

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-897**

**PHARMACOLOGY REVIEW**

*2nd cycle*

Reviewer: R. Daniel Mellon, Ph.D.

NDA No. 21-897



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

## PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 21-897  
SERIAL NUMBER: 000  
DATE RECEIVED BY CENTER: 14-Feb-2006  
PRODUCT: Vivitrol™ (naltrexone for extended-release injectable suspension)  
INTENDED CLINICAL POPULATION: Patients seeking treatment for alcohol dependence  
SPONSOR: Alkermes® Inc.  
DOCUMENTS REVIEWED: Complete response to AE Letter  
REVIEW DIVISION: Division of Anesthesia, Analgesia, and Rheumatology Products (HFD-170)  
PHARM/TOX REVIEWER: Mamata De, Ph.D.  
PHARM/TOX SUPERVISOR: R. Daniel Mellon, Ph.D.  
DIVISION DIRECTOR: Bob A. Rappaport, M.D.  
PROJECT MANAGER: Lisa Basham-Cruz, M.S.

Date of review submission to Division File System (DFS): 12-Apr-2006

## **EXECUTIVE SUMMARY**

### **I. Recommendations**

#### **A. Recommendation on approvability**

From the pharmacology toxicology perspective, NDA 21-897 may be APPROVED, pending agreement on the labeling and Phase 4 commitments outlined below.

In the original action letter dated December 23, 2005, the Sponsor was requested to address the following nonclinical deficiency:

*Provide pharmacokinetic/toxicokinetic exposure data in the appropriate species necessary for interpreting the existing carcinogenicity and reproductive toxicology data in the product labeling. In the absence of adequate bridging data, the following nonclinical studies would have to be conducted:*

- a. a Segment I reproductive and developmental toxicology study including toxicokinetic data in a single species with the final drug product formulation;*
- b. Segment II reproductive and developmental toxicology studies in two species including toxicokinetic data with the final drug product formulation;*
- c. a Segment III reproductive and developmental toxicology study including toxicokinetic data with the final drug product formulation; and*
- d. carcinogenicity assessment in two species using the final drug product formulation.*

Following discussions with the Sponsor during a post-action teleconference on January 3, 2006, the Division informed the sponsor of the following (e-mail dated February 7, 2006):

*The review team has considered your proposal to submit a response to the December 23, 2005 action letter that employs human comparative PK data as an interim bridging strategy and proposes definitive bridging in animals as a Phase 4 study. We are willing to accept for review a response to our action letter that uses your proposed approach to deficiency #2 of our December 23, 2005, action letter, although the review team is not in exact agreement with some aspects of the proposed labeling.*

The Sponsor has not provided adequate nonclinical bridging data, nor have they completed the requested toxicology studies. From the nonclinical perspective, the potential for reproductive toxicity and carcinogenicity of oral naltrexone was adequately assessed to support the approval of the referenced drug product, ReVia®. The exposure to naltrexone via the Vivitrol™ drug product could theoretically alter the potential for naltrexone-related tumor development compared to that of ReVia®. Therefore, with respect to the Vivitrol™ label,

/ / / / / / / /

Currently, ReVia® is a Pregnancy Category C drug due to embryocidal and fetotoxic effects noted in rats and rabbits treated orally with naltrexone as described in the ReVia® labeling. Although the exposure to naltrexone may be greater following Vivitrol™ administration, a Pregnancy Category of C is currently the most restrictive category a drug can receive in the absence of well-controlled clinical trial data documenting teratogenic effects in humans.

/ / / / /

The results of the carcinogenicity studies conducted for ReVia® and described in the ReVia® package insert are relevant to the Vivitrol™ drug product and should be included in the labeling;

/ / /

The potential for Vivitrol™ to alter the incidence of the reported testicular mesotheliomas in males and tumors of vascular origin in males and females should be included in the product labeling. However, it is important to note nonclinical carcinogenicity studies are designed to assess the potential for lifelong exposure of a drug to alter tumor formation, and the tumors described in the ReVia® labeling were observed following lifelong exposure of the animals to naltrexone hydrochloride. However, there is no evidence that altering the naltrexone pharmacokinetic profile via Vivitrol™ will significantly change the risk:benefit analysis with respect to this patient population.

Following extensive discussions, the review team has agreed to allow the nonclinical studies requested in the original Approvable letter to be completed during Phase 4. As outlined in Dr. Rappaport's Division Director's Memorandum for this action, from the clinical perspective, specific

quantification of both the potential reproductive toxicity and carcinogenic potential following exposure to naltrexone via Vivitrol™ product is outweighed by the potential clinical benefit that Vivitrol™ may have for this patient population. The reader is referred to Dr. Rappaport's memorandum regarding the specific details supporting the decision to allow the studies to be completed as a phase 4 commitment.

**B. Recommendation for nonclinical studies**

The following nonclinical studies should be conducted as a Phase 4 commitment:

1. a Segment I reproductive and developmental toxicology study including toxicokinetic data in a single species with the final drug product formulation,

Protocol Submission: by October 7, 2006

Study Start: by January 7, 2007

Final Report Submission: by January 7, 2008

2. Segment II reproductive and developmental toxicology studies in two species including toxicokinetic data with the final drug product formulation,

Protocol Submission: by October 7, 2006

Study Start: by January 7, 2007

Final Report Submission: by January 7, 2008

3. a Segment III reproductive and developmental toxicology study including toxicokinetic data with the final drug product formulation, and

Protocol Submission: by October 7, 2006

Study Start: by January 7, 2007

Final Report Submission: by January 7, 2008

4. Carcinogenicity assessment in two species using the final drug product formulation.

Protocol Submission: by April 7, 2007

Study Start: by August 7, 2007

Final Report Submission: by August 8, 2010

5. In lieu of the animal studies listed in commitments 1 through 4 above, you may be able to obtain adequate

pharmacokinetic/toxicokinetic exposure data in the appropriate species necessary for interpreting the existing carcinogenicity and reproductive toxicology data on oral naltrexone in the product labeling. Bridging data will be needed for the mouse, rat, pregnant rat and pregnant rabbit. The following timelines should be followed for this option:

Protocol Submission: by October 7, 2006

Study Start: by January 7, 2007

Final Report Submission: by January 7, 2008

### **C. Recommendations on labeling**

At the time of this action, the following labeling is recommended:

#### **Carcinogenesis, mutagenesis, impairment of fertility**

Carcinogenicity studies have not been conducted with VIVITROL.

Carcinogenicity studies for 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<sup>2</sup>/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 when given orally to rats at doses  $\geq$  30 mg/kg/day (180 mg/m<sup>2</sup>/day) and rabbits administered  $\geq$  60 mg/kg/day (720 mg/m<sup>2</sup>/day).

There are no adequate and well-controlled studies of oral naltrexone and 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 $\beta$ -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.

R. Daniel Mellon, Ph.D.  
Pharmacology Toxicology Supervisor, DAARP

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R. Daniel Mellon  
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PHARMACOLOGIST  
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DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

## PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 21-897  
SERIAL NUMBER: 000  
DATE RECEIVED BY CENTER: 31-Mar-2005  
PRODUCT: Vivitrol®  
INTENDED CLINICAL POPULATION: Alcohol dependence  
SPONSOR: Alkermes Inc.  
DOCUMENTS REVIEWED: Pharmacology Toxicology Review by Dr. Mamata De, with reference to the Sponsor's electronic submissions and the relevant literature  
REVIEW DIVISION: Division of Anesthesia, Analgesia, and Rheumatology Products (HFD-170)  
PHARM/TOX REVIEWER: Mamata De, Ph.D.  
PHARM/TOX SUPERVISOR: R. Daniel Mellon, Ph.D.  
DIVISION DIRECTOR: Bob A. Rappaport, M.D.  
PROJECT MANAGER: Lisa Basham-Cruz

Date of review submission to Division File System (DFS): 21-Dec-2005

***EXECUTIVE SUMMARY***

**I. Recommendations**

**A. Recommendation on approvability**

From the pharmacology toxicology perspective, NDA 21-897 is **Approvable**.

**B. Recommendation for nonclinical studies**

The Sponsor has not provided data necessary to demonstrate the adequacy of the existing carcinogenicity or reproductive and developmental toxicology data referenced as part of this 505(b)(2) NDA. The Sponsor should either complete the following studies to support the NDA:

The Sponsor must provide pharmacokinetic/toxicokinetic exposure data in the appropriate species necessary for interpreting the existing carcinogenicity and reproductive toxicology data in the product labeling. In the absence of adequate bridging data, the following nonclinical studies would have to be conducted:

1. a Segment I reproductive and developmental toxicology study including toxicokinetic data in a single species with the final drug product formulation,
2. Segment II reproductive and developmental toxicology studies in two species including toxicokinetic data with the final drug product formulation,
3. a Segment III reproductive and developmental toxicology study including toxicokinetic data with the final drug product formulation, and
4. carcinogenicity assessment in two species using the final drug product formulation.

In addition, the proposed label

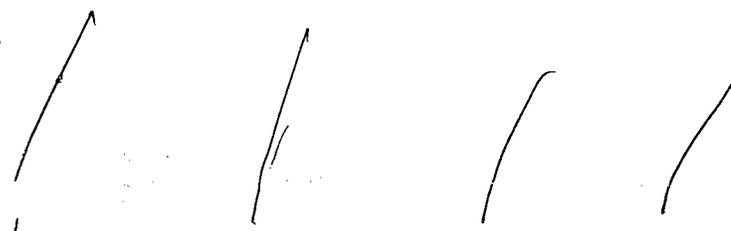
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       Trade Secret / Confidential

       Draft Labeling

       Deliberative Process



## **BASIS OF CONCLUSIONS AND RECOMMENDATIONS**

Following review of Dr. Mamata De's primary review of NDA 21-897, the numerous discussions that took place between Dr. De and myself during the review process, my own reference to the NDA application, and discussion with Dr. Kenneth Hastings, Ph.D. (Associate Director for Pharmacology and Toxicology for ODE 2 and 3), it is my opinion that from the pharmacology and toxicology perspective, the NDA is Approvable. There are several deficiencies that could be overcome with additional toxicokinetic studies or toxicology studies that, from this discipline's perspective, could make the NDA approvable. This memo was written to outline the key areas of concern and delineate how they could be resolved.

