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TITLE: Ocular safety of Topical Naltrexone

PRINCIPAL INVESTIGATOR: Joseph W. Sassani, MD, MHA

CONTRACTING ORGANIZATION:
Pennsylvania State University
Hershey, PA 17033-2360

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14. ABSTRACT During the past year we have obtained approval from our institutional and University Conflict of Interest Committees, which limited the ability of Dr. Sassani to actively participate in data collection or interpretation in the study. In order to compensate for this reduction in effective researchers, Dr. Esther Bowie, an Ophthalmologist on the faculty of our Department of Ophthalmology, will assist Dr. David Liang in performing the clinical studies and data collection. To date we have completed our first cohort of 4 volunteers at the once daily, 1 x 10-6 dosage, of topical Naltrexone in Vigamox® eyedrops in one eye of each volunteer. No untoward side effects were noted in this group of volunteers. We also have recruited and treated three patients for the second cohort who have completed the treatment schedule. We need to recruit one more volunteer for this cohort and complete the other three cohorts. We are committed to completing the study, and have requested a one year extension of the grant period with no additional funds in order to complete our study.					
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Table of Contents:

Page(s):

4.	Table of Contents
5.	Introduction
5.	Body (background, objective/hypothesis, specific aims, study design, impact)
6.	Body – continued (public abstract)
6.	Key Research Accomplishments
6.	Reportable Outcomes
7.	Conclusions and References
8.	Appendices to Annual Report:
	Appendix A: Protocol
13.	Protocol Addendum

Introduction:

Dr. Sassani and his associates have been funded to perform a Phase I Clinical Trial of Naltrexone dissolved in Vigamox® and applied topically as eye drops preliminary to a therapeutic trial of that medication in the treatment of corneal epithelial defects in diabetic individuals. During the past year, we have obtained Institutional and University Conflict of Interest approval for our study. As a result, Dr. Sassani has elected not to participate directly in data collection for the study. We have recruited Dr. Esther Bowie, an Ophthalmologist in the Department of Ophthalmology to assist Dr. Liang in volunteer examination and data collection. The recruitment of Dr. Bowie, who has a clinic schedule that complements that of Dr. Liang, should facilitate the examination of volunteers.

Body:

Background: Over the past 18 years, Dr. Sassani has worked with Dr. Zagon's research team delineating the role of the Opioid Growth Regulatory System in corneal epithelial homeostasis and wound healing. We have demonstrated that the native opioid peptide, [Met⁵]-enkephalin, termed opioid growth factor (OGF) is a tonically active, receptor mediated, inhibitor of corneal epithelial cell division. Conversely, blockade of the opioid growth factor receptor (OGFr) by the opioid antagonist Naltrexone (NX) up-regulates corneal epithelial cell division. We have demonstrated, further, that NTX accelerates the rate of corneal epithelial wound healing in healthy rodents and rabbits, and reverses the delay in corneal epithelial wound healing characteristic of diabetic keratopathy. No drug-related side effects have been found in animals treated with NTX.

Objective/Hypothesis: Our research suggests that NTX will be useful to expedite corneal epithelial wound healing in normal individuals who suffer ocular trauma, or in individuals with delayed corneal wound healing, such as diabetics. Moreover, our animal experiments indicate that such treatment will be safe as well as effective.

Specific Aims: Phase I Clinical Trials, demonstrating the safety of topically applied NTX in normal volunteers, are required by the FDA before it can before its clinical evaluation relative to expediting human corneal epithelial wound healing can be undertaken. The study we propose has been delineated by the FDA as fulfilling its requirements for the Phase I Clinical Trial. Therefore, its specific aim is to demonstrate in human volunteers the safety of the most concentrations of topical NTX most likely to be used in the clinical setting.

Study Design: Utilizing concentrations of 1×10^{-6} M applied once daily, and 1×10^{-6} M, 5×10^{-6} M, 1×10^{-5} M, and 5×10^{-5} M NTX four time daily dissolved in Vigamox® brand of moxifloxacin hydrochloride ophthalmic solution (Alcon), applied as eyedrops in volunteers who will receive the test solution or Ocuflax without NTX over a 24 hour period. They will be examined utilizing clinical observation and standard clinical tests of ocular health within the first 24 hours of drug administration and one week later for evidence of adverse side effects from the medication.

Impact: Corneal epithelial wounds, whether secondary to Combat trauma or to systemic diseases, such as diabetes mellitus, expose the cornea to significant complications such as infection, ulceration scarring, or even perforation. Expediting corneal epithelial wound healing through the use of topical NTX will reduce the likelihood of such complications in a safe and effective manner using the characteristics of the naturally occurring Opioid Growth Regulatory System.

Public Abstract:

The cornea of the eye is the clear tissue through which light enters the front of the eye so that it can be focused as an image on the retina in the back of the eye. The cornea is protected by a thin, five cell thick, skin-like tissue called its epithelium. Breaks in this tissue frequently occur from eye injuries, such as may occur in warfighters from blast-related trauma. These injuries expose the cornea to further damage such as from infections or ulcers, which can result in scarring and permanent vision loss. Abnormalities of corneal epithelial wound healing, such as occur in individuals with diabetes mellitus, may further inhibit wound healing and increase the likelihood complications from corneal epithelial injuries.

There are multiple treatments for corneal epithelial injuries. Unfortunately, none are uniformly successful, particularly in individuals, such as diabetics. Therefore, there is a need for treatments to enhance corneal epithelial wound healing.

Although we commonly think of opioids as pain medications and consciousness altering drugs, they perform many other bodily functions unrelated to these stereotypes. For the past 18 years, we have studied the role of a naturally occurring Opioid Growth Regulatory system in controlling cell division and wound healing of the corneal epithelium. We have demonstrated that one component of this system, the naturally occurring opioid growth factor (OGF), metenkephalin, decreases the rate of corneal epithelial cell division and wound healing. Conversely, blocking the effect of OGF by applying eyedrops containing the strong blocking agent, Naltrexone (NTX) significantly increases the rate of corneal epithelial cell division and wound healing in normal and in diabetic animals.

Before we can use NTX as a treatment for corneal wounds, we must demonstrate that it is safe to use in patients. The proposed study has been designed in consultation with the U.S. Food and Drug Administration to determine the safety and tolerability of NTX eyedrops in 16 human volunteers. Multiple tests will be performed to document the side effects of this medication if any. The medication is approved to be taken by mouth to treat overdose of substances, such as heroin. It is extremely doubtful, therefore, that the medication will have any adverse side effects when taken in eyedrop form.

NTX has the potential to be a significant improvement in the treatment of corneal injuries in warfighters and in their family members, especially those with abnormalities of corneal wound healing, such as diabetics. The proposed study is a major step in achieving this goal.

Key Research Accomplishments:

- Dr. Sassani and his associates have obtained approval from the Institutional and University Conflict of Interest Committees.
- They completed the first cohort of 4 volunteers at the once daily, 1×10^{-6} dosage, of topical Naltrexone in Vigamox® eyedrops in one eye of each volunteer
 - No untoward side effects were noted in this group of volunteers.
- They also have recruited and treated three patients for the second cohort who have completed the treatment schedule.
- They must recruit one more volunteer for this cohort and complete the other three cohorts.

Reportable Outcomes:

The research still is in progress. Therefore no reports have been made to scientific publications, nor have any presentations been delivered.

Conclusions:

Dr. Sassani and his associates have been funded to perform a Phase I Clinical Trial of Naltrexone dissolved in Vigamox® and applied topically as eye drops preliminary to a therapeutic trial of that medication in the treatment of corneal epithelial defects in diabetic individuals. During the past year, we have obtained Institutional and University Conflict of Interest Committee approval, for our study. As a result, Dr. Sassani has elected not to participate directly in data collection for the study. We have recruited Dr. Esther Bowie, an Ophthalmologist in the Department of Ophthalmology to assist Dr. Liang in volunteer examination and data collection. The recruitment of Dr. Bowie, who has a clinic schedule that complements that of Dr. Liang, should facilitate the examination of volunteers.

To date, we have completed our first cohort of 4 volunteers at the once daily, 1×10^{-6} dosage, of topical Naltrexone in Vigamox® eyedrops in one eye of each volunteer. No untoward side effects were noted in this group of volunteers. We also have recruited and treated three patients for the second cohort who have completed the treatment schedule. We need to recruit one more volunteer for this cohort and complete the other three cohorts.

In order to achieve this goal, we have requested a one year extension of the grant period, and a continuation of the present funding for twelve months, but are not requesting addition funds over those originally provided by the present award.

References: None

APPENDICES TO ANNUAL REPORT

APPENDIX A
Protocol

Research Proposal: **Phase I Clinical Trial of Topical Naltrexone Applied as Eyedrops**

Principal Investigator: Joseph W. Sassani, MD, MHA

IRB No. 29780

I. Specific Aims or Objectives:

The specific aim of the proposed research is to determine the safety of the potent opioid antagonist Naltrexone (NTX) applied topically in healthy human volunteers, preliminary to determining its effectiveness in facilitating the healing of corneal epithelium removed intentionally to improve operator visibility during vitrectomy surgery.

II. Background and Significance:

Naltrexone is a potent opioid antagonist that we have utilized dissolved in commercially available Vigamox® (moxifloxacin hydrochloride ophthalmic solution 0.5%, Alcon Laboratories, Inc., Fort Worth, Texas 76134). We will apply it topically to expedite corneal epithelial wound healing.

Appendix A is the USP Material Safety Data Sheet and Appendix B is the USP Certificate for Naltrexone. Appendix C is the manufacturer's package insert for Vigamox.

Naltrexone is an opioid antagonist that is approved for the treatment of both opioid dependence and alcohol dependence (Appendix D is the U.S. Department of Health and Human Services Division of Pharmacologic Therapies web site document on the use of Naltrexone for the treatment of alcohol and opioid dependence) Appendix E is the is the FDA October 2007 MedWatch Safety Labeling Changes Approved by the FDA Center for Drug Evaluation and Research (CDER) regarding Vivitrol® (naltrexone for extended-release injectable suspension, Alkermes).

As noted above, we propose to use Naltrexone topically to facilitate corneal epithelial healing in diabetic humans following elective removal at the time of vitrectomy for vitreous hemorrhage secondary to diabetic retinal

neovascularization (proliferative retinopathy). Such patients often have delayed corneal epithelial wound healing as a manifestation of diabetic keratopathy.

Diabetic keratopathy is a common complication that affects 50% of diabetic individuals sometime during the course of their disease.¹ Specific manifestations of this entity include nonhealing corneal epithelial defects, which can result from surgical or non-surgical trauma.^{1;2;2} For example, corneal epithelium frequently is abraded intentionally to improve operator visibility during vitrectomy surgery, such as that for diabetes-associated vitreous hemorrhage.

Nonhealing corneal epithelial defects are a source of prolonged patient discomfort, hinder post-operative fundus examination, and can result in secondary complications including infection and corneal decompensation. Multiple treatments, including lubricants, patching, and bandage contact lenses have been tried to prevent the development of such delayed epithelial wound healing. Unfortunately, none are uniformly successful.³⁻⁵ Therefore, there is a need for a safe and effective means to facilitate epithelial wound healing in diabetic patients in order to prevent these complications.

A. Opioid Growth Factor:

The native opioid peptide, [Met⁵]-enkephalin, termed opioid growth factor (OGF) is a pentapeptide with the sequence, Tyr-Gly-Gly-Phe-Met. Although there are numerous endogenous opioids and respective receptors, only OGF has been determined to serve a growth regulatory role. Thus, it functions in ontogeny, and in the proliferation of human and animal cancers.⁶⁻²⁶ OGF acts as a tonic inhibitor of cell division and does so in a receptor mediated fashion.^{7;18;20;27-35} Therefore, blockade of the opioid receptor by a strong blocking agent, such as naltrexone (NTX), results in up-regulation of DNA synthesis and cell division.^{6;14;19;36-39}

Endogenous opioid systems have been demonstrated to modulate development of the mammalian retina, and the mRNA for preproenkephalin A (PPE), the prohormone for OGF, has been demonstrated in the developing and mature rat retina.^{40;41} Moreover, OGF, itself, has been found in the developing rat retina.⁴²

B. OGF and the Opioid Growth Regulatory System (OGRS):

For the past 17 years, we have been exploring the role of the OGF and its receptor, (OGFr) in the homeostasis and healing of corneal epithelium. These studies included evaluating the impact of the Opioid Growth Regulatory System (OGRS) on homeostatic and wounded corneal epithelium utilizing cell and organ culture, and *in vivo* experiments in animals, and cell and organ culture experiments utilizing human eye bank corneas not suitable for transplantation.

As noted above, opioids perform many biologic functions; however, only OGF has been demonstrated to regulate cell division. OGF is a tonic inhibitor of cell division, which indicates that there appears to be some degree of cell division inhibition chronically being exerted on all mitotically capable cells under the control of OGF. OGF exerts this down regulatory influence in a receptor mediated fashion. Its receptor previously was termed the “zeta” receptor but now is signified by “OGFr”. The relatively weak opioid antagonist, naloxone (NAL) is specific for OGFr and prevents exogenously administered OGF from further depressing the rate of cell

division. It does not, however, increase the rate of cell division when added to cultures of corneal epithelial cells. In contrast, naltrexone, (NTX) is a potent blocker of the OGF_r. Its exogenous administration to a population of homeostatic or healing cells significantly increases the rate of cell division. Utilizing the characteristics of OGF, OGF_r, and their blocking agents given singly or in combination, it is possible to document the presence of the OGRS and examine its level of function. We have used these techniques repeatedly over the years in order to elucidate the function of the OGRS in corneal epithelial homeostasis and wound healing.

