneous (SC) doses up to 5 mg/kg/day (estimated exposure was approximately 3 and 6 times, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis), after IV doses up to 0.8 mg/kg/day (estimated exposure was approximately 0.5 times and equal to, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis), or after oral doses up to 160 mg/kg/day in rats (estimated exposure was approximately 95 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) and 25 mg/kg/day in rabbits

(estimated exposure was approximately 30 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis). Significant increases in skeletal abnormalities (e.g., extra thoracic vertebra or thoraco-lumbar ribs) were noted in rats after SC administration of 1 mg/kg/day and up (estimated exposure was approximately 0.6 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis), but were not observed at oral doses up to 160 mg/kg/day. Increases in skeletal abnormalities in rabbits after IM administration of 5 mg/kg/day (estimated exposure was approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) or oral administration of 1 mg/kg/day or greater (estimated exposure was approximately equal to the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) were not statistically significant.

In rabbits, buprenorphine produced statistically significant pre-implantation losses at oral doses of 1 mg/kg/day or greater and post-implantation losses that were statistically significant at IV doses of 0.2 mg/kg/day or greater (estimated exposure approximately 0.3 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis).

Dystocia was noted in pregnant rats treated intramuscularly with buprenorphine 5 mg/kg/day (approximately 3 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis). Fertility, peri-, and post-natal development studies with buprenorphine in rats indicated increases in neonatal mortality after oral doses of 0.8 mg/kg/day and up (approximately 0.5 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis), after IM doses of 0.5 mg/kg/day and up (approximately 0.3 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis), and after SC doses of 0.1 mg/kg/day and up (approximately 0.06 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis). An apparent lack of milk production during these studies likely contributed to the decreased pup viability and lactation indices. Delays in the occurrence of righting reflex and startle response were noted in rat pups at an oral dose of 80 mg/kg/day (approximately 50 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis).

8.3 Nursing Mothers

Risk Summary

Based on two studies in 13 lactating women, buprenorphine and its metabolite norbuprenorphine are present in low levels in human milk and infant urine, and available data have not shown adverse reactions in breastfed infants. There are no data on the combination product buprenorphine/naloxone in breastfeeding, however oral absorption of naloxone is minimal. Caution should be exercised when SUBOXONE is administered to a nursing woman. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SUBOXONE and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

Clinical Considerations

Advise the nursing mother taking SUBOXONE to monitor the infant for increased drowsiness and breathing difficulties.

Data

Based on limited data from a study of 6 lactating women who were taking a median oral dose of buprenorphine of 0.29 mg/kg/day 5-8 days after delivery, breast milk contained a median infant dose of 0.42 mcg/kg/day of buprenorphine and 0.33 mcg/kg/day of norbuprenorphine, which are equal to 0.2% and 0.12% of the maternal weight-adjusted dose.

Based on limited data from a study of 7 lactating women who were taking a median oral dose of buprenorphine of 7 mg/day an average of 1.12 months after delivery, the mean milk concentrations of buprenorphine and norbuprenorphine were 3.65 mcg/L and 1.94 mcg/L respectively. Based on the limited data from this study, and assuming milk consumption of 150 mL/kg/day, an exclusively breastfed infant would receive an estimated mean of 0.55 mcg/kg/day of buprenorphine and 0.29 mcg/kg/day of norbuprenorphine, which are 0.38% and 0.18% of the maternal weight-adjusted dose.

No adverse reactions were observed in the infants in these two studies.

8.4 Pediatric Use

The safety and effectiveness of SUBOXONE sublingual film have not been established in pediatric patients. This product is not appropriate for the treatment of neonatal abstinence syndrome in neonates, because it contains naloxone, an opioid antagonist.

8.5 Geriatric Use

Clinical studies of SUBOXONE sublingual film, SUBOXONE (buprenorphine and naloxone) sublingual tablets, or SUBUTEX (buprenorphine) sublingual tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone has been evaluated in a pharmacokinetic study. Both drugs are extensively metabolized in the liver. While no clinically significant changes have been observed in subjects with mild hepatic impairment; the plasma levels have been shown to be higher and half-life values have been shown to be longer for both buprenorphine and naloxone in subjects with moderate and severe hepatic impairment. The magnitude of the effects on naloxone are greater than that on buprenorphine in both moderately and severely impaired subjects. The difference in magnitude of the effects on naloxone and buprenorphine are greater in subjects with severe hepatic impairment than in subjects with moderate hepatic impairment, and therefore the clinical impact of these effects is likely to be greater in patients with severe hepatic impairment than in patients with moderate hepatic impairment. Buprenorphine/naloxone products should be avoided in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment *[see Warnings and Precautions (5.11) and Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

No differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following IV administration of 0.3 mg buprenorphine. The effects of renal failure on naloxone pharmacokinetics are unknown.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Buprenorphine is a Schedule III narcotic under the Controlled Substances Act.