Although the Sponsor's application is deficient from a regulatory perspective in terms of failing to provide adequate patent certification for the multiple referenced NDAs, it is my opinion that in the absence of the referenced findings from NDAs other than the referenced oral naltrexone drug product Revia (NDA 18-932), the deficiencies noted above for NDA 21-897 Vivitrol) would be the same. In other words, the other NDAs discussed in the Sponsor's submission were not required for this action.

### **Sponsor's Basis for NDA Application:**

As stated in the NDA application (Nonclinical overview, page 1-2):

Alkermes Inc., is submitting this NDA under Section 505(b)(2) of the FDC Act. The non-clinical safety of Vivitrex (naltrexone long-acting injection) is established based upon:

- The Agency's previous determination of the safety of oral naltrexone tablets, 50 mg (Revia NDA 18-932, approved December 30, 1994 for the treatment alcohol dependence). A paragraph II patent certification which certifies to the patents listed in the Orange Book is included in Section 1.3.5.2.
- The following specific studies conducted with Vivitrex microspheres in accordance with the agreements from the pre-NDA meeting (March 25, 2004):

STUDY NUMBER	TITLE
AT-21-01	A Local Tolerance Study of Medisorb Naltrexone in Rabbits Following a Single Subcutaneous Injection
AT-21-02	One-Month Toxicokinetic Study of Medisorb Naltrexone in Rhesus Monkeys with One-Month Recovery
AT-21-03	A 3-month Repeated-Dose Toxicokinetic Study of Medisorb Naltrexone Administered by Subcutaneous Injection to Rhesus Monkeys, With a 3-Month Recovery Period.
AT-21-04	Chronic Local Tolerance Study of Medisorb Naltrexone in Rabbits following a Single Subcutaneous and Intramuscular Injection
AT-21-05	Chronic Local Tolerance and Pharmacokinetic Evaluation of Medisorb Naltrexone in Dogs following Repeated Intramuscular Injections
AT-21-06	Investigative Acute Local Tolerance Evaluation of Medisorb Naltrexone in Dogs following Intramuscular Administration
AT-21-07	Investigative Local Tolerance Study of Medisorb Naltrexone in Rabbits following Intramuscular Administration

- Information from published literature on the safety of naltrexone available in the public domain

Upon review of the NDA application and the submitted labeling, it is clear that the Sponsor refers to the Agency's previous findings for more than just the Revia NDA. Specifically, the table below outlines the nonclinical data the Sponsor references in the NDA application in support Vivitrol formulation. The Sponsor did not submit nonclinical studies with Vivitrol formulation for any of the nonclinical requirements listed in the table. The table therefore breaks down the references to naltrexone alone and references to data on polylactide-co-glycolide microspheres that were either published or submitted in support of other NDA applications.

Non-clinical Requirements	Naltrexone Referenced Data	PLG microspheres Referenced Data
Reproduction and Developmental Toxicology: Segment I	NDA 18-932 (Revia)	
Reproduction and Developmental Toxicology: Segment II	NDA 18-932 (Revia)	
Reproduction and Developmental Toxicology: Segment III	NDA 18-932 (Revia)	
Genetic Toxicology	NDA 18-932 (Revia)	

**Table 2.6: Comparison of NOAELs from Oral Naltrexone Studies and Dose Multiples Relative to Vivitrex suspension**

SPECIES	TYPE OF STUDY	NOAEL* (mg/kg/day)	ORAL DOSE MULTIPLE†	DOSE MULTIPLE RELATIVE TO VIVITREX 380 mg‡	
				mg/kg BASIS	BSA BASIS‡
Monkey	Chronic	20	20	5.1	1.7
Rat	Subchronic	70	70	18	3.0
Dog	Subchronic	40	40	10	5.0
Rat	Reproductive	30	30	7.7	1.3
Rat	Teratology	200	200	51	8.5
Rabbit	Teratology	60	60	15.4	5.1
Mouse	Carcinogen <sup>ty</sup>	100	100	26	2.1
Rat	Carcinogen <sup>ty</sup>	100	100	26	4.3

\* NOAEL: No Observed Adverse Effect Level

† Calculated using a therapeutic human dose of 1 mg naltrexone/kg/day (derived for the standard daily oral naltrexone dose of 50 mg, and an assumed body weight of 50 kg).

‡ Calculated by comparison of the AUC<sub>0-24h</sub> for Vivitrex to the aggregate AUC<sub>13-28</sub> for oral formulation (AUC<sub>0-24h</sub> 41.2 ng·day/mL for oral and 160 ± 24 ng·day/mL for a 380 mg dose of Vivitrex resulting in a conversion factor of 3.9)

§ mg/kg to BSA conversion factors adapted from Freireich 1966 (20) and Casarett and Doull's Toxicology (21).

The Sponsor's exposure margin assessments as noted in the table above are not adequate for the following reasons:

1. Due to the differences between routes of administration and PK profile, a direct comparison of doses on a mg/kg basis is not informative. Therefore, the dose multiples in the second column from the right above cannot be taken into consideration for interpretation and labeling.
2. The determination of the multiples of exposure based on body surface area is not appropriate for this formulation either due to the differences in PK between the daily oral route and that produced by monthly Vivitrol injections. Specifically,
  - a. The toxicology studies supporting the Revia NDA utilized the oral route of administration whereas Vivitrol is administered via IM injection and did not provide toxicokinetic data.
  - b. Oral naltrexone is subjected to significant first pass metabolism by the liver. The IM route of administration provides greater exposure, in part due to reducing drug lost to first pass metabolism in the liver.

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Dr. Srikanth Nallani, the clinical pharmacology and biopharmaceutics reviewer for NDA 21-897 stated the following in his review:

The proposed 380 mg dose of IM Vivitrol is approximately 1/3<sup>rd</sup> compared to oral naltrexone (50 mg QD for 28 days = 1400 mg over 28 days). However, the exposure to naltrexone (AUC<sub>0-28</sub>) over 28 days is approximately four-fold higher than that observed with oral naltrexone. This appears to be a result of bypassing of first pass metabolism by the IM route.

As outlined in Dr. Nallani's Clinical Pharmacology and Biopharmaceutics review, differences between these two formulations include: 1) differences in C<sub>max</sub> and AUC such that Vivitrol has on average a 4-fold greater AUC, and 2) differences in the effects of first pass metabolism due to the different routes of administration (Vivitrol resulted in significantly lower levels of 6β-naltrexol). However, even using a mean value over the course of the month is an oversimplification of the exposure margin, which can be illustrated by the Sponsor's Clinical data. Specifically, the figure below (Figure 6, page 43 of 66 of Study Report ALK21-005) illustrates the plasma concentration of naltrexone (open circles) after 4 injections of 380 mg once every 28 days. It is clear from the time course that the AUC over the interval from Day 0 to Day 7 is far greater than the AUC over the interval from Day 21 to Day 28.

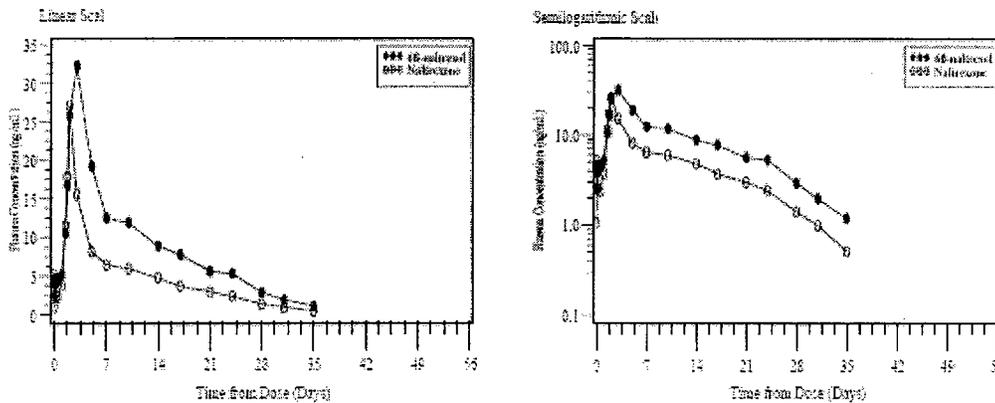


Figure 6 Mean Naltrexone and 6β-Naltrexol Plasma Concentration versus Time Profile (0-56 Days) Following Dose 4 of 4 of Medisorb Naltrexone 380 mg (Cohort B, N=12)

A further limitation of the data referenced in the Revia NDA is that the studies that were completed for the Revia NDA do not contain toxicokinetic values that could be as the basis for comparison. Without toxicokinetic exposure data for the conditions tested in the nonclinical studies submitted for Revia, the results cannot be put into perspective to the clinical exposure to the Vivitrol product.

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**Regulatory Status of the Polylactide-co-glycolide Polymer**

The NDA submission states that the 75:25 poly lactide-co-glycolide polymer (also referred to as 7525 polymer by the Sponsor) is listed in the FDA Inactive Ingredient Database under Polyglactin (CAS # 026780-50-7), and there is considered to be safe. Specifically, Section 3.2.P.2.1.2.1 7525 POLYMER of the NDA describes the drug product component as follows:

The biodegradable polymer excipient used for Vivitrex microspheres is 7525 a © polymer comprised of lactide and glycolide monomers in a mole ratio of 75:25. 7525 polymer is a member of the poly lactide-co-glycolide (PLG) class of biodegradable copolymers.

PLG is a common, biodegradable medical polymer having a history of safe human usage in sutures, orthopedics, bone plates and extended release pharmaceuticals. It is also listed in the FDA Inactive Ingredients Database (polyglactin, CAS # 026780507) and is used in a similar dosage form, the same route of administration, and in essentially the same concentration in Vivitrex microspheres.