C. OGF and Epithelial Wound Healing:

Early studies on the effects of the OGRS on corneal epithelial healing were performed in the rabbit because its larger corneal diameter permitted larger initial abrasions, thereby facilitating comparison between the growth regulatory impact of manipulations of the OGRS. In this model, in which 10 mm abrasions are created, we are able to demonstrate a significant increase in the rapidity of the re-epithelialization of the abrasions following the topical administration of the strong opioid receptor blocking agent, NTX.⁴³ Moreover, the presence of both OGF and its receptor are confirmed in both the normal and injured corneal epithelium utilizing immunocytochemical techniques. Similarly, either systemically or topically administered NTX has been demonstrated to accelerate rate of re-epithelialization of 4 mm abrasions in the rat corneal epithelium.⁴⁴ This effect is seen as early as 8 hrs. following injury; however, only the experimental group receiving systemic NTX experiences a marked increase in the incidence of complete re-epithelialization.

D. Cell Biology of OGF:

The above experiments demonstrate that OGF is a tonically active inhibitor of corneal epithelial wound healing as evidenced by the fact that blockade of its action by the strong opioid antagonist, NTX, results in a significant increase in the rapidity with which corneal abrasions are re-epithelialized. Utilizing a probe for mRNA of preproenkephalin A (PPE), the prohormone for OGF, and *in situ* hybridization techniques, we have demonstrated PPE-related silver grains on basal and suprabasal cells located in the central and peripheral cornea, limbus, and conjunctiva.⁴⁵ No regional differences were found in the distribution of the PPE. Thus, OGF appears to be produced in an autocrine manner thereby permitting self-regulation of cell proliferation by corneal epithelium.

E. Human Corneal Epithelial Wound Healing:

In the human organ culture model, 8mm central corneal abrasions are created in corneas not suitable for human transplantation, and are cultured in media containing 10^{-6} M naltrexone or in control media supplemented with an equal volume of water. NTX accelerates the rate of epithelial migration by 21% to 89% during the period 24 to 96 hours after wounding.⁴⁶ As a result of this wound healing acceleration, all NTX treated corneas are healed between 96 and 120 hours after wounding, whereas all of the control corneas are not healed until 168 hours. Conversely, supplementation of culture medium with 10^{-6} M OGF delays wound healing resulting in 24% to 260% more defect being present in the treated specimens at day seven. As would be anticipated, OGF significantly depresses the labeling index with radioactive thymidine relative to control specimens by 75%. Importantly, both OGF and its receptor are detected in the healing epithelium utilizing immunocytochemical techniques. Thus, OGF regulates corneal epithelial wound healing as a tonically active inhibitory peptide that is subject to reversal by its antagonist NTX.

F. IOGRS and Corneal Epithelial Wound Healing in Diabetes:

Diabetes mellitus can be complicated by multiple ocular abnormalities including non-healing corneal erosions and corneal ulcers.² Abnormalities of endogenous opioid systems have been documented in association with diabetes. For example, genetically diabetic mice (*db/db*) have elevated plasma [Met⁵]-enkephalin levels.^{47;48} Elevated [Met⁵]-enkephalin levels also are present in the plasma of diabetic humans.^{49;50} The role of such opioid system abnormalities in the generation of diabetic corneal complications remains to be determined. Nevertheless, these data are suggestive, and encouraged us to investigate whether manipulation of the IOGRS might be helpful in facilitating corneal epithelial wound healing in diabetic animals.

Accordingly, we produced standardized corneal abrasions in rats with four or eight weeks of streptozotocin-induced diabetes.⁵¹ Utilizing immunocytologic techniques, such diabetic animals were shown to possess a similar distribution of OGF and its receptor as non-diabetic control rats. When diabetic rats were treated with NTX (30 mg/kg twice daily), depending upon the duration of the diabetic state, untreated animals displayed delays in epithelial wound healing from 11% to 1700% compared to non-diabetic control animals. NTX treatment of diabetic animals resulted in accelerated epithelial wound healing that approximated or surpassed untreated non-diabetic control animals. Untreated diabetic animals experienced a 90% reduction in DNA synthesis compared to non-diabetic animals; however, NTX treatment resulted in up to an 800% increase in DNA synthesis. Thus, for the first time, the IOGRS was demonstrated to be functional in the corneal epithelium of diabetic rats, and its manipulation by treatment with NTX was capable of up-regulating DNA synthesis in the corneal epithelium of these diabetic animals, thereby restoring the rate of re-epithelialization of wounded corneas to a “normal” or faster rate. The therapeutic implications of these results are obvious.

Subsequent studies have demonstrated that topically applied NTX is effective over a one hundred fold dosage (10^{-4} to 10^{-5} M concentration) for accelerating corneal wound healing in diabetic rats subjected to standardized corneal abrasions.^{52;53} No differences in intraocular pressures, corneal thickness, endothelial cell number, or epithelial apoptosis, necrosis, or organization were observed between untreated diabetic rats (DB), diabetic rats treated with systemic insulin (DB-IN), or normal rats with and without treatment with NTX. The DB group had a twofold decrease in corneal sensitivity from the normal and DB-IN groups prior to NTX treatment but were comparable to the normal and DB-IN groups for at least 2 weeks after chronic exposure to 10^{-3} to 10^{-7} M NTX was terminated. No differences between normal and DB-IN groups were noted. Therefore, topical application of NTX over a 10,000-fold range of dosage had no overt toxicity for the parameters studied.⁵⁴ Moreover, such therapy does not compromise adhesion complexes in normal or diabetic corneal epithelium.⁵⁵

G. Need for Human Studies

The above findings strongly suggest that NTX therapy should be useful in the treatment of diabetic keratopathy in humans. NTX is approved to be taken systemically for the treatment of drug and alcohol abuse.⁵⁶⁻⁶² Nevertheless, it is not approved for topical administration to facilitate corneal epithelial healing in diabetic individuals. Therefore, safety and efficacy studies that address these issues are necessary in order to acquire Investigational New Drug status for NTX for these purposes.

We have been in contact with the US Food and Drug Administration (FDA) regarding the appropriate studies to document the safety and efficacy of NTX for these purposes.

The initial study will consist of short term (24 hr) administration of NX or control vehicle to volunteer human subject who meet inclusion/exclusion criteria.

III. Research Design, Methods and Human Subjects

1. Population to be studied (including control subjects)

The study population will consist of 20 normal volunteers who can range in age from 21 to 50 years. This limited age range has been selected to decrease study group variability that might be attributed to normal variations in corneal thickness or endothelial cell count attributable to age. Only individuals who can personally give informed consent will be eligible. Women of child bearing age must be taking birth control pills or have been sterilized for other reasons. Men must be using contraceptives.

2. Inclusion/exclusion criteria

The following individuals are excluded from participation in the study:

- a. Outside the age criteria
- b. Women who are not sterile and who are not using oral contraceptive, or men not using contraceptive.
- c. Previous corneal or other ocular surface disease
- d. Systemic disease associated with ocular surface complications such as autoimmune or rheumatologic disorder, diabetes, etc.
- e. Contact lens wearers who cannot be without their lenses for the first 24 hours of the study during which medication or control treatment are being administered
- f. Individuals who cannot give informed consent
- g. Allergy to opioids, or to components of the proprietary antibiotic vehicle utilized, which will be Vigamox topical antibiotic solution

3. Study design

All test medications will be prepared by the Skip's Pharmacy using sterile techniques and will be responsible for assigning test bottle numbers. The Skip's Pharmacy will record which bottles they have assigned to contain the test medication or vehicle only. The investigators will not know whether the contents of a bottle from any given dosage group contains medication or sterile vehicle. That list, in turn, will be given to the monitor so that the investigator can have access to the code should untoward side effects develop. Medication will be stored and accounted for by the Clinical Discovery Group of the Department of Ophthalmology.

All eyedrops will be administered to one eye only, and any repeat dosage will be to the same eye. Two to three minutes of nasolacrimal occlusion will follow the administration of each test medication drop administration. Initially, one drop of 10^{-6} topical Naltrexone will be administered to three normal volunteers and then three members of each treatment group, respectively, will receive one of the following concentrations (10^{-6} M, 5×10^{-6} M, 10^{-5} M, 5×10^{-5} M) dissolved in Vigamox eye drops. Five other individuals (one from each treatment group) will serve as control subjects and will receive only the Vigamox drop without the test medication.. Thus, each study group will consist of four individuals randomly assigned to be either treated or control subjects. In order to maximize safety, the order of medication testing will be from lowest to highest concentration, and one concentration group will have completed the full one week course before a second treatment concentration is begun.

The medication or control solutions will be administered according to the following schedule:

Study Visit #1

Baseline history and complete dilated eye examination plus pachymetry, corneal topography, endothelial specular microscopy, Shirmer test, corneal sensitivity, and fundus photography are performed. Subjects may not wear contact lenses after midnight of the preceding night.

Study Visit #2

8:00 AM: Patient arrives and eyes are examined externally and at the slit lamp; however, no intraocular pressure (IOP) is measured so that topical anesthetic need not be administered. Pupil examination and comparison between each eye will precede and follow each test eyedrop administration.

9:00 AM: DROP #1 is given (the first treatment group will only receive one drop but all subsequent groups will receive 24 hours of treatment).

Eyes are examined 1 hr later but IOP is not measured.

12:30 PM (4 hr): Eyes are examined but IOP is not measured

1:00 PM: DROP #2 is given

2:00 PM Eyes are examined and IOP is measured

DROP #3 is given at home (~ 5:00 PM)

DROP #4 is given at home (~9:00 PM)

Study Visit #3

The following morning, the patient arrives around 8:30 am next day for complete eye examination plus pachymetry, corneal topography, endothelial specular microscopy, Shirmer test, corneal sensitivity, and fundus photography are performed. Subjects may resume contact lens wear after this meeting.

Study Visit #4

7 days later: patient arrives for complete eye examination plus pachymetry, corneal topography, endothelial specular microscopy, Shirmer test, corneal sensitivity, and fundus photography are performed. Subjects may not wear contact lenses after midnight of the preceding night.

All eyedrop bottles should be returned at the last follow-up visit.

4. Recruitment and consent process

Potential volunteers will be informed of the existence of the study through posters on HMC public bulletin boards. The poster will include information on how an interested individual can contact a study coordinator within the Department of Ophthalmology who will do preliminary phone screening to exclude known conditions that would preclude participation in the study.

At Study Visit #1, prior to any examination, informed written consent will be obtained by the study coordinator after discussion with one of the two clinicians participating in the study.

5. Procedures to be followed

The procedures and their timing will be as described in the Study Design section.

Examination reporting forms will be the standard, pre-printed forms utilized for patients within the Department of Ophthalmology including the standard recording forms for each of the special tests (corneal topography and endothelial cell count). These forms include subject numerical grading of pain or discomfort.

6. Primary and secondary outcome measures

The primary outcome is the detection of any untoward subjective or objective consequences of the medication. The latter as measured by the examination and ancillary tests enumerated in the Study Design section.

7. Statistical and sample size justification

The sample size is as suggested by the FDA.

8. Risks and discomforts

No differences in intraocular pressures, corneal thickness, endothelial cell number, or epithelial apoptosis, necrosis, or organization were observed between untreated diabetic rats (DB), diabetic rats treated with systemic insulin (DB-IN), or normal rats with and without treatment with NTX treated for at least 2 weeks after chronic exposure to 10(-3) to 10(-7) M NTX was terminated. No differences between normal and DB-IN groups were noted. Therefore, topical application of NTX over a 10,000-fold range of dosage had no overt toxicity for the parameters studied in rats.⁵⁴

Thus, our animals studies would predict no significant ocular toxicity from the course of treatment proposed in this study. Moreover, as noted above, NTX is approved for chronic systemic administration in the treatment of drug and alcohol abuse.

It is possible that transient burning may occur at the time of eyedrop administration and idiosyncratic reactions always are possible, but are extremely doubtful given the safety of the medication for systemic administration.

Clinical observation during examination and drop administration will minimize risks to subjects.

9. Benefits

The study subjects will not benefit from taking part in this research. Results of the study may prepare the way for a treatment that may provide significant benefit to those who suffer from the corneal complications of diabetes mellitus.

10. Safeguards and Confidentiality

The study will comply with all Hershey Medical Center Human Subjects Protection policies regarding the protection of humans subjects in research. The study subjects will be followed intensively during the duration of the study and will receive multiple standard clinical tests to assist in detecting any untoward effects on the study subjects. All involved in the study will be required to observe the Health Insurance Portability and Accountability Act (HIPAA) regulations regarding patient confidentiality. The study monitor will be able to break the test drug masking immediately to determine if any untoward effects are study drug related. This trial will be conducted in compliance with the protocol, GCP, and applicable regulatory requirements.

A. Recruitment and consent process

Potential volunteers will be informed of the existence of the study through posters on HMC public bulletin boards. The poster will include information on how an interested individual can contact a study coordinator within the Department of Ophthalmology who will do preliminary phone screening to exclude known conditions that would preclude participation in the study.

At Meeting #1, prior to any examination, informed written consent will be obtained by the study coordinator after discussion with one of the two clinicians participating in the study.