Under the Drug Addiction Treatment Act (DATA) codified at 21 U.S.C. 823(g), prescription use of this product in the treatment of opioid dependence is limited to physicians who meet certain qualifying requirements, and who have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence and have been assigned a unique identification number that must be included on every prescription.

9.2 Abuse

Buprenorphine, like morphine and other opioids, has the potential for being abused and is subject to criminal diversion. This should be considered when prescribing or dispensing buprenorphine in situations when the clinician is concerned about an increased risk of misuse, abuse, or diversion. Healthcare professionals should

contact their state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

Patients who continue to misuse, abuse, or divert buprenorphine products or other opioids should be provided with or referred for more intensive and structured treatment.

Abuse of buprenorphine poses a risk of overdose and death. This risk is increased with the abuse of buprenorphine and alcohol and other substances, especially benzodiazepines.

The physician may be able to more easily detect misuse or diversion by maintaining records of medication prescribed including date, dose, quantity, frequency of refills, and renewal requests of medication prescribed.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper handling and storage of the medication are appropriate measures that help to limit abuse of opioid drugs.

9.3 Dependence

Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces physical dependence of the opioid type, characterized by moderate withdrawal signs and symptoms upon abrupt discontinuation or rapid taper. The withdrawal syndrome is typically milder than seen with full agonists and may be delayed in onset *[see Warnings and Precautions (5.5)]*.

A neonatal withdrawal syndrome has been reported in the infants of women treated with buprenorphine during pregnancy *[see Warnings and Precautions (5.9)]*.

10 OVERDOSAGE

The manifestations of acute overdose include pinpoint pupils, sedation, hypotension, respiratory depression, and death.

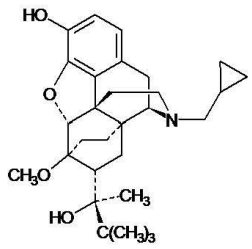
In the event of overdose, the respiratory and cardiac status of the patient should be monitored carefully. When respiratory or cardiac functions are depressed, primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Oxygen, IV fluids, vasopressors, and other supportive measures should be employed as indicated.

In the case of overdose, the primary management should be the re-establishment of adequate ventilation with mechanical assistance of respiration, if required. Naloxone may be of value for the management of buprenorphine overdose. Higher than normal doses and repeated administration may be necessary.

11 DESCRIPTION

SUBOXONE (buprenorphine and naloxone) sublingual film is an orange film, imprinted with a logo identifying the product and strength in white ink. It contains buprenorphine HCl, a mu-opioid receptor partial agonist and a kappa-opioid receptor antagonist, and naloxone HCl dihydrate, an opioid receptor antagonist, at a ratio of 4:1 (ratio of free bases). It is intended for sublingual administration and is available in four dosage strengths, 2 mg buprenorphine with 0.5 mg naloxone, 4 mg buprenorphine with 1 mg naloxone, 8 mg buprenorphine with 2 mg naloxone and 12 mg buprenorphine with 3 mg naloxone. Each sublingual film also contains polyethylene oxide, hydroxypropyl methylcellulose, maltitol, acesulfame potassium, lime flavor, citric acid, sodium citrate, FD&C yellow #6, and white ink.

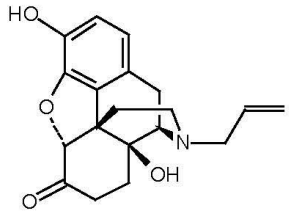
Chemically, buprenorphine HCl is (2S)-2-[17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol hydrochloride. It has the following chemical structure:



• HCl

Buprenorphine HCl has the molecular formula $C_{29}H_{41}NO_4$ • HCl and the molecular weight is 504.10. It is a white or off-white crystalline powder, sparingly soluble in water, freely soluble in methanol, soluble in alcohol, and practically insoluble in cyclohexane.

Chemically, naloxone HCl dihydrate is 17-Allyl-4,5 α -epoxy-3, 14-dihydroxymorphinan-6-one hydrochloride dihydrate. It has the following chemical structure:



$HCl \bullet 2H_2O$

Naloxone hydrochloride dihydrate has the molecular formula $C_{19}H_{21}NO_4$ • HCl • $2H_2O$ and the molecular weight is 399.87. It is a white to slightly off-white powder and is freely soluble in water, soluble in alcohol, and practically insoluble in toluene and ether.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

SUBOXONE sublingual film contains buprenorphine and naloxone. Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Naloxone is a potent antagonist at mu-opioid receptors and produces opioid withdrawal signs and symptoms in individuals physically dependent on full opioid agonists when administered parenterally.