The Inactive Ingredients Database does report that polyglactin 370 (CAS 26780-50-7) is an inactive ingredient in approved implanted and injected drug products.

The Vivitrol drug product is a member of the class of polymers that has a specific lactide:glycolide mole ratio of 75:25. Changing the lactide:glycolide mole ratio alters the rate of biodegradation. In general, the greater glycolide content, the faster the rate of biodegradation. This characteristic of the class of copolymers is illustrated by the figure below which depicts the amount of radioactivity that is recovered from the rat when the radiolabel is attached to the lactide component of the polymer [reproduced from (Anderson and Shive, 1997)].

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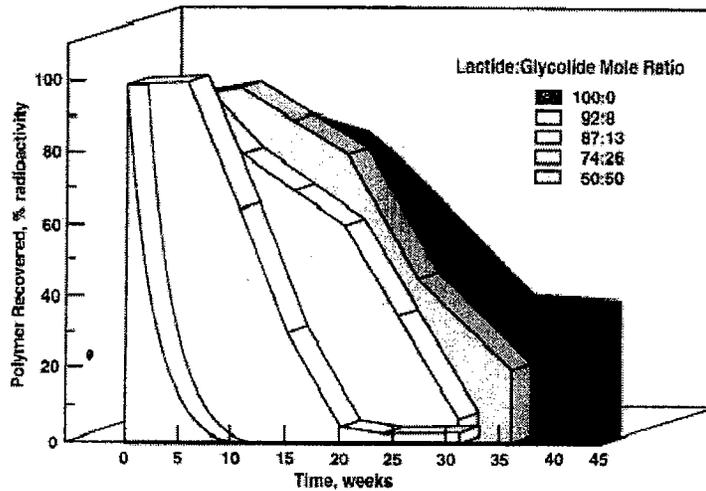


Fig. 1. In vivo resorption rates of radiolabelled poly(DL-lactide-co-glycolide) microspheres injected intramuscularly in rats. The fastest rate of degradation occurs with the 50:50 copolymer and as the glycolic acid content decreases, the rate of degradation decreases. Modified from Figure 3 in Reference [20].

As illustrated above the biodegradation of a copolymer with a lactide:glycolide mole ratio of 50:50 is relatively rapid, with the polymer being virtually eliminated from the rat by ~10 weeks after IM injection. In contrast, decreasing the glycolide content to make a copolymer with a lactide:glycolide mole ratio of 74:26 has a significant effect on the biodegradation rate. As illustrated above, approximately 20% of the injected 74:26 polylactide-co-glycolide polymer was still present in the rat over 35 weeks after IM injection. All of the copolymers described in the figure above are poly(lactide-co-glycolide) compounds with the same CAS number.

In addition to the lactide:glycolide ratio, the characteristics of the drug incorporated into the polylactide-co-glycolide polymers alters the release rate and biodegradation of the drug product. The effect of \_\_\_\_\_ on the biodegradation rate of the polymer was noted in the NDA submission. Specifically, the Drug Product Overview states the following:

*"In vitro* release data show drug content strongly affects naltrexone microsphere drug release behavior."

"Because \_\_\_\_\_ it

Collectively, the Sponsor's references to data reported in NDAs drug products \_\_\_\_\_ do not provide adequate support for the safety of the Vivitrol drug product.

Based upon these clear differences in PK and inability to provide a meaningful assessment of the potential exposure margins extrapolated from the referenced Revia

data, I must conclude that the NDA should be supported by either adequate toxicokinetic exposure data necessary to interpret the referenced reproductive and developmental toxicology and carcinogenicity data and to complete these portions of the label for Vivitrol.

**Unresolved toxicology issues (if any):**

***Reproduction and Developmental Toxicology:***

The Sponsor elected to reference the NDA for Revia to support the requirement for reproduction and developmental toxicology assessment of their drug product. I agree with Dr. De's conclusion that the existing data on naltrexone alone is inadequate to support the Vivitrol NDA. The basis for this conclusion, as outlined above, is that inadequate data were provided to determine meaningful exposure margins for Vivitrol based on the studies submitted for Revia. The Sponsor's proposed use of body surface area comparisons to establish the exposure margins for the carcinogenicity data are do not provide meaningful assessment of the study findings due to differences in PK.

***Carcinogenicity:***

The Sponsor elected to reference the NDA for Revia to support the requirement for carcinogenicity assessment of their drug product. I agree with Dr. De's conclusion that the existing data on naltrexone alone is inadequate to support the Vivitrol NDA. The basis for this conclusion, as outlined above, is that inadequate data were provided to determine meaningful exposure margins for Vivitrol based on the studies submitted for Revia. The Sponsor's proposed use of body surface area comparisons to establish the exposure margins for the carcinogenicity data are do not provide meaningful assessment of the study findings due to differences in PK.

**Recommendations:**

The Sponsor has not provided data necessary to demonstrate the adequacy of the existing carcinogenicity or reproductive and developmental toxicology data referenced as part of this 505(b)(2) NDA. The Sponsor should either complete the following studies to support the NDA:

The Sponsor must provide pharmacokinetic/toxicokinetic exposure data in the appropriate species necessary for interpreting the existing carcinogenicity and reproductive toxicology data in the product labeling. In the absence of adequate bridging data, the following nonclinical studies would have to be conducted:

1. a Segment I reproductive and developmental toxicology study including toxicokinetic data in a single species with the final drug product formulation,

2. Segment II reproductive and developmental toxicology studies in two species including toxicokinetic data with the final drug product formulation,
3. a Segment III reproductive and developmental toxicology study including toxicokinetic data with the final drug product formulation, and
4. carcinogenicity assessment in two species using the final drug product formulation.

#### Reference List

Anderson JM and Shive MS (1997) Biodegradation and biocompatibility of PLA and PLGA microspheres. *Advanced Drug Delivery Reviews* 28:5-24.

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R. Daniel Mellon  
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PHARMACOLOGIST  
Pharmacology Toxicology Supervisor



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PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

## PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 21-897  
SERIAL NUMBER: 000  
DATE RECEIVED BY CENTER: 03/30/05  
PRODUCT: Vivitrol®  
INTENDED CLINICAL POPULATION: Treatment of alcohol dependence  
SPONSOR: Alkermes, Inc.  
DOCUMENTS REVIEWED: eCTD Module 2 and 4  
REVIEW DIVISION: Division of Anesthesia, Analgesia, and  
Rheumatology Products (HFD-170)  
PHARM/TOX REVIEWER: Mamata De, Ph.D.  
PHARM/TOX SUPERVISOR: R. Daniel Mellon, Ph.D.  
DIVISION DIRECTOR: Bob A. Rapaport, M.D.  
PROJECT MANAGER: Lisa Basham Cruz, M.S.

Date of review submission to Division File System (DFS): December 16, 2005

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***EXECUTIVE SUMMARY***

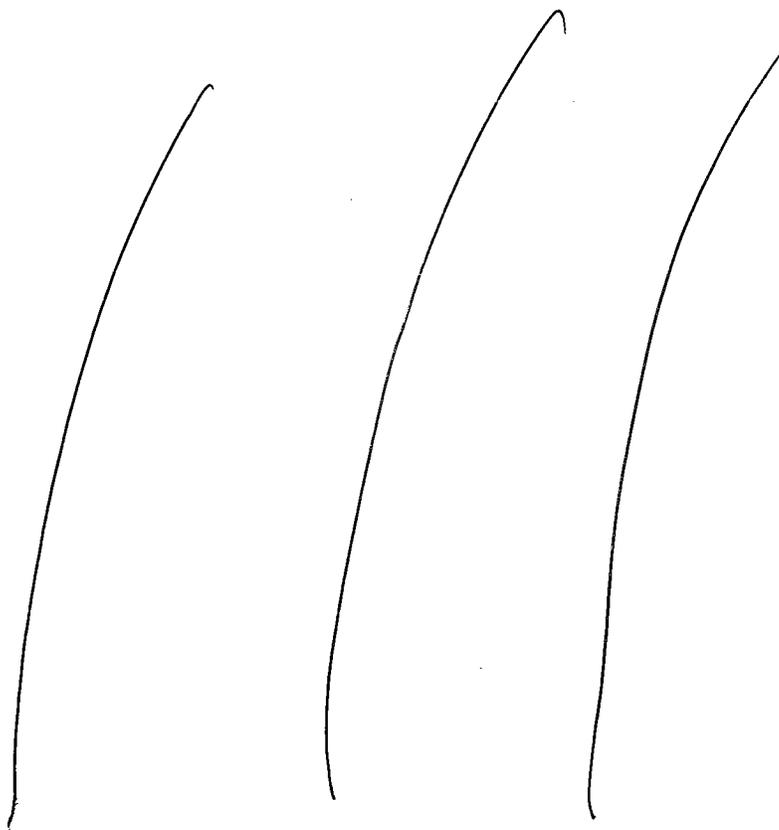
**I. Recommendations**

A. Recommendation on approvability:

Not approvable from the Pharmacology /Toxicology perspective. Following non clinical studies should be performed (see section B). However, if it is recommended for approval from other discipline in regards to the safety evaluation following risk benefit analysis, sponsor should perform the recommended nonclinical study to update the label for the sake of public safety.

B. Recommendation for nonclinical studies:

1. Carcinogenicity study with current formulation of vivitrol in two species.
2. Segment I, II, and III of the reproductive toxicity study in rat.