B. Risks and discomforts

No differences in intraocular pressures, corneal thickness, endothelial cell number, or epithelial apoptosis, necrosis, or organization were observed between untreated diabetic rats (DB), diabetic rats treated with systemic insulin (DB-IN), or normal rats with and without treatment with NTX treated for at least 2 weeks after chronic exposure to 10(-3) to 10(-7) M NTX was terminated. No differences between normal and DB-IN groups were noted. Therefore, topical application of NTX over a 10,000-fold range of dosage had no overt toxicity for the parameters studied in rats.⁵⁴

Thus, our animals studies predict no significant ocular toxicity from the course of treatment proposed in this study. Moreover, as noted above, NTX is approved for chronic systemic administration in the treatment of drug and alcohol abuse.

It is possible that transient burning may occur at the time of eyedrop administration and idiosyncratic reactions always are possible, but are extremely doubtful given the safety of the medication for systemic administration.

11. Data Safety and Monitoring Plan

The study involves low risk to subjects because it involves medication that is approved by the Food and Drug Administration to be taken internally, although it has not previously been used in eyedrop form.

An investigator with no conflict of interest related to this study (Dr. David Liang) will have primary responsibility for the conduct of the study, including subject selection, informed consent, and the making and interpretation of subjective outcome measurements. The safety monitor for the research group will be Thomas Gardner, a physician who will not participate in the actual collection of data or the performance of the examinations for the study (see specific duties in the following paragraph, responsibilities of the Medical Monitor. The Clinical Discovery Group of the Department of Ophthalmology will ensure that all eligibility criteria and consent requirements are met prior to a subject's participation in the study and that all study procedures and adverse event reporting occur according to the IRB approved protocol. Their work will be supervised by Dr. Gardner.

Responsibilities of the Medical Monitor

The medical monitor is required to review all unanticipated problems involving risk to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event. At a minimum, the medical monitor must comment on the outcomes of the event or problem and in case of a serious adverse event or death, comment on the relationship to participation in the study. The medical monitor must also indicate whether he/she concurs with the details of the report provided by the principal investigator. Reports for events determined by either the investigator or medical monitor to be possibly or definitely related to participation and reports of events resulting in death must be promptly forwarded to the USAMRMC ORP HRPO.

Medical Monitor: David Quillen, MD

All data forms and study specific information will be kept in locked file cabinets and in a password protected computer database with access limited to the PI, the non-conflicted investigator and the Clinical Discovery Group. Any presentation or publication of the data will be done in aggregate fashion without identifiers.

All adverse events will be documented on study specific case report forms and entered into a computer-based log. Anticipated adverse events for this study include the following: mild burning on eyedrop administration. Nevertheless, each participant will be evaluated utilizing multiple measurements of eye health even though no such complications are anticipated.

Any presumed complication from the medication will be reported by the PI or the non-conflicted investigator to the IRB according to HSPO policies, and the occurrence of such a complication will be grounds for stopping the Protocol until the presumed complication is evaluated. The study will be suspended if any participants experience an ocular toxicity after receiving the study drug. Such toxicity might include but is not limited to decreased vision, persistent symptomatic ocular irritation, elevated intraocular pressure, intraocular inflammation, cataract, or retinal abnormality. This event will be reported to and reviewed by the IRB before the study may resume. Additionally, all data on each treatment group will be reviewed at the completion of each drug dosage treatment group to evaluate the data for any indication of side effects that are not clinically apparent. A summary of adverse events, study progress and protocol modifications will be included for IRB review in the continuing review report.

All adverse events will be followed until their resolution.

Research results that impact the health of the subjects, including findings detected as part of the ophthalmic examinations, screening or diagnostic tests will be shared with volunteers. Compensation

12. Compensation:

As noted above, study subjects will receive \$300 for completing participation in the study. Compensation will not be provided to study subjects for injuries sustained during the study, which must be covered by the subject's personal insurance, etc. Individuals who withdraw early will receive no compensation. If someone chooses to withdraw from the study before the administration of the test medication or control substance there will be no compensation. If they withdraw after that time they will receive 1/3 of the compensation for each of the Meeting days in which they participate.

If an individual withdraws from the study follow-up will be as required depending upon whether or not the individual experienced an adverse event that resulted in their withdrawing from the study. As stated above, all adverse events will be followed until their resolution. No followup is necessary if there are no adverse reactions.

13. Drugs or Biologicals

As stated in Section II, USP, FDA, and manufacturer's information on the medications used in this study are contained in the following: Appendix A is the USP Material Safety Data Sheet and Appendix B is the USP Certificate for Naltrexone. Appendix C is the manufacturer's package insert for Vigamox.

Naltrexone is an opioid antagonist that is approved for the treatment of both opioid dependence and alcohol dependence (Appendix D is the U.S. Department of Health and Human Services Division of Pharmacologic Therapies web site document on the use of Naltrexone for the treatment of alcohol and opioid dependence) Appendix E is the is the FDA October 2007 MedWatch Safety Labeling Changes Approved by the FDA Center for Drug Evaluation and Research (CDER) regarding Vivitrol® (naltrexone for extended-release injectable suspension, Alkermes).

All eyedrop bottles should be returned at the last follow-up visit.

IV. Investigator qualifications and roles in the conduct of the study

A. Joseph W. Sassani MD, MHA is the Principal Investigator. He is Professor of Ophthalmology and Pathology, having had two years of Ophthalmic Pathology training at the Scheie Eye Institute of the University of Pennsylvania. He has been a practicing Ophthalmologist on the staff of the Hershey Medical Center. Additionally, for the past 17 years, has been working with Drs. Ian Zagon and Patricia Mc Laughlin delineating the role of the OGRS in corneal epithelial health and healing.

B. David Liang MD is a Co-investigator and a practicing Ophthalmologist with Sub-specialty training in Corneal and External Diseases. He will be most helpful in identifying corneal complications should they arise secondary to drug treatment during the study.

C. Ian S. Zagon PhD is a basic scientist who first delineated the OGRS and has worked with Dr. Sassani in identifying its role in corneal epithelial health and healing.

D. Esther Bowie MD is a Co-investigator, and practicing Ophthalmologist and Retinal specialist in the Department of Ophthalmology. Her retinal expertise will complement Dr. Liang's expertise in Cornea and External Diseases.

V. Facilities

The research will be conducted in the clinical facilities of the HMC Department of Ophthalmology.

VI. Protocol Addendum

Phase I Clinical Trial of Topical Naltrexone Applied as Eyedrops
HRPO Log Number A-15749

The following are reporting requirements and responsibilities of the Principal Investigator to the United States Army Medical Research and Materiel Command's (USAMRMC) Office of Research Protections (ORP), Human Research Protection Office (HRPO).

(1) The protocol will be conducted in accordance with the protocol submitted to and approved by the USAMRMC ORP HRPO and will not be initiated until written notification of approval of the research project is issued by the USAMRMC ORP HRPO.

(2) Accurate and complete study records will be maintained and made available to representatives of the U.S. Army Medical Research and Materiel Command as a part of their responsibility to protect human subjects in research. Research records will be stored in a confidential manner so as to protect the confidentiality of subject information.

(3) All unanticipated problems involving risk to subjects or others, serious adverse events related to participation in the study and subject deaths related to participation in the study will be promptly reported by phone (301-619-2165), by email (hsrrb@amedd.army.mil), or by facsimile (301-619-7803) to the USAMRMC, Office of Research Protections, Human Research Protection Office. A complete written report will follow the initial notification. In addition to the methods above, the complete report will be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RP, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

(4) Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the IRB, the institution, the Sponsor, or regulatory agencies will be promptly reported to the USAMRMC ORP HRPO.

(5) Any deviation to the protocol that may have an adverse effect on the safety or rights of the subject or the integrity of the study will be reported to the USAMRMC ORP HRPO as soon as the deviation is identified.

(6) Major modifications to the research protocol and any modifications that could potentially increase risk to subjects will be submitted to the USAMRMC ORP HRPO for approval prior to implementation. All other amendments will be submitted with the continuing review report to the USAMRMC ORP HRPO for acceptance.

(7) A copy of the approved continuing review report and the local IRB approval notification will be submitted to the USAMRMC ORP HRPO as soon as these documents become available. A copy of the approved final study report and local IRB approval notification will be submitted to the USAMRMC ORP HRPO as soon as these documents become available.

(8) The knowledge of any pending compliance inspection/visit by the FDA, OHRP, or other government agency concerning this clinical investigation or research, the issuance of Inspection Reports, FDA Form 483, warning letters or actions taken by any Regulatory Agencies including legal or medical actions and any instances of serious or continuing noncompliance with the regulations or requirements that relate to this clinical investigation or research will be reported immediately to USAMRMC ORP HRPO.

VII. Reference List

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APPENDIX a



Material Safety Data Sheet

12601 Twinbrook Parkway, Phone Calls: 301-816-8129 Rockville, MD 20852 USA 8 a.m. to 5 p.m. EST Mon. -Fri.

ATTENTION !

USP Reference Standards are sold for chemical test and assay purposes only, and NOT for human consumption. The information contained herein is applicable solely to the chemical substance when used as a USP Reference Standard and does not necessarily relate to any other use of the substance described, (i.e. at different concentrations, in drug dosage forms, or in bulk quantities). USP Reference Standards are intended for use by persons having technical skill and at their own discretion and risk. This information has been developed by USP staff from sources considered reliable but has not been independently verified by the USP. Therefore, the USP Convention cannot guarantee the accuracy of the information in these sources nor should the statements contained herein be considered an official expression. NO REPRESENTATION OR WARRANTY, EXPRESS OR IMPLIED, INCLUDING THE WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR PURPOSE is made with respect to the information contained herein.

NALTREXONE **Catalog Number:** 1453504 **Revision Date:** November 16, 2006

SECTION 1 - PRODUCT AND COMPANY IDENTIFICATION

Common Name: Naltrexone

Manufacturer: U. S. Pharmacopeia **Responsible Party:** Reference Standards Technical Services **Mailing Address:** 12601 Twinbrook Parkway, Rockville, MD 20852 USA **Phone:** 301-816-8129 **Hours:** 8 a.m. to 5 p.m. EST Mon. - Fri. **Product Use:** USP Reference Standards and Authentic Substances are used for chemical tests and assays in analytical, clinical, pharmaceutical, and research laboratories.

SECTION 2 - HAZARD INFORMATION

EMERGENCY OVERVIEW: Irritant.

Adverse Effects: Adverse effects may include anxiety; nervousness, restlessness, and/or trouble sleeping; drowsiness; unusual tiredness; lightheadedness; nausea or vomiting; headache; chills; cough; hoarseness; increased thirst; runny, stuffy nose; sinus problems; sneezing; sore throat; diarrhea; sweating; slowed breathing; fast or pounding heartbeat; constricted pupils; decreased body temperature; mental depression; joint, muscle pain, or abdominal pain; skin rash; and sexual problems in males. Possible allergic reaction to material if inhaled, ingested or in contact with skin.

Overdose Effects: Overdose effects may include salivation, lethargy, tremors, and convulsions.

Acute: Eye, skin, gastrointestinal and/or respiratory tract irritation.

Chronic: Possible hypersensitization.

Medical Conditions Aggravated by Exposure: Hypersensitivity to the material, heart problems, impaired liver or kidney function, and

opioid dependence.

Cross Sensitivity: n/f

Target Organs: Central nervous system and liver

For additional information on toxicity, see Section 11.

SECTION 3 - COMPOSITION/INFORMATION ON INGREDIENTS

Common Name: Naltrexone

Formula: C₂₀H₂₃NO₄ **Synonym:** N-Cyclopropylmethylnoroxymorphone **Chemical Name:** Morphinan-6-one, 17-

(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-, (5α) **CAS:** 16590-41-3 **RTECS Number:** QD2155000 **Chemical Family:**

Noroxymorphone derivative **Therapeutic Category:** Antagonist (to narcotics) **Composition:** Pure Material

SECTION 4 - FIRST AID MEASURES

Inhalation: Causes irritation. Avoid inhalation. Remove to fresh air.

Eye: May cause irritation. Flush with copious quantities of water.

Skin: May cause irritation. Flush with copious quantities of water.

Ingestion: May cause irritation. Flush out mouth with water. This material is rapidly and almost completely absorbed from the gastrointestinal tract. Effects can last between 24 and 72 hours.

General First Aid Procedures: Remove from exposure. Remove contaminated clothing. Persons developing serious hypersensitivity (anaphylactic) reactions must receive immediate medical attention. If person is not breathing give artificial respiration. If breathing is difficult give oxygen. Obtain medical attention.

Note to Physicians

Overdose Treatment: Treatment of overdose should be symptomatic and supportive and may include the following:

- 1 Do NOT induce vomiting.
- 2 Administer activated charcoal as a slurry.
- 3 For seizures, administer intravenous diazepam or lorazepam. If seizures recur, consider phenobarbital. Monitor for hypotension, dysrhythmias, respiratory depression, and need for endotracheal intubation. Evaluate for hypoglycemia, electrolyte disturbances, and hypoxia.
- 4 For acute lung injury, maintain ventilation and oxygenation and evaluate frequent arterial blood gas or pulse oximetry monitoring. Early use of PEEP and mechanical ventilation may be needed.
- 5 For hypertension, sedate with intravenous benzodiazepines. If unresponsive to sedation, administer intravenous nitroprusside.
- 6 For hypotension, administer intravenous fluids and place in Trendelenburg position. If unresponsive to these measures, administer dopamine or norepinephrine.
- 7 Monitor respiratory rate, heart rate, blood pressure, and temperature. [Meditext 2006]

SECTION 5 - FIREFIGHTING MEASURES

Extinguisher Media: Water spray, dry chemical, carbon dioxide or foam as appropriate for surrounding fire and materials.