12.2 Pharmacodynamics

***Subjective Effects**:*

Comparisons of buprenorphine to full opioid agonists such as methadone and hydromorphone suggest that sublingual buprenorphine produces typical opioid agonist effects which are limited by a ceiling effect.

In opioid-experienced subjects who were not physically dependent, acute sublingual doses of buprenorphine/naloxone tablets produced opioid agonist effects which reached a maximum between doses of 8 mg/2 mg and 16 mg/4 mg buprenorphine/naloxone.

Opioid agonist ceiling-effects were also observed in a double-blind, parallel group, dose-ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 4, 8, 16, or 32 mg), placebo and a full agonist control at various doses. The treatments were given in ascending dose order at intervals of at least one week to 16 opioid-experienced subjects who were not physically dependent. Both active drugs produced typical opioid agonist effects. For all measures for which the drugs produced an effect, buprenorphine produced a dose-

related response. However, in each case, there was a dose that produced no further effect. In contrast, the highest dose of the full agonist control always produced the greatest effects. Agonist objective rating scores remained elevated for the higher doses of buprenorphine (8-32 mg) longer than for the lower doses and did not return to baseline until 48 hours after drug administration. The onset of effects appeared more rapidly with buprenorphine than with the full agonist control, with most doses nearing peak effect after 100 minutes for buprenorphine compared to 150 minutes for the full agonist control.

Physiologic Effects:

Buprenorphine in IV (2, 4, 8, 12 and 16 mg) and sublingual (12 mg) doses has been administered to opioid-experienced subjects who were not physically dependent to examine cardiovascular, respiratory, and subjective effects at doses comparable to those used for treatment of opioid dependence. Compared to placebo, there were no statistically significant differences among any of the treatment conditions for blood pressure, heart rate, respiratory rate, O_2 saturation, or skin temperature across time. Systolic BP was higher in the 8 mg group than placebo (3 hour AUC values). Minimum and maximum effects were similar across all treatments. Subjects remained responsive to low voice and responded to computer prompts. Some subjects showed irritability, but no other changes were observed.

The respiratory effects of sublingual buprenorphine were compared with the effects of methadone in a double-blind, parallel group, dose ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 4, 8, 16, or 32 mg) and oral methadone (15, 30, 45, or 60 mg) in non-dependent, opioid-experienced volunteers. In this study, hypoventilation not requiring medical intervention was reported more frequently after buprenorphine doses of 4 mg and higher than after methadone. Both drugs decreased O_2 saturation to the same degree.

Effect of Naloxone:

Physiologic and subjective effects following acute sublingual administration of buprenorphine tablets and buprenorphine/naloxone tablets were similar at equivalent dose levels of buprenorphine. Naloxone had no clinically significant effect when administered by the sublingual route, although blood levels of the drug were measurable. Buprenorphine/naloxone, when administered sublingually to an opioid-dependent cohort, was recognized as an opioid agonist, whereas when administered intramuscularly, combinations of buprenorphine with naloxone produced opioid antagonist actions similar to naloxone. This finding suggests that the naloxone in buprenorphine/naloxone tablets may deter injection of buprenorphine/naloxone tablets by persons with active substantial heroin or other full mu-opioid dependence. However, clinicians should be aware that some opioid-dependent persons, particularly those with a low level of full mu-opioid physical dependence or those whose opioid physical dependence is predominantly to buprenorphine, abuse buprenorphine/naloxone combinations by the intravenous or intranasal route. In methadone-maintained patients and heroin-dependent subjects, IV administration of buprenorphine/naloxone combinations precipitated opioid withdrawal signs and symptoms and was perceived as unpleasant and dysphoric. In morphine-stabilized subjects, intravenously administered combinations of buprenorphine with naloxone produced opioid antagonist and withdrawal signs and symptoms that were ratio-dependent; the most intense withdrawal signs and symptoms were produced by 2:1 and 4:1 ratios, less intense by an 8:1 ratio.