1   Page(s) Withheld

       Trade Secret / Confidential

       Draft Labeling

       Deliberative Process

## II. Summary of nonclinical findings

### A. Brief overview of nonclinical findings

Vivitrol (formerly Vivitrex or Medisorb Naltrexone) suspension is intended to treat alcohol dependence disorder. The syndrome is manifested by problems that include tolerance, withdrawal, and several noticeable changes of behavioral loss of control over the use of alcohol, with distress and/or impaired function. The *dependence disorder* is discrete and distinguished from *alcohol abuse, alcohol withdrawal syndrome, or other alcohol-induced syndromes, such as alcohol amnestic disorder*. Alcohol use disorders are a major public health problem, which worldwide is one of the leading causes of disability. Alcohol dependence is present in a substantial proportion of the adult population, common among primary care patients, and increasingly recognized as a chronic disease. Current alcohol dependence pharmacotherapies, is indicated only for use after the patient has established abstinence, and often this requires detoxification treatment for alcohol withdrawal.

Vivitrex is a combination of extended release microspheres for injection and a diluent for parenteral, intramuscular use, consist of a sterile, off-white to light-tan powder that is available in dosage strength of 380 mg naltrexone per vial. Naltrexone is microencapsulated in 75:25 polylactide-co-glycolide (PLG) at a concentration of 337 mg of naltrexone per gram of microspheres. The diluent for parenteral use is a clear, colorless solution. The composition of the diluent includes carboxymethylcellulose sodium salt, polysorbate 20, sodium chloride, and water for injection. The microspheres are suspended in the diluent prior to injection. The intramuscular injection of the Vivitrex suspension may reduce the hepatic toxicity by avoidance of first-pass hepatic metabolism which will markedly reduce hepatic exposure to naltrexone. Also the total monthly dose of Vivitrex suspension is less than the daily oral naltrexone dosing; and administration of Vivitrex suspension by healthcare providers offers much greater control over administration of the recommended dose, which may in consequence, initiate effective pharmacotherapy may be sooner.

The Vivitrex nonclinical safety studies completed by the sponsor included programs of general toxicity and local tolerance testing. Reference is made to the agency's finding of safety (NDA 18-932 submitted by Dupont and Endo Laboratories for oral formulations of naltrexone), under the provisions of section 505(b)(2) of the United States Federal Food, Drug, and Cosmetic Act. Additionally, toxicity data from scientific publications are also considered for reviewing the safety of this product.

The proposed clinical dose of Vivitrex microspheres is predicted to produce a mean naltrexone exposure approximately 3.9-times the aggregate exposure generated by 28 days of the standard oral naltrexone dose of 50 mg/day. Despite this exposure increment, the doses in all of the naltrexone nonclinical studies (NDA 18-932) are calculated to exceed those resulting from the maximum proposed dose of Vivitrex microspheres. In the 3-month, 3-cycle SC repeated-dose toxicokinetic safety study in monkeys doses of 20, 50 and 75 mg naltrexone/kg (57, 143, 215 mg microspheres/kg) were administered in

dose volumes < 1.5 mL/ injection. Drug exposure was limited by the availability of suitable SC sites, since up to 6 injection sites were required in high-dose animals to administer a full dose. No evidence of systemic toxicity was observed in the study at any dose, but as with the single dose monkey study, local injection site effects were observed. Toxicokinetic analysis revealed a dose-related increase in naltrexone AUCs.

**Comparison of Human and Monkey Naltrexone Concentrations (Mean ± SD)**

STUDY	AT-21-02				AT-21-03			ALK21-005	
STUDY DESIGN	1-MO TOX (SINGLE DOSE) MONKEY				3-MO TOX (DOSE Q28 DAYS X3) MONKEY			CLINICAL SAFETY STUDY	
NTX Dose (mg/kg: nonclin) (mg: clin)	20	50	200	50	20	50	75	380	1400 mg 50 mg/day
Route	SC	SC	SC	IM	SC	SC	SC	IM	Oral
N	4	4	6	4	6	6	10	10	14
C <sub>max</sub> (ng/mL)									
Cycle 1	31.8 (8.4)	64.3 (6.4)	265 (25)	106 (30)	89.9 (107)	102 (75)	72.1 (36.6)	28.0 (12.2)	13.7 (10.6)
Cycle 2	-	-	-	-	38.9 (25.7)	72.6 (34.5)	214 (226)		
Cycle 3	-	-	-	-	27.8 (5.3)	82.5 (60.5)	123 (50.5)		
AUC <sub>0-28d</sub> (ng·day/mL)									
Cycle 1	187 (45.7)	449 (155)	2115 (654)	609 (20.5)	423 (389)	588 (277)	513 (130)	160 (24.2)	41.1 <sup>‡</sup>
Cycle 2	-	-	-	-	307 (125)	556 (260)	1567 (1323)		
Cycle 3	-	-	-	-	164 (38) <sup>†</sup>	447 (127) <sup>†</sup>	751 (282) <sup>†</sup>		

NTX = naltrexone

\* AUC<sub>0-29d</sub>

† AUC<sub>0-34d</sub>

‡ AUC<sub>28d</sub> was calculated as the mean of AUC<sub>1d</sub> \* 28

Human exposure to naltrexone in Vivitrex at the proposed dose of 380 mg/month (7.6 mg/kg) produced naltrexone exposures estimated by interpolation at approximately 388% of the aggregate exposure from 28 days of oral dosing with the 50 mg tablet (AUC<sub>0-28d</sub> 41.2 ng·day/mL for oral and 160 ± 24.2 ng·day/mL for a 380 mg dose of Vivitrex microspheres. Similarly, toxicology studies conducted with Vivitrex suspension also exceeded the clinical exposure level.

The monkey is the only nonclinical species to produce 6β-naltrexol in amounts sufficient to quantitate. Only minimal 6β-naltrexol is produced in rabbits. In nonclinical testing, adequate dose multiples were utilized in rhesus monkeys to produce a 6β-naltrexol AUC<sub>0-29d</sub> of approximately 43% that produced with the proposed clinical dose of naltrexone in humans. The opioid receptor antagonist activity of 6β-naltrexone is less than that of naltrexone by a factor of about 150 (based on hot plate test). However, despite its lower

potency, 6 $\beta$ -naltrexol may enhance the duration of opiate antagonism due to its longer half-life. The enzyme that is involved in the generation of 6 $\beta$ -naltrexol is dihydrodiol dehydrogenase (DD4), which is a cytosolic enzyme, found primarily in the liver of humans, but has been reported to be most concentrated in the kidney of the monkey.

The local tolerability studies in rabbits and the single dose and multiple dose monkey studies had substantially similar outcomes for injection site evaluations. The multiple dose IM local tolerability study conducted in the dog was significantly different in design and outcome and is described separately.

#### **Exposure Multiples for Vivitrex (naltrexone long-acting injection) Nonclinical Toxicology Studies**

SPECIES	STUDY TYPE	STUDY NUMBER	DOSE MULTIPLE RELATIVE TO VIVITREX 380 MG		
			MG/KG BASIS*	BODY SURFACE AREA BASIS	AUC BASIS
Monkey	Single-dose toxicity	AT-21-02	26	8.7	17.5 <sup>†</sup>
Monkey	Multiple-dose toxicity	AT-21-03	10	3.3	4.7 <sup>‡</sup>

\* Based on a 50 kg human

<sup>†</sup> AUC<sub>0-29d</sub> Monkey, AUC<sub>0-28d</sub> Human

<sup>‡</sup> AUC<sub>0-33d</sub> Monkey, AUC<sub>0-28d</sub> Human

SC and IM routes of administration were used in the rabbit and monkey single dose toxicity studies to aid in selecting a clinical route of administration and. The SC route was used for the repeated dose monkey study because insufficient IM sites were available for depot injection in that species. Both SC and IM injections of Vivitrex microspheres and Medisorb Placebo microspheres in monkeys and rabbits resulted in a clinically visible injection site enlargement attributable to the mass of test material and pathological evidence of a foreign body reaction at the depot site.

#### **Comparison of Human and Monkey 6 $\beta$ -naltrexol concentrations (Mean $\pm$ SD)**

STUDY	AT-21-02				AT-21-03			ALK21-005	
STUDY DESIGN	1-MO TOX (SINGLE DOSE) MONKEY				3-MO TOX (DOSE Q28 DAYS X3) MONKEY			CLINICAL SAFETY STUDY	
NTX Dose (mg/kg: nonclin) (mg: clin)	20	50	200	50	20	50	75	380	1400 mg (50 mg/day)
Route	SC	SC	SC	IM	SC	SC	SC	IM	Oral
N	4	4	6	4	6	6	10	10	14
C <sub>max</sub> (ng/mL)									
Cycle 1	1.6 (0.8)	4.9 (1.1)	12.3 (2.0)	4.0 (1.6)	2.7 (1.8)	5.1 (2.2)	6.1 (2.2)	34.2 (12.9)	138.7 (36)
Cycle 2	-	-	-	-	2.9 (0.9)	9.6 (8.5)	13.1 (7.3)		
Cycle 3	-	-	-	-	4.3 (2.9)	5.9 (2.3)	10.5 (4.0)		
AUC <sub>0-28d</sub> (ng·day/mL)									
Cycle 1	11.1 (5.6)*	40.6 (12.5)*	127 (22.7)*	35.0 (12.5)*	20.1 (7.3)	46.8 (13.7)	67.7 (22.1)	294 (70.4)	1002 <sup>†</sup>
Cycle 2	-	-	-	-	20.7 (7.8)	58.5 (31.3)	103 (32.3)		
Cycle 3	-	-	-	-	26.0 (12.4) <sup>‡</sup>	58.2 (20.6) <sup>‡</sup>	97.6 (28.5) <sup>‡</sup>		

NTX = naltrexone

\* AUC<sub>0-29d</sub>† AUC<sub>0-34d</sub>‡ AUC<sub>28d</sub> was calculated as the mean of AUC<sub>1d</sub> \* 28

In the intramuscular and subcutaneous 8-month local tolerance study in rabbits treatment related effects were found at the injection sites. Rabbits that received 195 mg naltrexone in 562 mg microspheres dosed SC in a 2 mL dose volume exhibited a local enlargement at the injection sites attributed to the presence of the test material depot. The intramuscular dose sites of Vivitrex suspension in rabbits (293 mg naltrexone; 843 mg microspheres; 3 mL dose volume) were clinically normal. Necropsies conducted at 8 and 30 days after dosing revealed that IM and SC sites consisted mainly of residual test material appearing as white to tan colored material. Clinically and by gross pathological examination, it was evident that the test materials were gradually resorbed as the study progressed. Microscopically the polymer microspheres were progressively degraded and the accompanying foreign-body response and fibrosis at the IM and SC injection sites also gradually diminished. These results confirm the observations made in the repeated dose monkey study where granulomatous inflammation consisting of macrophages and multinucleated giant cells along with fibrosis were observed at injection sites in the three month sacrifice and were subsequently seen to be resolving by the 6 month sacrifice. By 6 months after dosing in the monkey and 8 months after dosing in rabbits, residual polymer was either no longer present, or only present in small amounts. Additionally, the

histological changes related to the foreign body response were returning to normal. In the rabbit study, where IM and SC routes were both evaluated, local microsphere reactions appeared to resolve more rapidly at the IM sites.