Fire and Explosion Hazards: This material is assumed to be combustible. As with all dry powders it is advisable to ground mechanical equipment in contact with dry material to dissipate the potential buildup of static electricity.

Firefighting Procedures: As with all fires, evacuate personnel to a safe area. Firefighters should use self-contained breathing equipment and protective clothing.

SECTION 6 - ACCIDENTAL RELEASE MEASURES

Spill Response: Wear approved respiratory protection, chemically compatible gloves and protective clothing. Wipe up spillage or collect spillage using a high efficiency vacuum cleaner. Avoid breathing dust. Place spillage in appropriately labelled container for disposal. Wash spill site.

SECTION 7 - HANDLING AND STORAGE

Handling: As a general rule, when handling USP Reference Standards avoid all contact and inhalation of dust, mists, and/or vapors associated with the material. Wash thoroughly after handling.

Storage: Store in tight, light-resistant container as defined in the USP-NF. This material should be handled and stored per label instructions to ensure product integrity.

SECTION 8 - EXPOSURE CONTROL / PERSONAL PROTECTION

Engineering Controls: Engineering controls such as exhaust ventilation are recommended.

Respiratory Protection: Use a NIOSH-approved respirator, if it is determined to be necessary by an industrial hygiene survey

involving air monitoring. In the event that a respirator is not required, an approved dust mask should be used. **Gloves:** Chemically compatible **Eye Protection:** Safety glasses or goggles **Protective Clothing:** Protect exposed skin.

Exposure Limits: n/f

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES

Properties as indicated on the MSDS are general and not necessarily specific to the USP Reference Standard Lot provided.

Appearance and Odor: Creamy to off-white powder; odorless or faint odor

Odor Threshold: n/f

pH: n/f

Melting Range: 168 - 170° C

Boiling Point: n/f

Flash Point: n/f

Autoignition Temperature: n/f

Evaporation Rate: n/f

Upper Flammability Limit: n/f

Lower Flammability Limit: n/f

Vapor Pressure: n/f

Vapor Density: n/f

Specific Gravity: 1.3

Solubility in Water: Insoluble

Fat Solubility: n/f

Other Solubility: Soluble in ethanol

Partition Coefficient: n-octanol/water: 1.92

Percent Volatile: n/f

Reactivity in Water: n/f
Explosive Properties: n/f
Oxidizing Properties: n/f
Formula: C₂₀H₂₃NO₄
Molecular Weight: 341.40

SECTION 10 - STABILITY AND REACTIVITY

Conditions to Avoid: Avoid exposure to light and moisture.

Incompatibilities: Strong oxidizers

Decomposition Products: When heated to decomposition material emits toxic fumes of NO_x. Emits toxic fumes under fire conditions.

Stable? Yes **Hazardous Polymerization?** No

SECTION 11 - TOXICOLOGICAL PROPERTIES

Oral Rat: LD50: n/f

Oral Mouse: LD50: n/f

Other Toxicity Data: n/f

Irritancy Data: n/f

Corrosivity: n/f

Sensitization Data: n/f

Listed as a Carcinogen by: NTP: No IARC: No OSHA: No

Other Carcinogenicity Data: Studies in rats have shown that naltrexone caused small increases in the numbers of mesotheliomas in males and tumors of vascular origin in both sexes. However, only the incidence of vascular tumors in females (4%) exceeded the maximum (2%) reported in historical control groups. No evidence of carcinogenicity was observed in several other 2-year studies in mice or rats receiving naltrexone in doses of 30 or 100 mg/kg/day, respectively.

Mutagenicity Data: Naltrexone tested negative in the following in vitro tests: bacterial reverse mutation assay (Ames), the heritable translocation assay, Chinese hamster ovary (CHO) cell sister chromatid exchange assay, and the mouse lymphoma gene mutation assay. Naltrexone tested negative in the in vivo mouse micronucleus assay, but positive in the Drosophila recessive lethal frequency assay, the non-specific DNA damage in repair tests with E. Coli and WI-38 cells, and urinalysis for methylated histadine residues.

Reproductive and Developmental Effects: Naltrexone given orally caused a significant increase in pseudopregnancy and a decrease in pregnancy rates in rats at 100 mg/kg/day. There was no effect on male fertility at this dose level. Oral naltrexone has been shown to increase the incidence of early fetal loss in rats administered doses of 30 mg/kg/day and higher and in rabbits administered doses of 60 mg/kg/day and higher. Rats and rabbits administered oral naltrexone at doses up to 200 mg/kg/day during pregnancy did not experience fetal changes or birth defects in their offspring.

SECTION 12 - ECOLOGICAL INFORMATION

Ecological Information: n/f

SECTION 13 - DISPOSAL CONSIDERATIONS

Disposal: Dispose of waste in accordance with all applicable Federal, State and local laws.

SECTION 14 -TRANSPORT INFORMATION
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Shipping Name: n/f **Class:** n/f **UN Number:** n/f **Packing Group:** n/f **Additional Transport Information:** n/f

SECTION 15 - REGULATORY INFORMATION

U.S. Regulatory Information: n/f **International Regulatory Information:** EINECS: 240-649-9

SECTION 16 - OTHER INFORMATION

Revision: 16-Nov-06

Previous Revision Date: 31-Aug-04

APPENDIX b

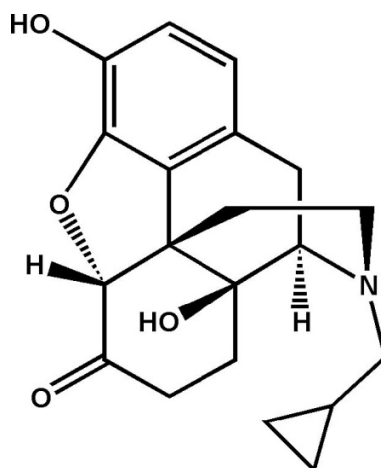
USP Certificate



U.S. Pharmacopeia
The Standard of QualitySM

Naltrexone

LOT H0C150



Molecular Weight

341.41

**Molecular
Formula**

$C_{20}H_{23}NO_4$

CAS Number

16590-41-3

LABEL TEXT

Naltrexone

on the as-is basis.

Keep container tightly closed.

Protect from light.

200 mg

Do not dry. For quantitative
applications, use a value of
987 µg of naltrexone per mg

**FOR USE WITH SPECIFIED USP–
NF TESTS • NOT FOR USE AS A
DRUG • READ MSDS BEFORE
USING**
CAT. NO. 1453504 USP
Rockville, MD LOT H0C150

USP certifies that the USP
Reference Standards
Committee, in accordance with
their rules and procedures,

Unless otherwise
stated on the
Reference Standard
label, a value of
100.0% should be
used in USP or NF
compendial

Current lots are identified in
the Official USP Reference
Standards catalog. In some
cases, the previous lot may
still be considered official. If
so, it is identified in the
column marked “Previous
Lot/Valid Use Date.”
Ordinarily, the previous lot is
carried in official status for
about one year after the
current lot enters distribution.

Follow the instructions in
the appropriate USP or NF
Monographs and General
Requirements for Tests and
Assays of the current USP–
NF. In the event that

determined that this USP Reference
Standard lot is suitable to assess
compliance with the monograph
standards for which it is specified. The
critical characteristics of this lot are
usually determined independently in
three or more laboratories, including
USP and academic or industrial
collaborators.



Page 1 of 2 14-Oct-2005
Calculation Value

applications for which the use
of this Reference Standard is
intended. Please refer to the
specific Reference Standard
label for further information.

Expiration

It is the responsibility of each user to
determine that this lot is current
when used. To ensure up-to-date
information, USP publishes the
Official USP Reference Standards
Catalog, which contains official lot
designations. This information is
also available on the USP web site,
at www.usp.org, as well as in the
bimonthly subscription publication,
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Page 2 of 2 14-Oct-2005

Appendix c:

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Appendix d

- [home](#)
- [regulations](#)
- [pharmacotherapy](#)
- [co-morbidities](#)
- [find treatment](#)
- [patient resources](#)
- [provider resources](#)

[Advanced Search](#) | [Help](#)

- [Opioid Treatment Regulation](#)
 - [Accreditation](#)
 - [Certification](#)
 - [Exception Requests](#)
 - [Buprenorphine](#)
 - [Guidance to OTPs](#)
 - [...more](#)
- [Pharmacotherapy](#)
 - [Buprenorphine](#)
 - [Methadone](#)
 - [Naltrexone](#)
 - [...more](#)
- [Co-morbidities](#)
 - [Hepatitis](#)
 - [HIV/AIDS](#)
 - [Co-Occurring Disorders](#)
 - [...more](#)

Naltrexone

Naltrexone is an opioid antagonist that is used in the treatment of both opioid dependence and alcohol dependence.

Naltrexone for alcohol dependence

Naltrexone in injectable form (Vivitrol®) is a new treatment option for patients diagnosed with alcohol dependence. In 2006, FDA approved the long-acting formulation of naltrexone which is designed for a once-monthly dosing of naltrexone. In people with alcohol dependence, it is believed that this blockade diminishes craving for alcohol and leads to a greater ability to resist urges to drink excessively. Naltrexone is also available in oral form (ReVia®).

Although the mechanism responsible for the reduction in alcohol consumption observed with treatment is not entirely understood, preclinical data suggests that occupation of the opioid receptors results in the blockade of the neurotransmitters in the brain that are believed to be involved with alcohol dependence. This blockade may result in the reduction in alcohol consumption observed in patients treated with IM naltrexone.

- [Medical Treatments for Alcohol Dependence](#). Internet Alcohol Recovery Center

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 - [Find Treatment in Your Area](#)
- [Patient & Family Resources](#)
 - [About MAT](#)
 - [Support Organizations](#)
 - [...more](#)
- [Provider Resources](#)
 - [SAMHSA D-ATM \(Digital Access to Medication\)](#)
 - [Buprenorphine Training](#)
 - [Addiction Technology Transfer Centers](#)
 - [...more](#)
- [About the Division of Pharmacologic Therapies \(DPT\)](#)

- [Evidence for the Efficacy of Naltrexone in the Treatment of Alcohol Dependence \(Alcoholism\)](#). (PDF, 686 KB)
Forum: Naltrexone Clinical Update.

Naltrexone for opioid dependence

Naltrexone is a non-opioid medication that is used in the treatment of opioid dependence. Naltrexone is an opioid receptor antagonist. It binds to opioid receptors, but instead of activating the receptors, it effectively blocks them. By antagonizing the opioid receptors it prevents opioids from exerting their euphorogenic (or therapeutic) effects.

- [Naltrexone and Lofexidine Combination Treatment Compared with Conventional Lofexidine Treatment for In-Patient Opiate Detoxification](#). Research Brief. November 30, 2000
- [Naltrexone Prescription for Heroin Addiction](#). Dr Andrew Byrne



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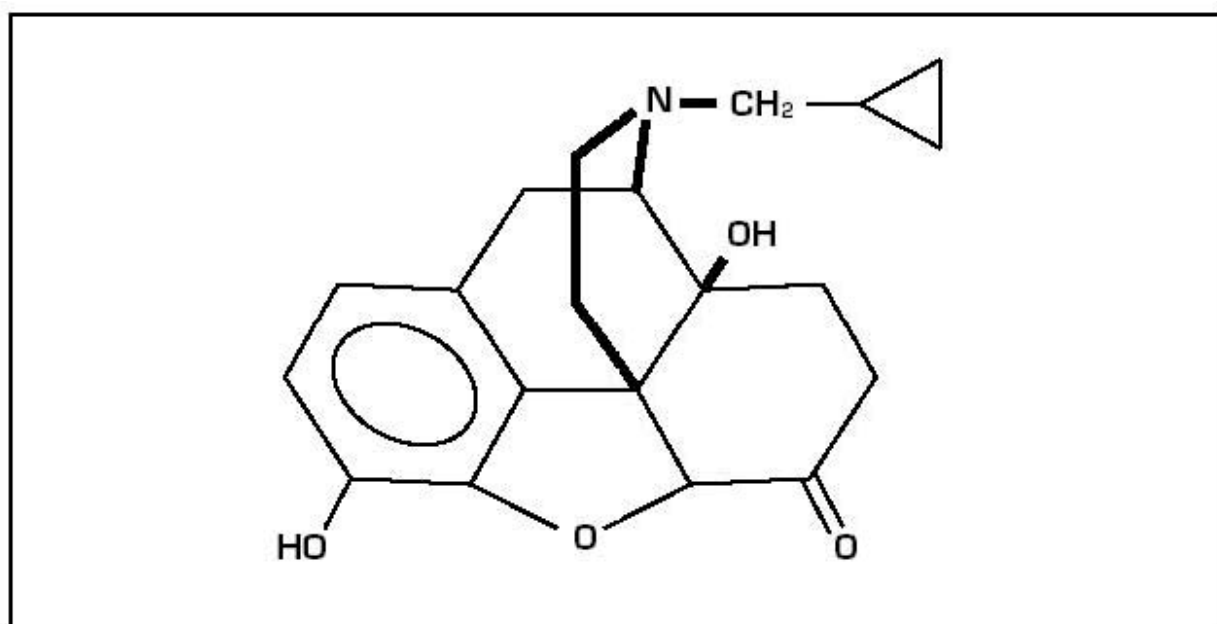
APPENDIX e

Vivitrol (naltrexone for extended-release injectable suspension)
[Alkermes]

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-(5 α) (CAS Registry # 16590-41-3). The molecular formula is C₂₀H₂₃NO₄ and its molecular weight is 341.41 in the anhydrous form (i.e., < 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 168-170° C (334-338° F). 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 ½-inch 20-gauge preparation needle, and two 1½-inch 20-gauge administration needles with safety device.