Reference ID: 3496928

12.3 Pharmacokinetics

Absorption:

In pharmacokinetic studies, the 2 mg/0.5 mg and 4 mg/1 mg doses administered as SUBOXONE sublingual films showed comparable relative bioavailability to the same total dose of SUBOXONE (buprenorphine and naloxone) sublingual tablets, whereas the 8 mg/2 mg and 12 mg/3 mg doses administered as SUBOXONE sublingual films showed higher relative bioavailability for both buprenorphine and naloxone compared to the same total dose of SUBOXONE (buprenorphine and naloxone) sublingual tablets. A combination of one 8 mg/2 mg and two 2 mg/0.5 mg SUBOXONE sublingual films (total dose of 12 mg/ 3 mg) showed comparable relative bioavailability to the same total dose of SUBOXONE (buprenorphine and naloxone) sublingual tablets *[see Dosage and Administration (2.6 and 2.7)]*.

Distribution:

Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin.

Naloxone is approximately 45% protein bound, primarily to albumin.

Metabolism:

Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated primarily by the CYP3A4. Norbuprenorphine, the major metabolite, can further undergo glucuronidation. Norbuprenorphine has been found to bind opioid receptors *in vitro*; however, it has not been studied clinically for opioid-like activity. Naloxone undergoes direct glucuronidation to naloxone-3-glucuronide as well as N-dealkylation, and reduction of the 6-oxo group.

Elimination:

A mass balance study of buprenorphine showed complete recovery of radiolabel in urine (30%) and feces (69%) collected up to 11 days after dosing. Almost all of the dose was accounted for in terms of buprenorphine, norbuprenorphine, and two unidentified buprenorphine metabolites. In urine, most of buprenorphine and norbuprenorphine was conjugated (buprenorphine, 1% free and 9.4% conjugated; norbuprenorphine, 2.7% free and 11% conjugated). In feces, almost all of the buprenorphine and norbuprenorphine were free (buprenorphine, 33% free and 5% conjugated; norbuprenorphine, 21% free and 2% conjugated). Based on all studies performed with SUBOXONE sublingual film, buprenorphine has a mean elimination half-life from plasma ranging from 24 to 42 hours and naloxone has a mean elimination half-life from plasma ranging from 2 to 12 hours.

Drug-drug Interactions:

CYP3A4 Inhibitors and Inducers: Subjects receiving SUBOXONE sublingual film should be monitored if inhibitors of CYP3A4 such as azole antifungal agents (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin) or HIV protease inhibitors and may require dose-reduction of one or both agents. The interaction of buprenorphine with all CYP3A4 inducers has not been studied, therefore it is recommended that patients receiving SUBOXONE sublingual film be monitored for signs and symptoms of opioid withdrawal if inducers of CYP3A4 (e.g., phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered *[see Drug Interactions (7.1)]*.

Buprenorphine has been found to be a CYP2D6 and CYP3A4 inhibitor and its major metabolite, norbuprenorphine, has been found to be a moderate CYP2D6 inhibitor in *in vitro* studies employing human liver microsomes. However, the relatively low plasma concentrations of buprenorphine and norbuprenorphine resulting from therapeutic doses are not expected to raise significant drug-drug interaction concerns.

Special Populations:

Hepatic Impairment: In a pharmacokinetic study, the disposition of buprenorphine and naloxone were determined after administering a SUBOXONE 2.0/0.5 mg (Buprenorphine/Naloxone) sublingual tablet in subjects with varied degrees of hepatic impairment as indicated by Child-Pugh criteria. The disposition of buprenorphine and naloxone in patients with hepatic impairment were compared to disposition in subjects with normal hepatic function.

Reference ID: 3496928

In subjects with mild hepatic impairment, the changes in mean C_{max}, $AUC_{0\text{-last}}$, and half-life values of both buprenorphine and naloxone were not clinically significant. No dosing adjustment is needed in patients with mild hepatic impairment.

For subjects with moderate and severe hepatic impairment, mean C_{max}, $AUC_{0\text{-last}}$, and half-life values of both buprenorphine and naloxone were increased; the effects on naloxone are greater than that on buprenorphine (Table 4).

Table 4. Changes in Pharmacokinetic Parameters in Subjects With Moderate and Severe Hepatic Impairment

Hepatic Impairment	PK Parameters	Increase in buprenorphine compared to healthy subjects	Increase in naloxone compared to healthy subjects
Moderate	C_{max}	8%	170%
	$AUC_{0\text{-last}}$	64%	218%
	Half-life	35%	165%
Severe	C_{max}	72%	1030%
	$AUC_{0\text{-last}}$	181%	1302%
	Half-life	57%	122%

The difference in magnitude of the effects on naloxone and buprenorphine are greater in subjects with severe hepatic impairment than subjects with moderate hepatic impairment, and therefore the clinical impact of these effects is likely to be greater in patients with severe hepatic impairment than in patients with moderate hepatic impairment. Buprenorphine/naloxone products should be avoided in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment *[see Warnings and Precautions (5.11) and Use in Specific Populations (8.6)]*.