A 10-month local tolerance study was completed in dogs (AT-21-05). No systemic toxicity was apparent after administration of Vivitrex suspension in this study. The objective of this study was to accurately mimic human dosing conditions (i.e., multiple dosing at the same or closely spaced sites while utilizing a dose and administered volume comparable to that proposed for human dosing). Vivitrex microspheres (394 mg naltrexone; 400 µg microspheres; 4 mL dose volume) was administered on day 1 in all groups, followed by further doses on day 30 in groups 1 and 2, day 60 in group 3, and days 60 and 120 in group 4. All animals received active formulation. The study also included a treatment arm in which dogs were dosed in the same location at an interval of 30 days, rather than the recommended 60-day interval when gluteal injections are alternately administered on left and right sides. No systemic toxicity was apparent after administration of Vivitrex suspension on any occasion during the study. A prominent injection site reaction occurred in all animals. The local reaction consisted of skin swelling approximately 1 to 5 cm in diameter. An area of discoloration up to 7 cm in diameter was also noted at the injection sites of some animals. Residual test material within the muscle and in some cases on the proximal muscle surface was observed at all necropsy intervals and at all injection sites. Adhesions between the skin and skeletal muscle were also observed grossly at the injection sites in some animals sacrificed 2 weeks after dosing.

Histopathological findings at injection sites consisted predominantly of an inflammatory reaction with fibrosis. At sites evaluated approximately 2 weeks after dosing, a chronic active inflammatory reaction (moderate to severe) was observed that was characterized mainly by macrophages and multinucleated giant cells with smaller numbers of neutrophils, eosinophils and lymphoplasmacytic cells. Granulomatous inflammation (minimal to moderately severe) was the primary histopathological change observed at the Day 210 sacrifice (6 to 7 months post-dose). The inflammatory response and accompanying fibrosis diminished significantly between the 2-week post-dose sacrifices and the Day 210 sacrifice.

The injection site reactions in dogs were apparent soon after administering the first dose and were most severe between 1 to 3 weeks post-dose. Gross and microscopic examinations both indicated that injection site reactions were not enhanced when three successive 4 mL injections of Vivitrex suspension were administered at monthly intervals in very close proximity to each other. Additionally, there was also no effect on pharmacokinetic parameters after multiple dosing. All reactions gradually diminished and the sites were essentially normal in appearance upon gross examination by the end of the study period.

The proposed clinical Vivitrex dose (380 mg) produced one-month human naltrexone exposure levels approximately 3.9-times that observed with one month of oral dosing

at 50 mg of naltrexone/day (The 3.9 factor is based on the AUC<sub>0-28d</sub> for Vivitrex suspension versus the AUC<sub>1d</sub> \* 28 days for oral naltrexone). Naltrexone exposure in animal studies supporting the NDA for the oral formulation exceeded the proposed Vivitrex human naltrexone exposure based on mg/kg and BSA comparisons.

**Comparison of NOAELs from Oral Naltrexone Studies and Dose Multiples Relative to Vivitrex suspension**

SPECIES	TYPE OF STUDY	NOAEL* (mg/kg/day)	ORAL DOSE MULTIPLE†	DOSE MULTIPLE RELATIVE TO VIVITREX 380 mg‡	
				mg/kg BASIS	BSA BASIS‡
Monkey	Chronic	20	20	5.1	1.7
Rat	Subchronic	70	70	18	3.0
Dog	Subchronic	40	40	10	5.0
Rat	Reproductive	30	30	7.7	1.3
Rat	Teratology	200	200	51	8.5
Rabbit	Teratology	60	60	15.4	5.1
Mouse	Carcinogen <sup>ty</sup>	100	100	26	2.1
Rat	Carcinogen <sup>ty</sup>	100	100	26	4.3

\* NOAEL: No Observed Adverse Effect Level

† Calculated using a therapeutic human dose of 1 mg naltrexone/kg/day (derived for the standard daily oral naltrexone dose of 50 mg, and an assumed body weight of 50 kg).

‡ Calculated by comparison of the AUC<sub>0-28d</sub> for Vivitrex to the aggregate AUC<sub>1d</sub> \* 28 days for oral formulation (AUC<sub>0-28d</sub> 41.2 ng·day/mL for oral and 160 ± 24 ng·day/mL for a 380 mg dose of Vivitrex resulting in a conversion factor of 3.9)

§ mg/kg to BSA conversion factors adapted from Freireich 1966 (20) and Casarett and Doull's Toxicology (21).

Naltrexone increased the incidence of early fetal loss when given to rats or rabbits. Findings of an increased incidence of pseudopregnancy and decreased pregnancy rates were seen in rats at 100 mg/kg (13-times the recommended monthly human dose of Vivitrex microspheres on a mg/kg basis). Other observations included reports of increased resorptions, increased incidence of stillborn pups, and lower body weights of pups. However, no epidemiological evidence of developmental and reproductive toxicities attributable to naltrexone has emerged after nearly 20 years of clinical use. Further evidence of the clinical reproductive safety of naltrexone is provided by the finding that use of naltrexone in the management of pregnant heroin users has not resulted in any identifiable effects of naltrexone on the mother or fetus.

Genetic toxicity testing of naltrexone resulted in no positive findings except in a few minor assays. Negative genotoxicity studies (covering the ICH standard battery of tests) included the *Salmonella* and *E. coli* microbial gene mutation assays, the mouse micronucleus assay, the heritable translocation assay, CHO cell sister chromatid

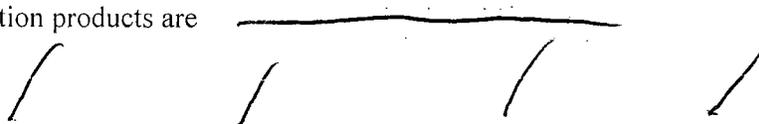
exchange assay, and the mouse lymphoma gene mutation assay. The following minor assays gave positive results: *Drosophila* recessive lethal frequency assay, non-specific DNA damage in repair tests with *Escherichia coli* and WI-38 cells, and urinalysis for methylated histidine residues. The significance of these findings is unknown.

In rat and mouse carcinogenicity studies 30 and 100 mg/kg/day of naltrexone in the diet for 2 years was not found to be carcinogenic. At the doses evaluated growth rates were slightly depressed in a dose related manner in both species and food consumption was reduced in mice (Rosenkrantz, 1984). The frequency and location of predominant tumors in both species were similar in treated and untreated groups with the exception of a small increase in the incidence of vascular tumors and mesotheliomas in rats receiving naltrexone. Trend analysis adjusted for mortality revealed a significant positive dose-related increase in the incidence of vascular origin tumors for both males and females. However, this positive relationship was due to a small increase in tumors for males and females in the high dose group only. When the high dose rates were compared with those of matched controls by Fisher Exact Test, there were no significant differences. The trend analysis also showed a weak positive dose response relationship for mesothelioma in males. These tumors were generally late occurring and were not thought to contribute significantly to the overall mortality of treated groups.

The medical use of biodegradable polymers, such as the polylactide-co-glycolide (PLG) polymer of Vivitrex microspheres, is well established. Polyesters of the alpha-hydroxy carboxylic acids, including copolymers of lactide and glycolide, and homo-polymers containing poly-L-lactide, poly-D-lactide or polyglycolide are among the most widely used, having been successfully employed in medical devices such as sutures (Dexone and Vicryle) and in a variety of forms for soft tissue and bone fixation (meshes, screws, pins, nails, plates and splints). PLG polymers have been used in sustained delivery of proteins and peptides (Nutropin Depot, Zoladex, Lupron Depot, De-Capeptide SR and Sandostatin LAR Depot). The wide use of the polymers is based in part on evidence of good tissue tolerance and unimpaired tissue regeneration in animals and humans.

Degradation of PLG depends largely on hydrolysis of ester linkages, the rate of which is influenced by the physical and chemical characteristics of the polymer and is also dependent in part on cellular and enzymatic effects.

The degradation products are



Polymer degradation products are generated slowly over time as the microspheres degrade, and this slow rate of formation and release contributes to their low toxicity. Animal safety studies performed by the Sponsor showed no acute, subacute, or chronic systemic toxicity is anticipated at the doses of PLG administered in Vivitrex microspheres. PLG produces local inflammation at the site of injection, but this is reversible.

Local tolerance studies with PLG microspheres completed by the Sponsor in rabbits found a non-irritating inflammation at injection sites consisting of macrophage infiltration and diffuse intralesional fibrosis. PLG microspheres remained localized at the subcutaneous injection site. By about 5 months after dosing, PLG microspheres (approximately 150 mg subcutaneous dose) were fully degraded and the inflammatory tissue reaction was resolved at the local subcutaneous injection site.