VIVITROL microspheres consist of a sterile, off-white to light tan powder that is available in a dosage strength of 380-mg 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.

CLINICAL PHARMACOLOGY:

Pharmacodynamics

Mechanism of Action

Naltrexone is an opioid antagonist with highest affinity for the mu opioid receptor. Naltrexone has few, if any, intrinsic actions besides its opioid blocking properties. However, it does produce some pupillary constriction, by an unknown mechanism.

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. 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.

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 6 β -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 6 β -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, 6 β -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-6 β -naltrexol and 2-hydroxy-3-methoxy-naltrexone. Naltrexone and its metabolites are also conjugated to form glucuronide products.

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

Special Populations

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 PRECAUTIONS**).

Renal Impairment: 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 (**see PRECAUTIONS**). VIVITROL pharmacokinetics have not been evaluated in subjects with moderate and severe renal insufficiency (**see PRECAUTIONS**).

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

Age: The pharmacokinetics of VIVITROL have not been evaluated in the geriatric population.

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

Pediatrics: The pharmacokinetics of VIVITROL have not been evaluated in a pediatric population.

Drug-Drug Interactions

Clinical drug interaction studies with VIVITROL have not been performed.

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

CLINICAL STUDIES:

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.

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.

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

CONTRAINDICATIONS:

VIVITROL is contraindicated in:

- z Patients receiving opioid analgesics (**see PRECAUTIONS**).
- z Patients with current physiologic opioid dependence (**see WARNINGS**).
- z Patients in acute opiate withdrawal (**see WARNINGS**).
- z Any individual who has failed the naloxone challenge test or has a positive urine screen for opioids.
- z Patients who have previously exhibited hypersensitivity to naltrexone, PLG,

carboxymethylcellulose, or any other components of the diluent. **WARNINGS: Hepatotoxicity**

Naltrexone has the capacity to cause hepatocellular injury when given in excessive doses.

Naltrexone is contraindicated in acute hepatitis or liver failure, and its use in patients with active liver disease must be carefully considered in light of its hepatotoxic effects.

The margin of separation between the apparently safe dose of naltrexone and the dose causing hepatic injury appears to be only five-fold or less. VIVITROL does not appear to be a hepatotoxin at the recommended doses.

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.

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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.

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. Should a person receiving VIVITROL develop progressive dyspnea and hypoxemia, the diagnosis of eosinophilic pneumonia should be considered (**see ADVERSE REACTIONS**). 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.

Unintended Precipitation of Opioid Withdrawal To prevent occurrence of an acute abstinence syndrome (withdrawal) in patients dependent on opioids, or exacerbation of a pre-existing subclinical abstinence syndrome, patients must be opioid-free for a minimum of 7-10 days before starting VIVITROL treatment. Since the absence of an opioid drug in the urine is often not sufficient proof that a patient is opioid-free, a naloxone challenge test should be employed if the prescribing physician feels there is a risk of precipitating a withdrawal reaction following administration of VIVITROL.

Opioid Overdose Following an Attempt to Overcome Opiate Blockade

VIVITROL is not indicated for the purpose of opioid blockade or the treatment of opiate dependence. Although VIVITROL is a potent antagonist with a prolonged pharmacological effect, the blockade produced by VIVITROL is surmountable. This poses a potential risk to individuals who attempt, on their own, to overcome

the blockade by administering large amounts of exogenous opioids. Indeed, any attempt by a patient to overcome the antagonism by taking opioids is very dangerous and may lead to fatal overdose. Injury may arise because the plasma concentration of exogenous opioids attained immediately following their acute administration may be sufficient to overcome the competitive receptor blockade. As a consequence, the patient may be in immediate danger of suffering life-endangering opioid intoxication (e.g., respiratory arrest, circulatory collapse). Patients should be told of the serious consequences of trying to overcome the opioid blockade (see INFORMATION FOR PATIENTS).

There is also the possibility that a patient who had been treated with VIVITROL will respond to lower doses of opioids than previously used. This could result in potentially life-threatening opioid intoxication (respiratory compromise or arrest, circulatory collapse, etc.). Patients should be aware that they may be more sensitive to lower doses of opioids after VIVITROL treatment is discontinued (see INFORMATION FOR PATIENTS).

PRECAUTIONS:

General

When Reversal of VIVITROL Blockade Is Required for Pain Management

In an emergency situation in patients receiving VIVITROL, a suggested plan for pain management is regional analgesia, conscious sedation with a benzodiazepine, and use of non-opioid analgesics or general anesthesia.

In a situation requiring opioid analgesia, the amount of opioid required may be greater than usual, and the resulting respiratory depression may be deeper and more prolonged.

A rapidly acting opioid analgesic which minimizes the duration of respiratory depression is preferred. The amount of analgesic administered should be titrated to the needs of the patient. Non-receptor mediated actions may occur and should be expected (e.g., facial swelling, itching, generalized erythema, or bronchoconstriction), presumably due to histamine release.

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.

Depression and Suicidality

In controlled clinical trials of VIVITROL, 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 which 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, 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.

Alcohol 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.

Injection Site Reactions

VIVITROL injections may be followed by pain, tenderness, induration, or pruritus. 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. Patients should be informed that any concerning injection site reactions should be brought to the attention of the physician (**see INFORMATION FOR PATIENTS**).

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.

Alcohol Withdrawal

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

Intramuscular injections

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

Information for Patients

Physicians should discuss the following issues with patients for whom they prescribe VIVITROL:

- z Patients should be advised 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 the patients obtain adequate medical treatment in an emergency.
- z Patients should be advised that administration of large doses of heroin or any other opioid while on VIVITROL may lead to serious injury, coma, or death.
- z Patients should be advised that because VIVITROL can block the effects of opiates and opiate-like drugs, patients will not perceive any effect if they attempt to self-administer heroin or any other opioid drug in small doses while on VIVITROL. Also, patients on VIVITROL may not experience the same effects from opioid containing analgesic, antidiarrheal, or antitussive medications.
- z Patients should be advised that if they previously used opioids, they may be more sensitive to lower doses of opioids after VIVITROL treatment is discontinued.
- z Patients should be advised that VIVITROL may cause liver injury in people who develop liver disease from other causes. Patients should immediately notify their physician if they develop symptoms and/or

signs of liver disease.

- z Patients should be advised 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.
- z Patients should be advised that a reaction at the site of VIVITROL injection may occur. Reactions include pain, tenderness, induration, and pruritus. Rarely, serious injection site reactions may occur. Patients should be advised to seek medical attention for worsening skin reactions, particularly if the reaction does not improve one month following the injection.
- z Patients should be advised 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.
- z Patients should be advised 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. z Patients should be advised that VIVITROL has been shown to treat alcohol dependence only when used as part of a treatment program that includes counseling and support.
- z Patients should be advised to notify their physician if they: z become pregnant or intend to become pregnant during treatment with VIVITROL. z are breast-feeding. z experience respiratory symptoms such as dyspnea, coughing, or wheezing when taking VIVITROL. z experience significant pain or redness at the site of injection, particularly if the reaction does not improve one month following the injection. z experience other unusual or significant side effects while on VIVITROL therapy.

Drug Interactions

Patients taking VIVITROL may not benefit from opioid-containing medicines (see **PRECAUTIONS, Pain Management**).

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. No clinical drug interaction studies have been performed with VIVITROL to evaluate drug interactions, therefore prescribers should weigh the risks and benefits of concomitant drug use.

The safety profile of patients treated with VIVITROL concomitantly with antidepressants was similar to that of patients taking VIVITROL without antidepressants.

Carcinogenesis, mutagenesis, impairment of fertility

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 rats, there were small increases in the numbers of testicular mesotheliomas in males and tumors of vascular origin in males and females. The clinical significance of these findings is not known.

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.

Naltrexone given orally caused a significant increase in pseudopregnancy and a decrease in pregnancy rates in rats at 100 mg/kg/day (600 mg/m /day). There was no effect on male fertility at this dose level. The relevance of these observations to human fertility is not known.

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: Oral naltrexone has been shown to increase the incidence of early fetal loss in rats administered ≥ 30 mg/kg/day (180 mg/m /day) and rabbits administered ≥ 60 mg/kg/day (720 mg/m /day).

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.

Labor and Delivery

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

Nursing Mothers

Transfer of naltrexone and 6 β -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.

Pediatric Use

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

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.

ADVERSE REACTIONS

In all controlled and uncontrolled trials during the premarketing development of VIVITROL, more than 900 patients with alcohol and/or opioid dependence have been treated with VIVITROL. Approximately 400 patients have been treated for 6 months or more, and 230 for 1 year or longer.

Adverse Events Leading to Discontinuation of Treatment

In controlled trials of 6 months or less, 9% of patients treated with VIVITROL discontinued treatment due to an adverse event, as compared to 7% of the patients treated with placebo. Adverse events in the VIVITROL 380-

mg group that led to more dropouts 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.

Common Adverse Events

The table lists all adverse events, regardless of causality, occurring in $\geq 5\%$ 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 events with a maximum intensity of “mild” or “moderate.”

Post-marketing Reports

Reports From Other Intramuscular Drug Products Containing Polylactide-co-glycolide (PLG) Microspheres – Not With VIVITROL

Retinal Artery Occlusion

Retinal artery occlusion after injection with another drug product containing polylactide-co-glycolide (PLG) microspheres has been reported very rarely during post-marketing 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 post-marketing 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**).

Common Adverse Events (by body system and preferred term/high level group term) in $\geq 5\%$ of patients treated with VIVITROL

Body system	Adverse Event/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 disorders	Nausea	24	11	8	32	68	33	53	25	129	29
	Vomiting NOS	12	6	3	12	28	14	22	10	53	12
	Diarrhea ¹	21	10	3	12	27	13	27	13	57	13
	Abdominal pain ²	17	8	4	16	23	11	23	11	50	11
	Dry mouth	9	4	6	24	10	5	8	4	24	5
Infections and infestations	Upper respiratory tract infection–Other ³	28	13	0	0	27	13	25	12	52	12
	Pharyngitis ⁴	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 ⁵	17	8	2	8	24	12	16	8	42	10
	Depression	9	4	0	0	17	8	7	3	24	5
General disorders and 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 ⁶	26	12	3	12	47	23	40	19	90	20
	Arthralgia, arthritis, joint stiffness	11	5	1	4	24	12	12	6	37	9
Musculoskeletal and connective tissue disorders	Back pain, back stiffness	10	5	1	4	12	6	14	7	27	6
	Muscle cramps ⁷	3	1	0	0	16	8	5	2	21	5
	Rash ⁸	8	4	3	12	12	6	10	5	25	6
Nervous system disorders	Headache ⁹	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 and nutrition disorders	Anorexia, appetite, decreased NOS, appetite disorder NOS	6	3	5	20	30	14	13	6	48	11

¹ Includes the preferred terms: diarrhea NOS; frequent bowel movements; gastrointestinal upset; loose stools

² Includes the preferred terms: abdominal pain NOS; abdominal pain upper; stomach discomfort; abdominal pain lower

³ Includes the preferred terms: upper respiratory tract infection NOS; laryngitis NOS; sinusitis NOS

⁴ Includes the preferred terms: nasopharyngitis; pharyngitis streptococcal; pharyngitis NOS

⁵ Includes the preferred terms: anxiety NEC; anxiety aggravated; agitation; obsessive compulsive disorder; panic attack; nervousness; post-traumatic stress

⁶ Includes the preferred terms: malaise; fatigue (these two comprise the majority of cases); lethargy; sluggishness

⁷ Includes the preferred terms: muscle cramps; spasms; tightness; twitching; stiffness; rigidity

⁸ Includes the preferred terms: rash NOS; rash papular; heat rash

⁹ Includes the preferred terms: headache NOS; sinus headache; migraine; frequent headaches

Laboratory Tests

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.

VIVITROL 380-mg was associated with a decrease in platelet count. Patients treated with high dose 3 VIVITROL experienced a mean maximal decrease in platelet count of $17.8 \times 10^3 /\mu\text{L}$, compared to $2.6 \times 10^3 /\mu\text{L}$ in placebo patients. In randomized controlled trials, VIVITROL was not associated with an increase in bleeding related adverse events.

In short-term, controlled trials, 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 short-term controlled trials, 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.

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.

Other Events Observed During the Premarketing Evaluation of VIVITROL

The following is a list of preferred terms that reflect events reported by alcohol and/or opiate dependent subjects treated with VIVITROL in controlled 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 which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening.

Gastrointestinal Disorders – constipation, toothache, flatulence, gastroesophageal reflux disease, hemorrhoids, colitis, gastrointestinal hemorrhage, paralytic ileus, perirectal abscess

Infections and Infestations – influenza, bronchitis, urinary tract infection, gastroenteritis, tooth abscess, pneumonia, cellulitis

General Disorders and Administration Site Conditions – pyrexia, lethargy, rigors, chest pain, chest tightness, weight decreased

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

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

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

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

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

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

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

Eye Disorders – conjunctivitis

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

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

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

Pregnancy, Puerperium, and Perinatal Conditions – abortion missed

Hepatobiliary Disorders – cholelithiasis, aspartate aminotransferase increased, alanine aminotransferase increased, cholecystitis acute

DRUG ABUSE AND DEPENDENCE:

Controlled Substance Class

VIVITROL is not a controlled substance.