HCV infection: In subjects with HCV infection but no sign of hepatic impairment, the changes in the mean C_{max}, $AUC_{0\text{-last}}$, and half-life values of buprenorphine and naloxone were not clinically significant in comparison to healthy subjects without HCV infection. No dosing adjustment is needed in patients with HCV infection.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity:

Carcinogenicity data on SUBOXONE sublingual film are not available.

A carcinogenicity study of buprenorphine/naloxone (4:1 ratio of the free bases) was performed in Alderley Park rats. Buprenorphine/naloxone was administered in the diet at doses of approximately 7, 31, and 123 mg/kg/day for 104 weeks (estimated exposure was approximately 4, 18, and 44 times the recommended human sublingual dose of 16 mg/4 mg buprenorphine/naloxone based on buprenorphine AUC comparisons). A statistically significant increase in Leydig cell adenomas was observed in all dose groups. No other drug-related tumors were noted.

Carcinogenicity studies of buprenorphine were conducted in Sprague-Dawley rats and CD-1 mice. Buprenorphine was administered in the diet to rats at doses of 0.6, 5.5, and 56 mg/kg/day (estimated exposure was approximately 0.4, 3, and 35 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) for 27 months. As in the buprenorphine/naloxone carcinogenicity study in rat, statistically significant dose-related increases in Leydig cell tumors occurred. In an 86-week study in CD-1 mice, buprenorphine was

not carcinogenic at dietary doses up to 100 mg/kg/day (estimated exposure was approximately 30 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis).

Mutagenicity:

The 4:1 combination of buprenorphine and naloxone was not mutagenic in a bacterial mutation assay (Ames test) using four strains of *S. typhimurium* and two strains of *E. coli.* The combination was not clastogenic in an *in vitro* cytogenetic assay in human lymphocytes or in an IV micronucleus test in the rat.

Buprenorphine was studied in a series of tests utilizing gene, chromosome, and DNA interactions in both prokaryotic and eukaryotic systems. Results were negative in yeast (*S. cerevisiae)* for recombinant, gene convertant, or forward mutations; negative in *Bacillus subtilis* "rec" assay, negative for clastogenicity in CHO cells, Chinese hamster bone marrow and spermatogonia cells, and negative in the mouse lymphoma L5178Y assay.

Results were equivocal in the Ames test: negative in studies in two laboratories, but positive for frame shift mutation at a high dose (5mg/plate) in a third study. Results were positive in the Green-Tweets (*E. coli*) survival test, positive in a DNA synthesis inhibition (DSI) test with testicular tissue from mice, for both *in vivo* and *in vitro* incorporation of [^{3}H]thymidine, and positive in unscheduled DNA synthesis (UDS) test using testicular cells from mice.

Impairment of Fertility:

Dietary administration of buprenorphine in the rat at dose levels of 500 ppm or greater (equivalent to approximately 47 mg/kg/day or greater; estimated exposure approximately 28 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) produced a reduction in fertility demonstrated by reduced female conception rates. A dietary dose of 100 ppm (equivalent to approximately 10 mg/kg/day; estimated exposure approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) had no adverse effect on fertility.

16 HOW SUPPLIED / STORAGE AND HANDLING

SUBOXONE sublingual film is supplied as an orange rectangular sublingual film with a white printed logo in child-resistant polyester/foil laminated pouches:

- NDC 12496-1202-3 (buprenorphine/naloxone 2 mg/0.5 mg/film; content expressed in terms of free base) - 30 films per carton
- NDC 12496-1204-3 (buprenorphine/naloxone 4 mg/1 mg/film; content expressed in terms of free base) - 30 films per carton
- NDC 12496-1208-3 (buprenorphine/naloxone 8 mg/2 mg/film; content expressed in terms of free base) -30 films per carton
- NDC 12496-1212-3 (buprenorphine/naloxone 12 mg/3 mg/film; content expressed in terms of free base) - 30 films per carton

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

Patients should be advised to store buprenorphine-containing medications safely and out of sight and reach of children.

Rx only

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

Patients should be advised NOT to cut, chew or swallow SUBOXONE sublingual film.

17.1 Safe Use

Before initiating treatment with SUBOXONE, explain the points listed below to caregivers and patients. Instruct patients to read the Medication Guide each time SUBOXONE is dispensed because new information may be available.

- Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines or other CNS depressants (including alcohol) while taking SUBOXONE sublingual film. Patients prescribed benzodiazepines or other CNS depressants should be cautioned to use them only as directed by their physician *[see Warnings and Precautions (5.2), Drug Interactions (7.3)]*.
- Patients should be advised that SUBOXONE sublingual film contains an opioid that can be a target for people who abuse prescription medications or street drugs. Patients should be cautioned to keep their films in a safe place, and to protect them from theft.
- Patients should be instructed to keep SUBOXONE sublingual film in a secure place, out of the sight and reach of children. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death. Patients should be advised that if a child is exposed to SUBOXONE sublingual film, medical attention should be sought immediately.
- Patients should be advised never to give SUBOXONE sublingual film to anyone else, even if he or she has the same signs and symptoms. It may cause harm or death.
- Patients should be advised that selling or giving away this medication is against the law.
- Patients should be cautioned that SUBOXONE sublingual film may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving or operating machinery. Caution should be taken especially during drug induction and dose adjustment and until individuals are reasonably certain that buprenorphine therapy does not adversely affect their ability to engage in such activities *[see Warnings and Precautions (5.11)]*.
- Patients should be advised not to change the dosage of SUBOXONE sublingual film without consulting their physician.
- Patients should be advised to take SUBOXONE sublingual film once a day.
- Patients should be advised that if they miss a dose of SUBOXONE they should take it as soon as they remember. If it is almost time for the next dose, they should skip the missed dose and take the next dose at the regular time.
- Patients should be informed that SUBOXONE sublingual film can cause drug dependence and that withdrawal signs and symptoms may occur when the medication is discontinued.
- Patients seeking to discontinue treatment with buprenorphine for opioid dependence should be advised to work closely with their physician on a tapering schedule and should be apprised of the potential to relapse to illicit drug use associated with discontinuation of opioid agonist/partial agonist medication-assisted treatment.
- Patients should be cautioned that, like other opioids, SUBOXONE sublingual film may produce orthostatic hypotension in ambulatory individuals *[see Warnings and Precautions (5.12)]*.
- Patients should inform their physician if any other prescription medications, over-the-counter medications, or herbal preparations are prescribed or currently being used *[see Drug Interactions (7.1, 7.2 and 7.3)]*.

Reference ID: 3496928

- Women of childbearing potential who become pregnant or are planning to become pregnant, should be advised to consult their physician regarding the possible effects of using SUBOXONE sublingual film during pregnancy *[see Use in Specific Populations (8.1)]*.
- Advise women who are breastfeeding to monitor the infant for drowsiness and difficulty breathing *[see Use in Specific Populations (8.3)]*.
- Patients should inform their family members that, in the event of emergency, the treating physician or emergency room staff should be informed that the patient is physically dependent on an opioid and that the patient is being treated with SUBOXONE sublingual film.
- Refer to the Medication Guide for additional information regarding the counseling information.

17.2 Disposal of Unused SUBOXONE Sublingual Films

Unused SUBOXONE sublingual films should be disposed of as soon as they are no longer needed. Unused films should be flushed down the toilet.

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Manufactured for Reckitt Benckiser
Pharmaceuticals Inc.,
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Warren, NJ 07059

Distributed by:
Reckitt Benckiser Pharmaceuticals Inc.
Richmond, VA 23235

Reference ID: 3496928

MEDICATION GUIDE
SUBOXONE® (Sub-OX-own)
(buprenorphine and naloxone)
Sublingual Film (CIII)

IMPORTANT:
Keep SUBOXONE in a secure place away from children. Accidental use by a child is a medical emergency and can result in death. If a child accidentally uses SUBOXONE, get emergency help right away.

Read this Medication Guide that comes with SUBOXONE before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your doctor. Talk to your doctor or pharmacist if you have questions about SUBOXONE.

Share the important information in this Medication Guide with members of your household.

What is the most important information I should know about SUBOXONE?

- SUBOXONE can cause serious and life-threatening breathing problems. Call your doctor right away or get emergency help if:
  - You feel faint, dizzy, or confused
  - Your breathing gets much slower than is normal for you

  These can be signs of an overdose or other serious problems.
- SUBOXONE contains an opioid that can cause physical dependence.
  - Do not stop taking SUBOXONE without talking to your doctor. You could become sick with uncomfortable withdrawal signs and symptoms because your body has become used to this medicine.
  - Physical dependence is not the same as drug addiction.
  - SUBOXONE is not for occasional or "as needed" use.
- An overdose and even death can happen if you take benzodiazepines, sedatives, tranquilizers, antidepressants, or alcohol while using SUBOXONE. Ask your doctor what you should do if you are taking one of these.
- Call a doctor or get emergency help right away if you:
  - Feel sleepy and uncoordinated
  - Have blurred vision
  - Have slurred speech
  - Cannot think well or clearly
  - Have slowed reflexes and breathing

Reference ID: 3496928

- Do not inject ("shoot-up") SUBOXONE
  - Injecting this medicine may cause life-threatening infections and other serious health problems.
  - Injecting SUBOXONE may cause serious withdrawal symptoms such as pain, cramps, vomiting, diarrhea, anxiety, sleep problems, and cravings.
- In an emergency, have family members tell emergency department staff that you are physically dependent on an opioid and are being treated with SUBOXONE.