A review of relevant literature indicated that PLG polymer or its metabolites do not cause reproductive and developmental effects in animal studies at the doses expected to result from PLG-polymer dosing. Subcutaneous implantation of suture material composed of PLG (Vicryle) was not teratogenic in rats and rabbits at 1000 mg/kg. Moreover, a search of the literature on clinical usage of various approved controlled release drug formulations that utilize PLG polymers did not identify any reports of adverse reproductive and developmental effects. No reproductive toxicity studies with Naltrexone along with the PLG polymer were done. Negative results have been reported for PLG in the Ames assay. No clastogenicity study with PLG polymer was found in the available literature. In a carcinogenicity study, intraperitoneal implants of Vicryl (50 mg/kg) for up to 2 years in rats did not cause any treatment-related tumors. The composition of the PLG component in this study was not given. No carcinogenicity study with the PLG along with Naltrexone has been done.

Microsphere Diluent is used to suspend Naltrexone microsphere products for injection. Microsphere Diluent is a viscous solution that consists of \_\_\_\_\_ carboxymethylcellulose sodium salt, \_\_\_\_\_ polysorbate 20 and \_\_\_\_\_ sodium chloride USP in Water for Injection (WFI). USP grade sodium chloride is considered non-toxic. Carboxymethylcellulose sodium salt is generally recognized as safe (GRAS) and is included in many currently marketed drugs and cosmetics with no signs of toxicity. Tween 20 is also widely used in cosmetics, foods and pharmaceutical preparations in customary use and is regarded as nontoxic and nonirritant at the concentration in Microsphere Diluent. Studies of Microsphere Diluent conducted by Alkermes include AT-03-09, AT-21-01 and AT-21-04, the latter two of which contained vehicle control groups, have found Microsphere Diluent to be well tolerated. Slight local redness and enlargement was noted upon administration of Microsphere Diluent to rabbits. Other than a weak inflammatory cell infiltration, no significant clinical, macroscopic, or microscopic findings were noted at SC injection sites 8 days post-administration.

## B. Pharmacologic activity

Naltrexone is a nonspecific pure opioid antagonist with highest affinity for the  $\mu$  opioid receptor. Occupation of brain opioid receptors by naltrexone blocks 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 understood. It has been proposed that, in patients with alcohol dependence, blockade of the endogenous opioid peptides leads to decreased craving for

alcohol, decreased urge to drink, and reduction in the consumption of alcohol. Naltrexone blocks the effects of opioids by competitive binding (i.e., analogous to competitive inhibition of enzymes) at opioid receptors. Opiate antagonists were initially developed to treat morphine and heroin addiction. It binds competitively to all classes of opioid receptors with the following order of preference:  $\mu > \kappa > \delta$ . Naltrexone, a synthetic derivative of the minor opium constituent thebaine, represented the next generation of opiate antagonists. Naltrexone, like naloxone, is a competitive antagonist and is non-selective for opioid receptor subtypes. In contrast to naloxone, naltrexone has a higher affinity for opioid receptors (6-fold  $\mu$  for to 11-fold for  $\kappa$ ), is more potent, orally bioavailable, and has a longer plasma half-life.

Structurally, naltrexone is a synthetic congener of oxymorphone that bears a cyclopropylmethyl group in place of the methyl group on the nitrogen atom of oxymorphone. Naltrexone blocks opioids by binding competitively at opioid receptors. In rodents, opiate blockade is observed at oral naltrexone doses below 1 mg/kg. In contrast, behavioral and autonomic effects occurring in rodents receiving naltrexone require much larger oral doses. For example, the mouse ED<sub>50</sub> for ataxia was 187 mg/kg and for loss of auditory pinna reflex the ED<sub>50</sub> was 450 mg/kg. No acute behavioral effects occurred up to 324 mg/kg in rats. When administered in clinically effective doses to patients who have not recently received opioids, naltrexone has few or no apparent subjective effects (Martin et al 1973).

Pharmacological evidence presented by the Sponsor demonstrate that Vivitrex microspheres provide a high level of opiate receptor blockade in rats for one month and that this pharmacodynamic effect is not diminished under conditions of repeated dosing. An increase in opiate receptors observed in specific locations in the brain of rats receiving Vivitrex microspheres did not impact naltrexone's opioid antagonist action.

Opioid receptor antagonists can alter the function of the hypothalamic-pituitary adrenocortical axis (HPA). For example, naltrexone and naloxone increase adrenocorticotrophic hormone (ACTH) secretions. Blockade of the tonic opioid inhibition of HPA axis activity also appears to result in release of proopiomelanocortin-derived hormones from the pituitary and cortisol from the adrenal gland. Reports of a direct immunomodulatory function for naltrexone were not found in the scientific literature. However, naltrexone has been reported to protect the thymus against the immunosuppressive effects of alcohol.

Nonclinical experience with oral naltrexone indicates no safety pharmacology concerns with doses in the therapeutic dose range. No safety pharmacology concerns were evident in nonclinical toxicology studies of Vivitrex microspheres in monkeys at doses up to 200 mg/kg/month of naltrexone or approximately 26-fold the human dose on a mg/kg basis. Importantly, opioid antagonists do not have significant effects in non-clinical species on cardiovascular responses including ECG profiles.

The pharmacokinetics/toxicokinetics of naltrexone following Vivitrex administration was evaluated as part of tolerability study in beagle dogs and as part of one- and three-month

toxicology evaluations in rhesus monkeys. The nonclinical pharmacokinetic studies focused on evaluating exposure to naltrexone and its major metabolite, 6p-naltrexol, following Vivitrex administration. Data pertaining to naltrexone distribution, metabolism and excretion were obtained from published scientific literature.

Naltrexone pharmacokinetics is characterized by rapid absorption and distribution, extensive metabolism and a high total body clearance that is independent of dose. Intravenous administration of naltrexone in rabbits resulted in rapid distribution from the plasma with a reported half-life of  $55 \pm 5$  and  $53 \pm 3$  minutes following 1 and 5 mg/kg doses, respectively. Similar results were obtained in mongrel dogs with a terminal plasma half-life of  $46.9 \pm 4.7$  min. In contrast, the half-life of naltrexone following intravenous administration to rhesus monkeys was determined to be 468 minutes, approximately 10-fold greater than that observed in the other two species. Naltrexone was extensively absorbed following oral administration in monkeys; however, naltrexone is subject to a high first-pass effect probably mediated by the liver resulting in a low systemic availability of 3.6%. Following oral administration in humans, naltrexone was rapidly absorbed from the gastrointestinal tract with peak concentrations occurring one-hour postdose. The oral bioavailability of naltrexone was reported to be low and varies between 5 and 40%. The half-life of naltrexone was determined to be 2.7 to 8.9 hours following IV and oral administration.

### Comparative Pharmacokinetic Data and Systemic Exposure to Naltrexone following Oral and Intravenous Administration in Rabbit, Dog

SPECIES	DOSE (mg/kg)	ROUTE	AUC (mg·hr/L)	CL <sub>TOT</sub> (mL/min/kg)	V <sub>D</sub> (L/kg)	T <sub>1/2</sub> (min)	F	REFERENCE
Rabbit (New Zealand)	5	IV	--	--	--	53 (3) <sup>*</sup> (n=5)	--	(3)
Dog (mongrel)	0.5 & 5	IV	--	52.8 <sup>†</sup> (12.1) (n=9)	3.4 <sup>†</sup> (0.7) (n=9)	46.9 <sup>†</sup> (4.7) (n=9)	--	(1)
Monkey (rhesus)	10	PO	0.086 (0.049) (n=5)	--	--	--	0.036	(2)
	10	IV	2.9 (0.93) (n=5)	65.7 (22.9) (n=5)	5.06 (2.23) (n=5)	468 <sup>**</sup>	--	(2)
Human	50 mg	PO	0.0804 <sup>‡</sup>	--	--	533	0.4 <sup>§</sup>	(6)
	1 mg	IV	0.004 <sup>‡</sup>	47.9 <sup>¶</sup>	--	161		(6)

Values represent the mean  $\pm$  (SD) unless otherwise specified. Naltrexone was administered as an aqueous buffered aqueous solution in all studies

-- Not reported

<sup>\*</sup> Values are mean  $\pm$  SEM.

<sup>†</sup> Mean value was calculated from data in original reference by dividing individual values [clearance values (mL/min) in Table II or Vd values (L) in Table III] by corresponding dog weight (kg) in Table I then calculating the overall mean for n=9.

<sup>‡</sup> AUC value was calculated from dose-normalized AUC values of 96.5 min/mL (oral) and 240 min/mL (IV) reported in original reference [Table 7] by converting to hr/L and multiplying by dose.

<sup>§</sup> Mean value was calculated from data in original reference [Table 7] assuming a body weight of 70 kg.

<sup>¶</sup> Obtained by dividing dose normalized AUC oral by AUC IV.

\*\* Harmonic Mean (n=6) (6)

Exposure to naltrexone achieved over approximately one month with Vivitrex administration may be compared to that following daily oral administration in monkeys and humans. In both species, IM Vivitrex administration afforded increased naltrexone exposure relative to the oral route with a substantially lower monthly dose. Specifically, in humans, the proposed dose of Vivitrex 380 mg provided -4 times the exposure compared to 50 mg oral daily dosing, but with 1/3 of the monthly dose. In monkeys, 20

mg/kg/day oral naltrexone for one month produced an estimated naltrexone exposure of 201 ng-day/mL, slightly in excess of human exposure with 380 mg Vivitrex (160 ng-day/mL).

#### Naltrexone Exposure Following Vivitrex or Oral Naltrexone Dosing

SPECIES	DOSE	ROUTE	AUC (ng·day/mL)	SOURCE
Rhesus monkey	Vivitrex 75 mg/kg Q28d	SC	751	AT-21-03
	naltrexone 20 mg/kg/d*	PO	201 <sup>†</sup>	Estimated from (43) <sup>†</sup>
Human	Vivitrex 380 mg Q28d	IM	160	ALK21-005
	naltrexone 50 mg/d	PO	41	ALK21-005

\* Dose used in the chronic toxicology study for oral naltrexone [Trexan NDA 18-932]

<sup>†</sup> AUC following 10 mg/kg orally = 0.0861 mg·hr/mL, CL = 65.7 mL/min/kg and F = 0.036. Assuming linear kinetics, the aggregate exposure over 28 days following 20 mg/kg/d can be estimated.