Physical and Psychological Dependence

Naltrexone, the active ingredient in VIVITROL, is a pure opioid antagonist that does not lead to physical or psychological dependence. Tolerance to the opioid antagonist effect is not known to occur.

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.

DOSAGE AND ADMINISTRATION:

VIVITROL must be administered by a health care professional.

The recommended dose of VIVITROL is 380 mg delivered intramuscularly every 4 weeks or once a month.

The injection should be administered by a health care professional as an intramuscular (IM) gluteal injection, alternating buttocks, using the carton components provided (see **HOW SUPPLIED**).

VIVITROL must not be administered intravenously.

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.

Reinitiation of Treatment in Patients Previously Discontinued

There are no data to specifically address reinitiation of treatment.

Switching From Oral Naltrexone for Alcohol Dependence

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

Preparation of Dose

VIVITROL must be suspended **only** in the diluent supplied in the carton and must be administered with the needle supplied in the carton. All components (i.e., the microspheres, diluent, preparation needle, and an administration needle with safety device) are required for administration. A spare administration needle is provided in case of clogging. Do not substitute any other components for the components of the carton.

HOW SUPPLIED:

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) Diluent for the suspension of VIVITROL, one 5-mL prepackaged syringe, one 20-gauge ½-inch needle, and two 20-gauge 1½-inch needles with safety device: NDC 63459-300-42.

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.

Keep out of Reach of Children.

US Patent Nos. 5,650,173; 5,654,008; 5,792,477; 5,916,598; 6,110,503; 6,194,006; 6,264,987;
6,331,317; 6,379,703; 6,379,704; 6,395,304; 6,403,114; 6,495,164; 6,495,166; 6,534,092;
6,537,586; 6,540,393; 6,596,316; 6,667,061; 6,705,757; 6,713,090; 6,861,016; 6,939,033

Directions for Use:

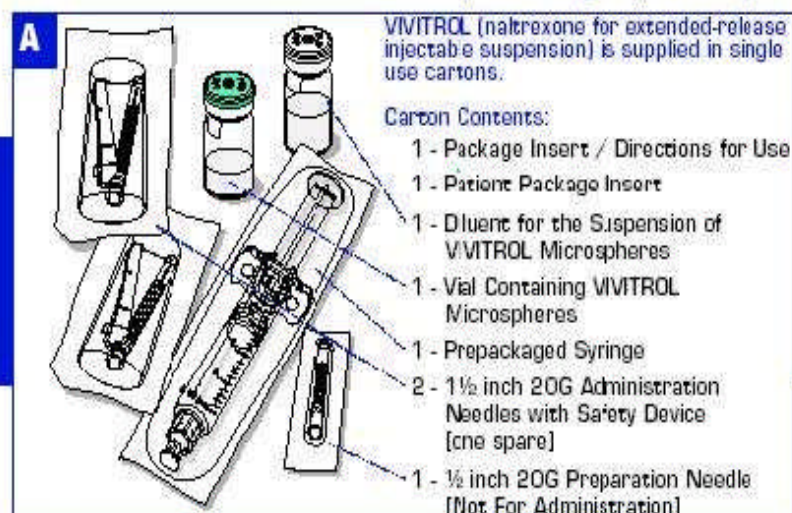
To ensure proper dosing, it is important that you follow the preparation and administration instructions outlined in this document.

Product to be prepared and administered by a healthcare professional.

Do not substitute carton components.

Keep out of reach of children.

Prepare and administer the VIVITROL suspension using aseptic technique.

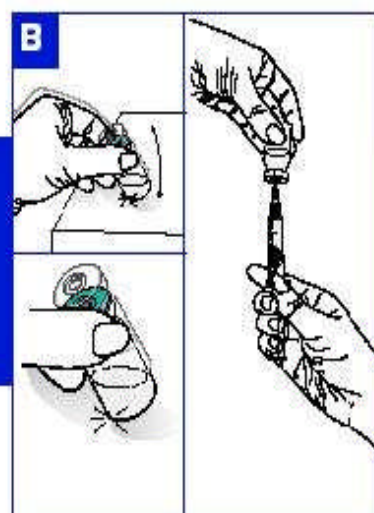


THE CARTON SHOULD NOT BE EXPOSED TO TEMPERATURES EXCEEDING 25 °C (77 °F).

VIVITROL must be suspended only in the diluent supplied in the carton, and must be administered with the needle supplied in the carton. Do not make any substitutions for components of the carton.

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 whenever solution and container permit.



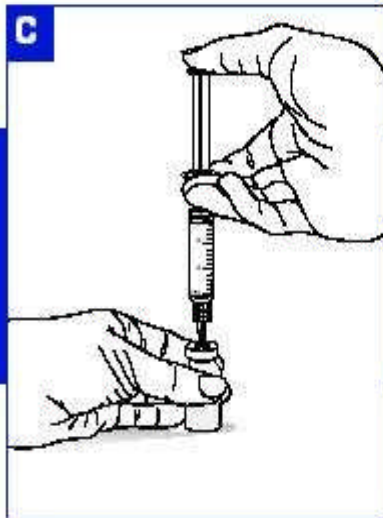
1. Remove the carton from refrigeration. Prior to preparation, allow drug to reach room temperature (approximately 45 minutes).

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

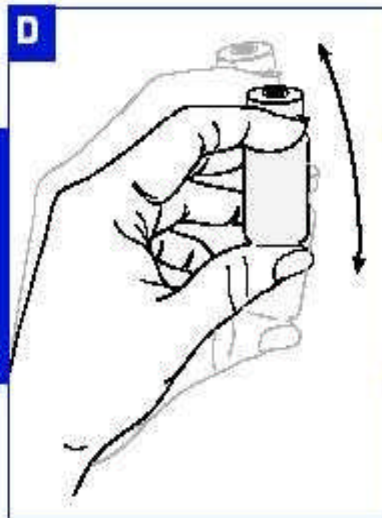
3. Remove flip-off caps from both vials. DO NOT USE IF FLIP-OFF CAPS ARE BROKEN OR MISSING.

4. Wipe the vial tops with an alcohol swab.

5. Place the 1/2 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)

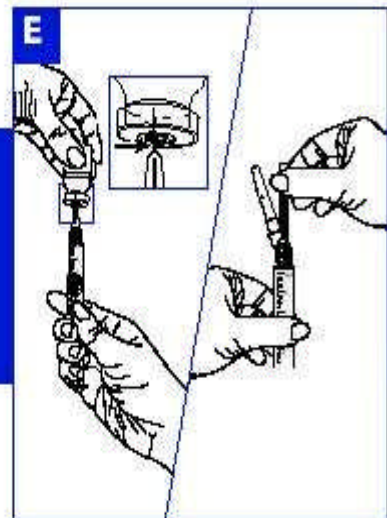


Inject the 3.4 mL of diluent into the VIVITROL Microsphere vial. (see Figure C)



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.

2. Remove the preparation needle and replace with a 1½ inch administration needle for immediate use. (see Figure E)

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VIVITROL is an injectable medicine for the treatment of alcohol dependence in adults 18 years and older. To benefit from VIVITROL, you need to stop drinking before starting the medicine.

file:///C:/Cdsesub1/evsprod/NDA021897/0084/m1/us/spl/vivitrol.xml

To be effective, treatment with VIVITROL must be used along with other alcoholism recovery measures such as counseling.

VIVITROL may not work for everyone.

VIVITROL has not been studied in children under the age of 18 years.

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

1. VIVITROL may be associated with liver damage or hepatitis.
 - z Call your doctor if you develop stomach area pain lasting more than a few days, light-colored bowel movements, dark urine, or yellowing of your eyes.
- 2 VIVITROL blocks the effects of opioid-containing medicines. z You may not feel the same effects of opioid-containing medicines including medicines for pain, cough
 - and diarrhea. z You may not feel the same effects if you use or abuse heroin and other illegal (street) opioids. z Do not take large amounts of opioid medicines to overcome the VIVITROL block. This can lead to serious injury, coma, or death.
3. VIVITROL has been associated with severe allergic pneumonia.
 - z Call your doctor if you develop shortness of breath, coughing or wheezing.

Who should not take VIVITROL?

Do not take VIVITROL if you:

- z Are taking or have a physical dependence on opioid-containing medicines. (See “What is the most important information I should know about VIVITROL?”) z Use or have a physical dependence on opioid street drugs. (See “What is the most important information I should know about VIVITROL?”)
- z Are allergic to VIVITROL. The active ingredient is naltrexone. See the end of this leaflet for a complete list of ingredients in VIVITROL.

What should I tell my doctor before starting VIVITROL?

Tell your doctor about all of your medical conditions, including if you:

- z Have liver problems
- z Use opioid-containing medicines
- z Use or abuse street (illegal) drugs
- z Have hemophilia or other bleeding problems
- z Have kidney problems
- z Are pregnant or plan to become pregnant. It is not known if VIVITROL can harm your unborn baby.
- z Are breastfeeding. It is not known if VIVITROL passes into your milk, and if it can harm your baby.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. Especially tell your doctor if you take any opioid-containing medicines for pain, cough, or diarrhea. (See “What is the most important information I should know about VIVITROL?”)

Carry written information to alert medical personnel that you are taking VIVITROL, so that they can treat you properly in an emergency.

How do I take VIVITROL?

VIVITROL is given as a “shot” (injection) in your buttocks. It is injected by your healthcare provider about once a month. Because VIVITROL is an injection, once it is given you cannot remove it from the body.

If you miss your appointment for VIVITROL injection, schedule another appointment as soon as possible.

file:///C:/Cdsesub1/evsprod/NDA021897/0084/m1/us/spl/vivitrol.xml

Whenever you need medical treatment, be sure to tell the treating doctor or nurse that you are receiving VIVITROL injections.

What should I avoid while taking VIVITROL?

VIVITROL may make you feel dizzy. Do not drive a car, work with machines, or do other dangerous activities until you know how VIVITROL affects you. (See “What are the possible side effects of VIVITROL?”)

What are the possible side effects of VIVITROL?

VIVITROL may cause side effects including:

- z A reaction at the injection site. The reaction could be pain, tenderness, swelling, redness, and/or itching. Tell your doctor if the reaction gets worse over time.
- z Nausea.

The other common side effects of VIVITROL are:

- z Headache
- z Fatigue
- z Dizziness
- z Vomiting
- z Decreased appetite
- z Painful joints
- z Muscle cramps

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

These are not all the side effects of VIVITROL. For more information, ask your doctor or pharmacist.

General information about VIVITROL

Medicines are sometimes prescribed for conditions other than those listed in patient information leaflets. VIVITROL was prescribed for your medical condition.

This leaflet summarizes the most important information about VIVITROL. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about VIVITROL that is written for health professionals. For additional information about VIVITROL and treatment support for alcohol dependence call 1800-848-4876 or visit www.vivitrol.com

What are the ingredients in VIVITROL?

Active ingredient: naltrexone

Inactive ingredients: polylactide-co-glycolide (PLG); Diluent: carboxymethylcellulose sodium salt, polysorbate 20, sodium chloride, and water

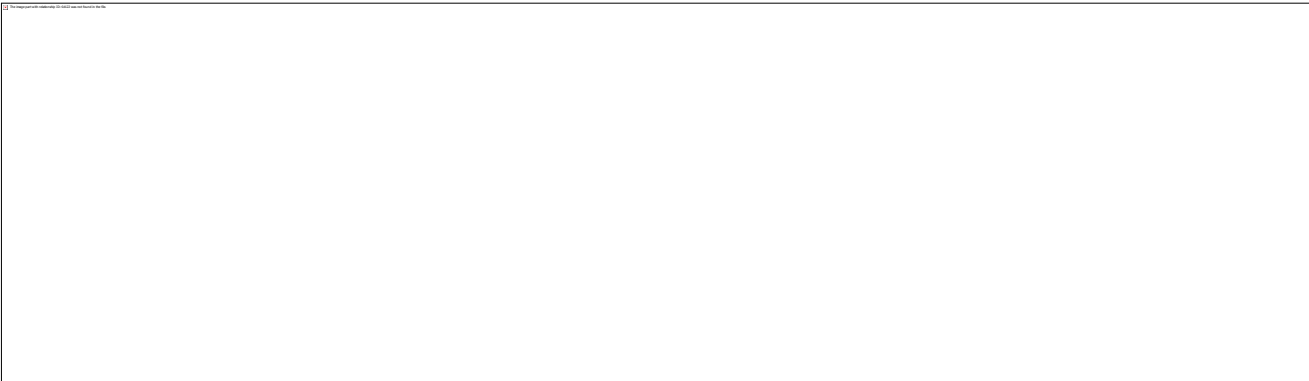
PRODUCT INFO

Product Code 63459-300 **Dosage Form** KIT

PACKAGING

NDC Package Description Multilevel Packaging

63459-300-42 1 KIT In 1 CARTON None



VIVITROL (naltrexone for extended-release injectable suspension)

QUANTITY OF PARTS Part # Package Quantity Total Product Quantity

Part 1 1 VIAL, SINGLE-DOSE 4 MILLILITER In 1 Part 2

1 VIAL, SINGLE-USE 4 MILLILITER In 1

Part 1 of 2

VIVITROL (naltrexone for extended-release injectable suspension)

Route Of Administration INTRAMUSCULAR Dosage Form INJECTION, SUSPENSION, EXTENDED RELEASE
DEA Schedule

INGREDIENTS Name (Active Moiety) Type Strength

naltrexone (naltrexone) Active 380 MILLIGRAM In 4 MILLILITER polylactide-co-glycolide
Inactive 0.84 MILLIGRAM In 4 MILLILITER

IMPRINT INFORMATION Characteristic Appearance Characteristic Appearance Color

Score Shape

Symbol
Imprint Code

Coating
Size

PACKAGING # NDC Package Description Multilevel Packaging 1

63459-300-38 4 MILLILITER In 1 VIAL, SINGLE-DOSE None

Part 2 of 2

Diluent ()

Dosage Form Route Of
Administration
INTRAMUSCULAR DEA
Schedule

INGREDIENTS Name (Active Moiety) Type Strength

carboxymethylcellulose sodium salt Inactive 30 MILLIGRAM In 4 MILLILITER

polysorbate 20 Inactive 1 MILLIGRAM In 4 MILLILITER

sodium chloride Inactive 9 MILLIGRAM In 4 MILLILITER **water for injection**

Inactive

APPENDIX B
CONSENT FOR MULTIPLE DROPS

CONSENT FOR RESEARCH

Penn State College of Medicine
The Milton S. Hershey Medical Center

This form is not valid unless this box
includes an approval stamp by the IRB

Title of Project: ***Phase I Clinical Trial of Topical Naltrexone Applied as Eyedrops (multiple drops, multiple dosage)***

Principal Investigator: *Joseph W. Sassani, MD, MHA*

Other Investigators: David Liang, MD, Ian Zagon, PhD

Participant's Printed Name: _____

This is a research study. Research studies include only people who want to take part. This form gives you information about this research, which will be discussed with you. It may contain words or procedures that you don't understand. Please ask questions about anything that is unclear to you. Discuss it with your family and friends and take your time to make your decision.