What is SUBOXONE?

- SUBOXONE is a prescription medicine used to treat adults who are addicted to (dependent on) opioid drugs (either prescription or illegal) as part of a complete treatment program that also includes counseling and behavioral therapy.

SUBOXONE is a controlled substance (CIII) because it contains buprenorphine, which can be a target for people who abuse prescription medicines or street drugs. Keep your SUBOXONE in a safe place to protect it from theft. Never give your SUBOXONE to anyone else; it can cause death or otherwise harm them. Selling or giving away this medicine is against the law.

- It is not known if SUBOXONE is safe or effective in children.

Who should not take SUBOXONE?

Do not take SUBOXONE if you are allergic to buprenorphine or naloxone.

What should I tell my doctor before taking SUBOXONE?

SUBOXONE may not be right for you. Before taking SUBOXONE, tell your doctor if you:

- Have trouble breathing or lung problems
- Have an enlarged prostate gland (men)
- Have a head injury or brain problem
- Have problems urinating
- Have a curve in your spine that affects your breathing
- Have liver or kidney problems
- Have gallbladder problems
- Have adrenal gland problems
- Have Addison's disease
- Have low thyroid (hypothyroidism)
- Have a history of alcoholism
- Have mental problems such as hallucinations (seeing or hearing things that are not there)
- Have any other medical condition
- Are pregnant or plan to become pregnant. It is not known if SUBOXONE will harm

Reference ID: 3496928

your unborn baby. If you take SUBOXONE while pregnant, your baby may have symptoms of withdrawal at birth. Talk to your doctor if you are pregnant or plan to become pregnant.

- Are breast feeding or plan to breast feed. SUBOXONE can pass into your milk and may harm your baby. Talk to your doctor about the best way to feed your baby if you take SUBOXONE. Monitor your baby for increased sleepiness and breathing problems.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. SUBOXONE may affect the way other medicines work, and other medicines may affect how SUBOXONE works. Some medicines may cause serious or life-threatening medical problems when taken with SUBOXONE.

Sometimes the doses of certain medicines and SUBOXONE may need to be changed if used together. Do not take any medicine while using SUBOXONE until you have talked with your doctor. Your doctor will tell you if it is safe to take other medicines while you are using SUBOXONE.

Be especially careful about taking other medicines that may make you sleepy, such as pain medicines, tranquilizers, antidepressant medicines, sleeping pills, anxiety medicines or antihistamines.

Know the medicines you take. Keep a list of them to show your doctor or pharmacist each time you get a new medicine.

How should I take SUBOXONE sublingual film?

- Always take SUBOXONE exactly as your doctor tells you. Your doctor may change your dose after seeing how it affects you. Do not change your dose unless your doctor tells you to change it.
- Do not take SUBOXONE more often than prescribed by your doctor.
- Each SUBOXONE sublingual film comes in a sealed child-resistant foil pouch. Wait to open SUBOXONE until right before you use it.
- To open your SUBOXONE sublingual film foil pouch, fold along the dotted line (see Figure 1)

Reference ID: 3496928

Figure 1

- Tear down at slit or cut with scissors along the arrow (see Figure 2).

Figure 2

- Before taking SUBOXONE, drink water to moisten your mouth. This helps the film dissolve more easily.
- Hold the film between two fingers by the outside edges.
- **Place SUBOXONE sublingual film under your tongue**, close to the base either to the left or right of the center (see Figure 3).

Reference ID: 3496928

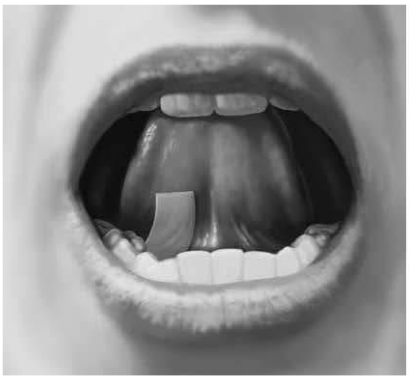

Figure 3

- If your doctor tells you to take 2 films at a time, place the second film under your tongue on the opposite side. Try to avoid having the films touch as much as possible.
- Keep the films in place until they have completely dissolved.
- If you are directed to take a third film, place it under your tongue on either side after the first 2 films have dissolved.