Naltrexone is metabolized primarily by dihydrodiol dehydrogenase, a cytosolic polymorphic family of enzymes; CYP 450 enzymes are not involved. There is no evidence that naltrexone or 6 $\beta$ -naltrexol inhibit the activity of 10 major CYP 450 isozymes to a clinically meaningful degree. Drug-drug interactions with Vivitrex microspheres were not conducted, however; based on the metabolic pathway of naltrexone, its low protein binding and lack of effect on CYP 450 isozymes, the probability of drug-drug interactions with Vivitrex administration is low. Urinary excretion is the primary route of elimination for naltrexone and its metabolites in guinea pigs, rabbits, dogs, monkeys, and humans, while the fecal route of elimination predominates in the rat.

A comparison of vivitrol exposure in human and non clinical species after single and repeat dose administration is presented in the following tables. Note that in the repeat dose monkey study at 20 mg/kg dosage where minimal local toxicity was observed, exposure is similar to that of the clinical dose. At 50 mg/kg in monkey local toxicity was moderately severe and the safety margin is less than 3 fold. Dog repeat dose local toxicity study resulted in several toxic findings, no NOAEL could be established in this study.

**PK Parameters Of vivitrol (NTX-MEDISORB) after Single Dose**

Dose/Species	Total AUC <sub>0-t</sub> (ng•day/mL)	Total AUC <sub>0-t</sub> (ng•days/mL)	Total AUC <sub>0-t</sub> (ng•days/mL)	Multiples of Human Exposure at day 1 (mg/kg)	Multiples of Human Exposure at day 28 (mg/kg)
	Days 0-1	Days 0-7	Days 0-29		
Human/IM/190 mg-vivitrol	1.01	25.2	61.5		
Human/IM/380 mg-vivitrol	1.61±0.47	37.4±13.5	121±19.6		
Monkey/IM/50 mg/kg-vivitrol HED=972 mg*	56.1±13.3	240±25.4	609±20.5	34.8	5.0
Monkey/SC/20 mg/kg-vivitrol, HED=388 mg*	19.2±3.28	64.3±9.35	187±45.7	11.9	1.54
Monkey/SC/50 mg/kg-vivitrol HED=972 mg*	44.4±2.44	143±16.1	449±155	27.5	3.7
Monkey/SC/200 mg/kg-vivitrol HED=3888 mg*	179±18.7	708±159	2115±654	111	17.4

**PK Parameters Of vivitrol (NTX-MEDISORB) after Repeat Dose**

Dose/Species	Total AUC <sub>0-t</sub> (ng•day/mL)	Total AUC <sub>0-t</sub> (ng•days/mL)	Multiples of Human Exposure at day 1 (mg/kg)	Multiples of Human Exposure at day 28 (mg/kg)
	Days 0-1	Days 0-29		
*Human/IM/380 mg-vivitrol	3.26±1.1	160±24.2		
**Monkey/SC/20 mg/kg vivitrol HED=388 mg*	16.9±4.4	164.±38	5.1	1.0
**Monkey/SC/50 mg/kg-vivitrol HED=972 mg*	40.6±5.83	447±127	12.4	2.8
**Monkey/SC/75 mg/kg-vivitrol HED=1458 mg*	80.3±27.3	751±282	24.6	4.7
Dog/IM/32.8/ mg/kg-vivitrol HED=1064 mg*	31.01±7.8	428±43.1	9.5	2.67

\*Human data is days 0-28 unlike dog which is days 0-29

\*\*Monkey data is days 0-33 unlike dog days which is days 0-29

**PK Parameters of Oral NTX**

Dose	Total AUC <sub>0-t</sub> (mg•hr/L)	Multiples of Human Exposure (mg/kg)
Human/oral/50 mg	0.0804	
Monkey/PO/10 mg/kg, HED=194 mg*	0.086	1 fold

**Rat Toxicity Study**

Dose	Toxicity observed	Reprotox Ratio
Rat/PO/30 mg/kg/day BSA=180 mg/m <sup>2</sup> HED=291.6 mg	Early fetal loss	3.9
Rabbit/PO/60 mg/kg BSA=720 mg/m <sup>2</sup> HED= 1166 mg	Early fetal loss	7.9
Human dose 380 mg/mo		
Rat /vivitrol/NOEL 25 mg/kg/month HED=243 mg/mo	Local irritation/ TK not done	Can not be compared

**C. Nonclinical safety issues relevant to clinical use**

In vitro release data for this compound submitted by the sponsor as well as from the published literature show drug content strongly affects naltrexone microsphere drug release behavior. Because

So, it can be concluded that the biodegradation should be unique to this polymer formulation and extrapolation of data from other products could be inaccurate. Local tissue reaction due to presence of the polymer greatly exceeds the therapeutic release of drug substance leading to accumulation of bioburden. A single injection of the product in rat and monkey requires 6-8 months after dosing to get rid of the residual polymer and complete reversal of the local histological changes. In the dog study the recovery sacrifices conducted 6 months after the last dosing and up to 10 months after the first dosing (Group 1), demonstrated that polymer degradation was progressive and that it was accompanied by evidence of reversal of local inflammation and fibrosis. Safety issues due to prolonged tissue inflammation, infection includes:

1. Polymer degradation characterization does not appear complete.

2. Due to increase in AUC with this product, reproduction studies based on total daily exposure based on body mass do not appear to be relevant.
3. Similar interpretation can be drawn for the carcinogenicity study. Therefore it is recommended that the reproductive toxicity studies and the carcinogenicity study be performed with this compound in current clinical formulation to accurately evaluate the safety of the compound and for labeling purposes. Although the polymer degradation characterization is not complete, since progressive recovery was observed repeat dose toxicity study with the recovery phase need not be done at this point. The local tissue reaction in the nonclinical studies appears to be consistent with the findings in the clinical studies.

**APPEARS THIS WAY  
ON ORIGINAL**

## 2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

### 2.6.1 INTRODUCTION AND DRUG HISTORY

**NDA number:** 21-897

**Review number:** 1

**Sequence number/date/type of submission:** 000 / 03-30-2005 / Original NDA

**Information to sponsor:** No

**Sponsor and/or agent:** Alkermes, Inc.

**Manufacturer for drug substance:** Alkermes, Inc.

**Reviewer name:** Mamata De, Ph.D.

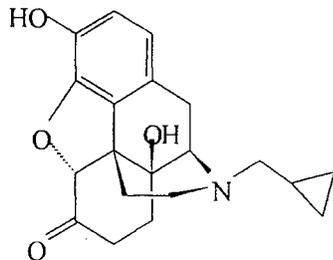
**Division name:** Division of Anesthesia, Analgesia, and Rheumatology Products

**HFD #:** 170

**Review completion date:** July 30, 2005

**Drug:**

Trade name: VIVITROL  
Generic name: Naltrexone long-acting injection  
Code name: 3940, Vivitrex, Medisorb Naltrexone  
Chemical name: Morphinan-6-one, 17-(cyclopropylmethyl)-4,5-epoxy-3, 14-dihydroxy-, (5 $\alpha$ )  
CAS registry number: 16590-41-3  
Molecular formula/molecular weight: C<sub>14</sub>H<sub>23</sub>NO<sub>4</sub> / 341.4  
Structure:



**Relevant INDs/NDAs/DMFs:**

NDA: 18,972

DMFs: \_\_\_\_\_

**Drug class:** Opioid antagonist

**Intended clinical population:** Treatment of alcohol dependence

**Clinical formulation:** Vivitrex microspheres are comprised of a polymer-naltrexone matrix consisting of 34% naltrexone and 66% polylactide-co-glycolide polymer (PLG)

(75:25 lactide to glycolide ratio), packaged in a 5 mL USP type 1 glass vial, as a white, off-white to tan free flowing powder containing a 380 mg dose of naltrexone. At the time of administration by gluteal intramuscular injection, Vivitrex microspheres are suspended in an aqueous diluent (Microsphere Diluent) of the following composition:

1. — Carboxymethylcellulose sodium
2. — Polysorbate 20
3. — sodium chloride in water for injection

The microsphere formulation releases naltrexone in a controlled fashion for approximately one month. In the presence of buffered aqueous media at physiological pH, osmolarity, and temperature, naltrexone is suppose to release from Vivitrex microspheres in a three-phase release pattern: 1) initial release phase 2) hydration phase and 3) sustained release phase.

Vivitrex microspheres are packaged into 5 mL USP Type 1 clear glass vials. Each 5 mL vial of Vivitrex microspheres is intended to deliver a single dose of 380 mg of naltrexone.

**Composition of Vivitrex Microspheres (380 mg):**

COMPONENTS	REFERENCE TO QUALITY STD	FORMULATION						FUNCTION
		% W/W	380 MG (5 MLVIAL)	AMOUNT PER BATCH <sup>1</sup>	% W/W	380 MG (5 MLVIAL)	AMOUNT PER BATCH <sup>1</sup>	
Drug: Naltrexone base anhydrous	USP or In-house standard	34% <sup>†</sup>						Active pharmaceutical ingredient
Polymer: 75:25 (poly lactide-co-glycolide)	In-house standard	66% <sup>†</sup>						Excipient
Total vial fill weight								

Three handwritten checkmarks are present below the table, indicating approval or verification of the data.

**Composition of the Microsphere Diluent (suspending agent for Vivitrex microspheres):**

COMPONENT	REFERENCE TO QUALITY STANDARD	AMOUNT/ML	% W/V
Carboxymethylcellulose Sodium	USP	/	/
Polysorbate 20	USP, NF		
Sodium Chloride	USP, NF		
Water For Injection	USP, Eur. Ph.		

The microsphere diluent vial is stoppered with a — gray — rubber stopper.

The Vivitrex microsphere vials and diluent vials are packaged in an individual kit containing necessary accessories, such as needles and syringes, required to deliver one dose of Vivitrex microspheres.