1. Purpose of the Research:

The purpose of the proposed research is to determine the safety of the potent opioid antagonist Naltrexone (NTX) applied topically in healthy human volunteers, preliminary to determining its effectiveness in facilitating the healing of corneal epithelium removed intentionally to improve operator visibility during vitrectomy surgery (removing some of the jelly-like material from within the eye, for example during surgery for bleeding within the eye from diabetes mellitus).

The specific aim of the research is to demonstrate the safety of topically applied (eyedrops) Naltrexone (NTX) dissolved in Vigamox antibiotic eyedrops in normal volunteers. Naltrexone is approved by the Federal Food and Drug Administration for long term oral (by mouth) and systemic (by injection) use in individuals with substance abuse. Nevertheless, it has not previously been applied to the eye in eyedrop form. Vigamox is an antibiotic eyedrop preparation commonly used to prevent eye infections in individuals who are about to undergo surgical procedures, and to treat infections of the eye surface. Approximately 20 individuals will be enrolled in the study.

You are being offered the opportunity to take part in this research because you are a healthy individual with no eye problems.

2. Procedures to be Followed:

1. Study Design: All eyedrops will be administered to one eye only, and any repeat dosing will be to the same eye. NTX will be administered at the following four (4) concentrations: 10^{-6} M, 5×10^{-6} M, 10^{-5} M, 5×10^{-5} M. The medication will be applied 4 times daily for 24 hours and you will be followed in the clinic 1, 2, and 7 days post-treatment. Medication testing will proceed from the lowest to the highest concentration. A one (1) week interval will occur between the end of testing for a given concentration and the start of testing at the next higher concentration. The one week interval will allow us to evaluate the biological response to NTX and identify any adverse events before proceeding to the next higher NTX concentration.

Volunteers for each NTX concentration group will be comprised of 3 volunteers that receive NTX drops and 1 volunteer that receives Vigamox drops alone.

Summary of Procedures (all test procedures are ones commonly used in the clinical setting and are not experimental in nature):

Study Visit#1

Baseline history and complete dilated eye examination plus corneal thickness and shape measurements, corneal cell count, Shirmer test of tear production (in which a drop of anesthetic is administered to the eye surface, a small strip of filter paper is placed inside the lower eyelid for 5 minutes, and the resulting amount of wetting is measured) , corneal sensitivity, and photography of the back of the eye. You may not wear contact lenses after midnight of the preceding

night. If you are eligible to participate, you will be randomly assigned to receive either the test medication in Vigamox® antibiotic eye drops or only the Vigamox® eye drops.

Study Visit #2

8:00 AM the following day: You arrive and eyes are examined externally and at the slit lamp; however, no intraocular pressure is measured.

9:00 AM: DROP #1 is given

Eyes are examined 1 hr later but intraocular pressure is not measured.

12:30 PM (4 hr): Eyes are examined but intraocular pressure is not measured

1:00 PM: DROP #2 is given

2:00 PM Your eyes are examined and intraocular pressure is measured

DROP #3 is given at home (~ 5:00 PM)

DROP #4 is given at home (~9:00 PM)

Study Visit #3

24 hr later: you arrive around 8:30 am next day for complete eye examination plus corneal thickness and shape measurements, corneal cell count, Shirmer test of tear production (in which a drop of anesthetic is administered to the eye surface, a small strip of filter paper is placed inside the lower eyelid for 5 minutes, and the resulting amount of wetting is measured) , corneal sensitivity, and photography of the back of the eye are performed. You may resume contact lens wear after this meeting. The bottle of study eye drops should be returned at this visit.

Study Visit #4

7 days later: you arrive for complete eye examination plus corneal thickness and shape measurements, corneal cell count, Shirmer test of tear production (in which a drop of anesthetic is administered to the eye surface, a small strip of filter paper is placed inside the lower eyelid for 5 minutes, and the resulting amount of wetting is measured) , corneal sensitivity, and photography of the back of the eye are performed. You may not wear contact lenses after midnight of the preceding night.

Study Site Location: The study will be performed in the clinical facilities of the HMC Department of Ophthalmology.

3. Discomforts and Risks:

NTX has not previously been administered to humans in eyedrop form, although it is taken orally and in injectable form, sometimes for prolonged periods, in the treatment of alcohol and opioid medication abuse or overdose.

In studies with rats and in our other animal studies, no significant eye toxicity occurred. So, from the treatment used in this study, we do not expect significant side effects.

Our animal studies predict no significant eye toxicity from the course of treatment proposed in this study. Moreover, as noted above, NTX is approved for chronic systemic administration in the treatment of drug and alcohol abuse.

It is possible that transient burning may occur at the time of eyedrop administration and unpredictable reactions always are possible. There is the possibility of currently unknown risks to the eye including infection, irritation, or other effects that might affect vision. The most frequently reported eye adverse events from Vigamox® are eye redness, blurred vision, dry eye, corneal irritation, eye discomfort, pain, eye itching, subconjunctival hemorrhage (bleeding under the tissue that covers the white of the eye), and tearing. These events occurred in approximately 1-6% of patients. It should not be used in individuals allergic to moxifloxacin or other quinolones. It is possible that an individual may have a reaction that cannot be predicted.

Minor burning at the time of eyedrop administration would require no treatment. If irritation persists, artificial tears would be administered. It is highly unlikely that stronger therapy, such as steroid eyedrops would be required.

If you are pregnant or nursing, you will be excluded from participation in the study. If you are a sexually active woman of childbearing potential you must be taking an oral contraceptive to participate in the study. Males also must use contraception.

Subjects will be monitored closely for problems during their exams.

The USP Material Safety Data Sheet lists the following potential side effects or complications from Naltrexone (Catalog Number 1453504). These actions apply primarily to Naltrexone not administered to the eye.

Adverse Effects: Adverse effects may include anxiety; nervousness, restlessness, and/or trouble sleeping; drowsiness; unusual tiredness; lightheadedness; nausea or vomiting; headache; chills; cough; hoarseness; increased thirst; runny, stuffy nose; sinus problems; sneezing; sore throat; diarrhea; sweating; slowed breathing; fast or pounding heartbeat; constricted pupils; decreased body temperature; mental depression; joint, muscle pain, or abdominal pain; skin rash; and sexual problems in males. Possible allergic reaction to material if inhaled, ingested or in contact with skin.

Overdose Effects: Overdose effects may include salivation, lethargy, tremors, and convulsions.

Acute: Eye, skin, gastrointestinal and/or respiratory tract irritation.

4. Possible Benefits:

a. Possible benefits to the participant:

You will not benefit from taking part in this research study.

b. Possible benefits to others:

Results of this study may guide the future use of naltrexone in treating eye disorders.

5. Other Options that Could be Used Instead of this Research:

You do not have to take part in this research study.

6. Time Duration of the Procedures and Study:

Each visit will take approximately 30 minutes to two hours, and there will be four visits.

7. Statement of Confidentiality:

a. Privacy and confidentiality measures:

Your records that are used in the research at The Milton S. Hershey Medical Center(HMC) and Penn State College of Medicine (PSU) will include code number, your name, address, phone number, date of birth, medical record number and be kept in a secured area in the Clinical Research facility of the Department of Ophthalmology.

In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

b. The use of private health information:

If you give your consent, health information about you will be collected for this research. Health information is protected by law as explained in the HMC Privacy Notice. If you have not received this notice, please request a copy from the researcher. At HMC/PSU your information will only be used or shared as explained in this consent form or when required by law. However, some of the other people/groups who receive your health information may not be required by Federal privacy laws to protect your information and may share it without your permission.

If you do not want us to use your protected health information, you may not participate in this research.

People usually have a right to see their medical records. However, you may not be allowed to see or copy certain information that is related to this research study. This is only for the period of the research. You will be allowed to see that information when the entire research project is complete.

If you choose to participate, you are free to withdraw your permission for the use and sharing of your health information at any time. You must do this in writing. Write to Dr. Sassani and let him know that you are withdrawing from the research study. His mailing address is Department of Ophthalmology, Hershey Medical Center, 500 University Drive, Hershey, P 17033.

If you withdraw your permission:

- We will no longer use or share medical information about you for this research study, except when the law requires us to do so.
- We are unable to take back anything we have already done or any information we have already shared with your permission.

- We may continue using and sharing the information obtained prior to your withdrawal if it is necessary for the soundness of the overall research.
- We will keep our records of the care that we provided to you as long as the law requires.

The research team may use the following sources of health information.

- Clinical history and examination information collected during the study
- Clinical test results: pachymetry (corneal thickness), corneal topography (corneal surface shape), endothelial specular microscopy (count of the number of cells lining the back surface of the cornea), fundus photography (photographs of the back of the eye).

Representatives of the following people/groups within HMC/PSU may use your health information and share it with other specific groups in connection with this research study.

- The principal investigator, Joseph W. Sassani, MD, MHA
- The HMC/PSU Institutional Review Board
- The HMC/PSU Human Subjects Protection Office
- Drs. David Liang, MD and Ian Zagon, PhD
- The Department of Ophthalmology Clinical Research Office

The above people/groups may share your health information with the following people/groups outside HMC/PSU for their use in connection with this research study. These groups, while monitoring the research study, may also review and/or copy your original PSU/HMC records.

- The Office of Human Research Protections in the U. S. Department of Health and Human Services
- Food and Drug Administration
- Representatives of the U.S. Army Medical Research and Materiel Command (USAMRMC)

8. Costs for Participation:

a. Costs:

- All tests and procedures described in this study are provided at no cost to you.

b. Treatment and compensation for injury:

Every effort to prevent injury as a result of your participation will be taken. It is possible, however, that you could develop complications or injuries as a result of participating in this research study. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. It

is the policy of this institution to provide neither financial compensation nor free medical treatment for research-related injury.

Costs for the treatment of research-related injuries will be charged to your insurance carrier or to you. Some insurance companies may not cover costs associated with research studies. If for any reason these costs are not covered by your insurance, they will be your responsibility. You will also be responsible for any deductible, co-insurance and/or co-pay.

You will not lose any legal rights by signing this form.

If you get hurt or sick because of this research study, you can receive medical care at an Army hospital or clinic free of charge. You will only be treated for injuries that are directly caused by the research study. The Army will not pay for your transportation to and from the hospital or clinic. If you have questions about this medical care, talk to the principal investigator for this study (Dr. John Sassani at 717-531-8783). If you pay out-of-pocket for medical care elsewhere for injuries caused by this research study, contact the principal investigator. If the issue cannot be resolved, contact the U.S. Army Medical Research and Materiel Command (USAMRMC) Office of the Staff Judge Advocate (legal office) at (301) 619-7663/2221.

9. Compensation for Participation:

You will receive \$300 for participation in the study. Your Social Security number will be required for compensation and accounting purposes. If you choose to withdraw from the study before the administration of the test medication or control substance there will be no compensation. If you withdraw after that time you will receive 1/3 of the compensation for each of the Meeting days in which you participate.

10. Research Funding:

The institution and investigators have received research funding from the Department of Defense to support this research.

11. Potential Conflict of Interest or Appearance of Such Conflict:

Dr. Ian Zagon, one of the co-investigators, holds a patent for the use of opioids and NTX in regulating wound healing, and Drs. Joseph Sassani and Ian Zagon have a provisional patent for the use of Naltrexone in the treatment of dry eyes. They may benefit financially if this research program is successful.

12. Voluntary Participation:

Taking part in this research study is voluntary. If you choose to take part in this research, your major responsibilities are described in the "Summary of Procedures" section, above. You do not have to participate in this research. If you choose to

take part, you have the right to stop at any time. If you decide not to participate or if you decide to stop taking part in the research at a later date, there will be no penalty or loss of benefits to which you are entitled.

Your research doctor, Dr. Sassani, may take you out of the research study without your permission. One possible reason for this is your inability or unwillingness to cooperate in the clinical procedures described in the "Summary of Procedures". Also, the sponsor of the research may end the research study early. If your participation in the research ends early, you may be asked to visit the research doctor for a final visit.