- While SUBOXONE is dissolving, do not chew or swallow the film because the medicine will not work as well.
- Talking while the film is dissolving can affect how well the medicine in SUBOXONE is absorbed.
- If you miss a dose of SUBOXONE, take your medicine when you remember. If it is almost time for your next dose, skip the missed dose and take the next dose at your regular time. Do not take 2 doses at the same time unless your doctor tells you to. If you are not sure about your dosing, call your doctor.
- Do not stop taking SUBOXONE suddenly. You could become sick and have withdrawal symptoms because your body has become used to the medicine. Physical dependence is not the same as drug addiction. Your doctor can tell you more about the differences between physical dependence and drug addiction. To have fewer withdrawal symptoms, ask your doctor how to stop using SUBOXONE the right way.
- **If you take too much SUBOXONE or overdose, call Poison Control or get emergency medical help right away.**

What should I avoid while taking SUBOXONE?

- **Do not drive, operate heavy machinery, or perform any other dangerous activities until you know how this medication affects you.** Buprenorphine can cause drowsiness and slow reaction times. This may happen more often in the first few weeks of treatment when your dose is being changed, but can also happen if you drink alcohol or take other sedative drugs when you take SUBOXONE.

Reference ID: 3496928

- **You should not drink alcohol** while using SUBOXONE, as this can lead to loss of consciousness or even death.

What are the possible side effects of SUBOXONE?

SUBOXONE can cause serious side effects, including:

- **See "What is the most important information I should know about SUBOXONE?"**
- **Respiratory problems**. You have a higher risk of death and coma if you take SUBOXONE with other medicines, such as benzodiazepines.
- **Sleepiness, dizziness, and problems with coordination**
- **Dependency or abuse**
- **Liver problems**. Call your doctor right away if you notice any of these signs of liver problems: Your skin or the white part of your eyes turning yellow (jaundice), urine turning dark, stools turning light in color, you have less of an appetite, or you have stomach (abdominal) pain or nausea. Your doctor should do tests before you start taking and while you take SUBOXONE.
- **Allergic reaction**. You may have a rash, hives, swelling of the face, wheezing, or a loss of blood pressure and consciousness. Call a doctor or get emergency help right away.
- **Opioid withdrawal.** This can include: shaking, sweating more than normal, feeling hot or cold more than normal, runny nose, watery eyes, goose bumps, diarrhea, vomiting, and muscle aches. Tell your doctor if you develop any of these symptoms.
- **Decrease in blood pressure**. You may feel dizzy if you get up too fast from sitting or lying down.

Common side effects of SUBOXONE sublingual film include:

- Nausea
- Vomiting
- Drug withdrawal syndrome
- Headache
- Sweating
- Numb mouth
- Constipation
- Painful tongue
- The inside of your mouth is more red than normal
- Intoxication (feeling lightheaded or drunk)
- Disturbance in attention
- Irregular heart beat (palpitations)
- Decrease in sleep (insomnia)
- Blurred vision
- Back pain
- Fainting
- Dizziness
- Sleepiness

Reference ID: 3496928

Tell your doctor about any side effect that bothers you or that does not go away.

These are not all the possible side effects of SUBOXONE sublingual film. For more information, ask your doctor or pharmacist.

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

How should I store SUBOXONE?

- Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F).
- **Keep SUBOXONE in a safe place, out of the sight and reach of children.**

How should I dispose of unused SUBOXONE sublingual film?

- Dispose of unused SUBOXONE as soon as you no longer need them.
- Unused films should be removed from the foil pouch and flushed down the toilet.

General information about the safe and effective use of SUBOXONE

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not take SUBOXONE for a condition for which it was not prescribed. Do not give SUBOXONE to other people, even if they have the same symptoms you have. It may harm them and it is against the law.

This Medication Guide summarizes the most important information about SUBOXONE. If you would like more information, talk to your doctor or pharmacist. You can ask your doctor or pharmacist for information that is written for healthcare professionals. For more information call 1-877-782-6966.

What are the ingredients in SUBOXONE sublingual film?

Active Ingredients: buprenorphine and naloxone.

Inactive Ingredients: polyethylene oxide, hydroxypropyl methylcellulose, maltitol, acesulfame potassium, lime flavor, citric acid, sodium citrate, FD&C yellow #6, and white ink.

Manufactured for Reckitt Benckiser Pharmaceuticals Inc.
Richmond, VA 23235 by MonoSol Rx LLC, Warren, NJ 07059

This Medication Guide has been approved by the US Food and Drug Administration.

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