If you will be participating in another clinical trial at Hershey Medical Center or elsewhere while in this research, you should discuss the procedures and/or treatments with your physician or the investigators. This precaution is intended to protect you from possible side effects from interactions of research drugs, treatments or testing.

During the course of the research you will be provided with any significant new findings that may affect your willingness to continue participating in this research.

13 . Contact Information for Questions or Concerns:

You have the right to ask any questions you may have about this research. If you have questions, complaints or concerns or believe you may have developed an injury related to this research, contact Joseph W. Sassani, MD, MHA at 717-531-8783 or the Ophthalmology doctor on call at (717) 531-8521.

If you have questions regarding your rights as a research participant or you have concerns or general questions about the research or about your privacy and the use of your personal health information}, contact the research protection advocate in the HMC Human Subjects Protection Office at 717-531-5687. You may also call this number if you cannot reach the research team or wish to talk to someone else.

For more information about participation in a research study and about the Institutional Review Board (IRB), a group of people who review the research to protect your rights, please visit the HMC IRB's Web site at <http://www.hmc.psu.edu/irb>. Included on this web site, under the heading "Participant Info", you can access federal regulations and information about the protection of human research participants. If you do not have access to the internet, copies of these federal regulations are available by calling the HSPO at (717) 531-5687.

14. Signature and Consent/Permission to be in the Research

Before making the decision regarding enrollment in this research you should have:

- Discussed this study with an investigator,
- Reviewed the information in this form, and
- Had the opportunity to ask any questions you may have.

Your signature below means that you have received this information, have asked the questions you currently have about the research and those questions have been answered. You will receive a copy of the signed and dated form to keep for future reference.

Participant: By signing this consent form, you indicate that you are voluntarily choosing to take part in this research.

Signature of Participant Date Time

Printed Name

Person Explaining the Research: Your signature below means that you have explained the research to the participant/participant representative and have answered any questions he/she has about the research.

Signature of person who explained this research:

Printed Name:

Date Time

(Only approved investigators for this research may explain the research and obtain informed consent.)

This form is not valid unless this box
includes an approval stamp by the IRB

CONSENT FOR RESEARCH

Penn State College of Medicine

The Milton S. Hershey Medical Center

Title of Project: ***Phase I Clinical Trial of Topical Naltrexone Applied as Eyedrops (single drop and single dosage)***

Principal Investigator: *Joseph W. Sassani, MD, MHA*

Other Investigators: David Liang, MD, Ian Zagon, PhD

Participant's Printed Name: _____

This is a research study. Research studies include only people who want to take part. This form gives you information about this research, which will be discussed with you. It may contain words or procedures that you don't understand. Please ask questions about anything that is unclear to you. Discuss it with your family and friends and take your time to make your decision.

1. Purpose of the Research:

The purpose of the proposed research is to determine the safety of the potent opioid antagonist Naltrexone (NTX) applied topically in healthy human volunteers, preliminary to determining its effectiveness in facilitating the healing of corneal epithelium removed intentionally to improve operator visibility during vitrectomy surgery (removing some of the jelly-like material from within the eye, for example during surgery for bleeding within the eye from diabetes mellitus).

The specific aim of the research is to demonstrate the safety of topically applied (eyedrops) Naltrexone (NTX) dissolved in Vigamox antibiotic eyedrops in normal volunteers. Naltrexone is approved by the Federal Food and Drug Administration for long term oral (by mouth) and systemic (by injection) use in individuals with substance abuse. Nevertheless, it has not previously been applied to the eye in eyedrop form. Vigamox is

an antibiotic eyedrop preparation commonly used to prevent eye infections in individuals who are about to undergo surgical procedures, and to treat infections of the eye surface. Approximately 20 individuals will be enrolled in the study.

You are being offered the opportunity to take part in this research because you are a healthy individual with no eye problems.

2. Procedures to be Followed:

2. Study Design: All eyedrops will be administered to one eye only, and any repeat dosing will be to the same eye. This study is an evaluation of topical NTX to be administered initially to three volunteers in the form of only one drop of NTX at a concentration of 10^{-6} M. No more medication will be given to these individuals. You will be followed in the clinic 1, 2, and 7 days post-treatment. Medication testing will proceed from the lowest to the highest concentration. A one (1) week interval will occur between the end of testing for a given concentration and the start of testing at the next higher concentration. The one week interval will allow us to evaluate the biological response to NTX and identify any adverse events before proceeding to the next higher NTX concentration.

Volunteers for each NTX concentration group will be comprised of 3 volunteers that receive NTX drops and 1 volunteer that receive Vigamox drops alone.

3. Summary of Procedures (all test procedures are ones commonly used in the clinical setting and are not experimental in nature):

Study Visit#1

Baseline history and complete dilated eye examination plus corneal thickness and shape measurements, corneal cell count, Shirmer test of tear production (in which a drop of anesthetic is administered to the eye surface, a small strip of filter paper is placed inside the lower eyelid for 5 minutes, and the resulting amount of wetting is measured) , corneal sensitivity, and photography of the back of the eye. You may not wear contact lenses after midnight of the preceding night. If you are eligible to participate, you will be randomly assigned to receive either the test medication in Vigamox® antibiotic eye drops or only the Vigamox® eye drops.

Study Visit #2

8:00 AM the following day: You arrive and eyes are examined externally and at the slit lamp; however, no intraocular pressure is measured.

9:00 AM: One drop is given

Eyes are examined 1 hr later but intraocular pressure is not measured.

12:30 PM (4 hr): Eyes are examined but intraocular pressure is not measured

2:00 PM Your eyes are examined and intraocular pressure is measured

Study Visit #3

24 hr later: you arrive around 8:30 am next day for complete eye examination plus corneal thickness and shape measurements, corneal cell count, Shirmer test of tear production (in which a drop of anesthetic is administered to the eye surface, a small strip of filter paper is placed inside the lower eyelid for 5 minutes, and the resulting amount of wetting is measured) , corneal sensitivity, and photography of the back of the eye are performed. You may resume contact lens wear after this meeting. The bottle of study eye drops should be returned at this visit.

Study Visit #4

7 days later: you arrive for complete eye examination plus corneal thickness and shape measurements, corneal cell count, Shirmer test of tear production (in which a drop of anesthetic is administered to the eye surface, a small strip of filter paper is placed inside the lower eyelid for 5 minutes, and the resulting amount of wetting is measured) , corneal sensitivity, and photography of the back of the eye are performed. You may not wear contact lenses after midnight of the preceding night.

Study Site Location: The study will be performed in the clinical facilities of the HMC Department of Ophthalmology.

3. Discomforts and Risks:

NTX has not previously been administered to humans in eyedrop form, although it is taken orally and in injectable form, sometimes for prolonged periods, in the treatment of alcohol and opioid medication abuse or overdose.

In studies with rats and in our animal studies, no significant eye toxicity occurred. So, from the treatment used in this study, we do not expect significant side effects.

It is possible that transient burning may occur at the time of eyedrop administration and unpredictable reactions always are possible. There is the possibility of currently unknown risks to the eye including infection, irritation, or other effects that might affect vision.

The most frequently reported eye adverse events from Vigamox® are eye redness, blurred vision, dry eye, corneal irritation, eye discomfort, pain, eye itching, subconjunctival hemorrhage (bleeding under the clear tissue that covers the white of the eye), and tearing. These events occurred in approximately 1-6% of patients. It should not be used in individuals allergic to moxifloxacin or other quinolones. It is possible that an individual may have a reaction that cannot be predicted.

Minor burning at the time of eyedrop administration would require no treatment. If irritation persists, artificial tears would be administered. It is highly unlikely that stronger therapy, such as steroid eyedrops would be required.

If you are pregnant or nursing, you will be excluded from participation in the study. If you are a sexually active woman of childbearing potential you must be taking an oral contraceptive to participate in the study. Males also must use contraception.

Subjects will be monitored closely for problems during their exams.

The USP Material Safety Data Sheet lists the following potential side effects or complications from Naltrexone (Catalog Number 1453504). These actions apply primarily to Naltrexone not administered to the eye.

Adverse Effects: Adverse effects may include anxiety; nervousness, restlessness, and/or trouble sleeping; drowsiness; unusual tiredness; lightheadedness; nausea or vomiting; headache; chills; cough; hoarseness; increased thirst; runny, stuffy nose; sinus problems; sneezing; sore throat; diarrhea; sweating; slowed breathing; fast or pounding heartbeat; constricted pupils; decreased body temperature; mental depression; joint, muscle pain, or abdominal pain; skin rash; and sexual problems in males. Possible allergic

reaction to material if inhaled, ingested or in contact with skin.

Overdose Effects: Overdose effects may include salivation, lethargy, tremors, and convulsions.

Acute: Eye, skin, gastrointestinal and/or respiratory tract irritation.

4. Possible Benefits:

a. Possible benefits to the participant:

You will not benefit from taking part in this research study.

b. Possible benefits to others:

Results of this study may guide the future use of naltrexone in treating eye disorders.

5. Other Options that Could be Used Instead of this Research:

You do not have to take part in this research study.

6. Time Duration of the Procedures and Study:

Each visit will take approximately 30 minutes to two hours, and there will be four visits.

7. Statement of Confidentiality:

a. Privacy and confidentiality measures:

Your records that are used in the research at The Milton S. Hershey Medical Center (HMC) and Penn State College of Medicine (PSU) will include code number, your name, address, phone number, date of birth, medical record number and be kept in a secured area in the Clinical Research facility of the Department of Ophthalmology.

In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

b. The use of private health information:

If you give your consent, health information about you will be collected for this research. Health information is protected by law as explained in the HMC Privacy Notice. If you have not received this notice, please request a copy from the researcher. At HMC/PSU your information will only be used or shared as explained in this consent form or when required by law. However, some of the other people/groups who receive your health information may not be required by Federal privacy laws to protect your information and may share it without your permission.

If you do not want us to use your protected health information, you may not participate in this research.

People usually have a right to see their medical records. However, you may not be allowed to see or copy certain information that is related to this research study. This is only for the period of the research. You will be allowed to see that information when the entire research project is complete.

If you choose to participate, you are free to withdraw your permission for the use and sharing of your health information at any time. You must do this in writing. Write to Dr. *Sassani* and let him know that you are withdrawing from the research study. His mailing address is Department of Ophthalmology, Hershey Medical Center, 500 University Drive, Hershey, P 17033.

If you withdraw your permission:

- We will no longer use or share medical information about you for this research study, except when the law requires us to do so.
- We are unable to take back anything we have already done or any information we have already shared with your permission.
- We may continue using and sharing the information obtained prior to your withdrawal if it is necessary for the soundness of the overall research.
- We will keep our records of the care that we provided to you as long as the law requires.

The research team may use the following sources of health information.

- Clinical history and examination information collected during the study
- Clinical test results: pachymetry (corneal thickness), corneal topography (corneal surface shape), endothelial specular microscopy (count of the number of cells lining the back surface of the cornea), fundus photography (photographs of the back of the eye).

Representatives of the following people/groups within HMC/PSU may use your health information and share it with other specific groups in connection with this research study.

- The principal investigator, Joseph W. Sassani, MD, MHA

- The HMC/PSU Institutional Review Board
- The HMC/PSU Human Subjects Protection Office
- Drs. David Liang, MD and Ian Zagon, PhD
- The Department of Ophthalmology Clinical Research Office

The above people/groups may share your health information with the following people/groups outside HMC/PSU for their use in connection with this research study. These groups, while monitoring the research study, may also review and/or copy your original PSU/HMC records.

- The Office of Human Research Protections in the U. S. Department of Health and Human Services
- Food and Drug Administration
- Representatives of the U.S. Army Medical Research and Materiel Command (USAMRMC)

8. Costs for Participation:

a. Costs:

- All tests and procedures described in this study are provided at no cost to you.

b. Treatment and compensation for injury:

Every effort to prevent injury as a result of your participation will be taken. It is possible, however, that you could develop complications or injuries as a result of participating in this research study. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. It is the policy of this institution to provide neither financial compensation nor free medical treatment for research-related injury.

Costs for the treatment of research-related injuries will be charged to your insurance carrier or to you. Some insurance companies may not cover costs associated with research studies. If for any reason these costs are not covered by your insurance, they will be your responsibility. You will also be responsible for any deductible, co-insurance and/or co-pay.

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IRB Protocol No. 29780
Version Date: 2/22/10

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Signature of Participant Date Time

Printed Name

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Signature of person who explained this research:

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Date Time

(Only approved investigators for this research may explain the research and obtain informed consent.)

IRB Protocol No. 29780
Version Date: 2/22/10

NOTE: The following is the text of our recruiting poster, but does not include graphics so that it can be included in this report:

Healthy volunteers needed EYE DROPS STUDY

Researchers at Penn State Milton S. Hershey Medical Center are determining the safety of eye drops containing a medication that may facilitate corneal wound healing and which is approved by the U.S. Food and Drug Administration to be taken internally. Researchers in the Department of Ophthalmology are conducting a study to document the safety of Naltrexone eye drops applied for one day to one eye of healthy volunteers.

You may be eligible if you:

- are from 21 to 50 years old.
- are not pregnant or will become pregnant through use of birth

control pills or are sterile.

- have not had corneal or other ocular surface disease.
- do not have systemic disease associated with ocular surface

complications including autoimmune or rheumatologic disorders or diabetes.

To see if you are eligible, contact
the Department of Ophthalmology at 717-531-8783.

Study director

Joseph Sassani, M.D. Penn State Hershey Department of Ophthalmology