**Route of administration:** Intramuscular

**Disclaimer:** Tabular and graphical information are constructed by the reviewer unless cited otherwise.

**Data reliance:** Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 21-897 are owned by Alkermes, Inc. or are data for which Alkermes, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 21-897 that Alkermes, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Alkermes, Inc. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 21-897.

**Studies reviewed within this submission:**

Study title: Oral Toxicity Screen with Glycolide Lactide Copolymer by Capsule Administration in Rabbits. (Study Number: — Sponsor Reference No: AT-09-01)

Study title: 1-Month Toxicokinetic Study of Medisorb® Naltrexone in Rhesus Monkeys with a 1-Month Recovery. (Study Number: — 6403-117; Sponsor Reference No: AT-21-02)

Study title: A 3-Month Repeated-Dose Toxicokinetic Study of Medisorb® Naltrexone Administered by Subcutaneous Injection to Rhesus Monkeys, with a 3-Month Recovery Period. (Study Number: — J944-54; Sponsor Reference No: AT-21-03)

Study title: 90-Day, Three Repeat Dose Subcutaneous- Toxicity Study of Medisorb® Naltrexone (VIVITREX) in Rats. (Study Number — N103485; Sponsor Reference No: AT-21-08)

Study title: An Acute Local Tolerance Study of — Vehicles Administered Subcutaneously to Rabbits. (Study Number: — A 074-716 Sponsor Reference No: AT-03-09)

Study title: An Acute Local Tolerance Study of — Formulations — and — , Administered Subcutaneously to Rabbits. (Study Number: — A071-716; Sponsor Reference No: AT-07-01)

Study title: Development of Drug Delivery System. (Study Number: — 89G-0102; Sponsor Reference No: AT-07-03)

Study title: Local Tolerance Study of Medisorb® Naltrexone in Rabbits Following Single Subcutaneous and Intramuscular Injections. (Study Number — 6403-118 Sponsor Reference No: AT-21-01)

Study title: Chronic Local Tolerance Study of Medisorb® Naltrexone in Rabbits Following Single Subcutaneous and Intramuscular Injections. (Study Number: — 6403-119; Sponsor Reference No: AT-21-04)

Study title: Local Tolerance and Pharmacokinetic Evaluation of Medisorb® in Dogs Following Repeated Intramuscular Injections. (Study Number: ; 6403-121 Sponsor Reference No: AT-21-05)

Study title: Investigative Local Tolerance Study of Medisorb® Naltrexone in Dogs Following Intramuscular Administration. ( — 6403-123 Sponsor Reference No: AT-21-06)

Study title: Investigative Local Tolerance Study of Medisorb® Naltrexone in Rabbits Following Intramuscular Administration. — 6403-122 Sponsor Reference No: AT-21-07)

**Studies not reviewed within this submission:** None

## 2.6.2 PHARMACOLOGY

### 2.6.2.1 Brief summary

Vivitrex suspension is intended to treat alcohol dependence disorder. The syndrome is manifested by problems that include tolerance, withdrawal, and several noticeable changes of behavioral loss of control over the use of alcohol, with distress and/or impaired function. The *dependence disorder* is discrete and distinguished from *alcohol abuse, alcohol withdrawal syndrome, or other alcohol-induced syndromes, such as alcohol amnestic disorder*. Alcohol use disorders are a major public health problem, which worldwide is one of the leading causes of disability. Alcohol dependence is present in a substantial proportion of the adult population, common among primary care patients, and increasingly recognized as a chronic disease. Current alcohol dependence pharmacotherapies, is indicated only for use after the patient has established abstinence, and often this requires detoxification treatment for alcohol withdrawal.

Vivitrex is a combination of extended release microspheres for injection and a diluent for parenteral, intramuscular use, consist of a sterile, off-white to light-tan powder that is available in dosage strength of 380 mg naltrexone per vial. Naltrexone is microencapsulated in 75:25 polylactide-co-glycolide (PLG) at a concentration of 337 mg of naltrexone per gram of microspheres. The diluent for parenteral use is a clear, colorless solution. The composition of the diluent includes carboxymethylcellulose sodium salt, polysorbate 20, sodium chloride, and water for injection. The microspheres are suspended in the diluent prior to injection. The intramuscular injection of the Vivitrex suspension may reduce the hepatic toxicity by avoidance of first-pass hepatic metabolism which will markedly reduce hepatic exposure to naltrexone. Also the total monthly dose of Vivitrex suspension is less than the daily oral naltrexone dosing; and administration of Vivitrex suspension by healthcare providers offers much greater control over administration of the recommended dose, which may in consequence, initiate effective pharmacotherapy may be sooner.

Structurally, naltrexone is a synthetic congener of oxymorphone that bears a cyclopropylmethyl group in place of the methyl group on the nitrogen atom of oxymorphone. Naltrexone blocks opioids by binding competitively at opioid receptors. In rodents, opiate blockade is observed at oral naltrexone doses below 1 mg/kg. In contrast, behavioral and autonomic effects occurring in rodents receiving naltrexone require much larger oral doses. For example, the mouse ED<sub>50</sub> for ataxia was 187 mg/kg and for loss of auditory pinna reflex the ED<sub>50</sub> was 450 mg/kg. No acute behavioral effects occurred up to 324 mg/kg in rats.

Opioid receptor antagonists can alter the function of the hypothalamic-pituitary adrenocortical axis (HPA). For example, naltrexone and naloxone increase adrenocorticotrophic hormone (ACTH) secretions. Blockade of the tonic opioid inhibition of HPA axis activity also appears to result in release of proopiomelanocortin-derived hormones from the pituitary and cortisol from the adrenal gland. Reports of a direct immunomodulatory function for naltrexone were not found in the scientific literature. However, naltrexone has been reported to protect the thymus against the immunosuppressive effects of alcohol.

Nonclinical experience with oral naltrexone indicates no safety pharmacology concerns with doses in the therapeutic dose range. No safety pharmacology concerns were evident in nonclinical toxicology studies of Vivitrex microspheres in monkeys at doses up to 200 mg/kg/month of naltrexone or approximately 26-fold the human dose on a mg/kg basis. Importantly, opioid antagonists do not have significant effects in non-clinical species on cardiovascular responses including ECG profiles.

### 2.6.2.2 Primary pharmacodynamics

Mechanism of action: Naltrexone is a nonspecific pure opioid antagonist with highest affinity for the  $\mu$  opioid receptor. Occupation of brain opioid receptors by naltrexone blocks 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 understood. It has been proposed that, in patients with alcohol dependence, blockade of the endogenous opioid peptides leads to decreased craving for alcohol, decreased urge to drink, and reduction in the consumption of alcohol. Naltrexone blocks the effects of opioids by competitive binding (i.e., analogous to competitive inhibition of enzymes) at opioid receptors. Opiate antagonists were initially developed to treat morphine and heroin addiction. It binds competitively to all classes of opioid receptors with the following order of preference:  $\mu > \kappa > \delta$ . Naltrexone, a synthetic derivative of the minor opium constituent thebaine, represented the next generation of opiate antagonists. Naltrexone, like naloxone, is a competitive antagonist and is non-selective for opioid receptor subtypes. In contrast to naloxone, naltrexone has a higher affinity for opioid receptors (6-fold  $\mu$  for to 11-fold for  $\kappa$ ), is more potent, orally bioavailable, and has a longer plasma half-life.

#### Drug activity related to proposed indication:

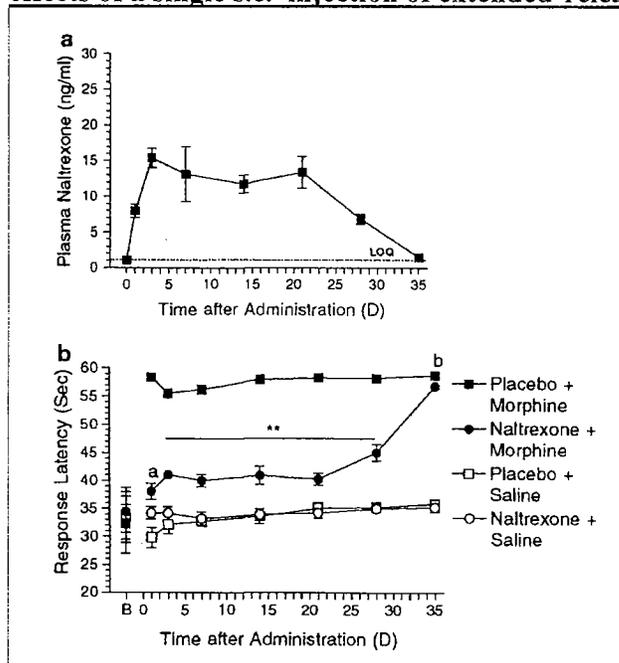
Sponsor discussed the published literature findings for Naltrexone in lieu of proposed indication as follows.

Naltrexone has repeatedly been shown to be effective in suppressing a number of indices of ethanol consumption in animal models, including decreasing ad libitum and limited access ethanol intake, while delaying the acquisition of voluntary ethanol consumption. Naltrexone has been shown to be effective in human studies in reducing alcohol consumption and relapse to heavy drinking when combined with psychosocial treatment. However, the efficacy of naltrexone in treatment did not achieve its maximal potential due to several reasons 1) the significant effort that is required to maintain an alcoholic patient on the daily, oral dose regimen of naltrexone rigorously for the several months 2) oral naltrexone's effects likely result from its suboptimal pharmacokinetic profile which is characterized by transiently high plasma levels within 4 h after each oral dose, followed by concentration troughs at 8-10 h after administration that persist until the next dose is taken the following day; 3) additional deficiencies with oral naltrexone include substantial first-pass metabolism and adverse effects (eg nausea, vomiting) likely associated with the blockade of  $\mu$ -opioid receptors in the gut.

Reviewer agreed with the adequacy of the rationale and the interpretation of the published literature by the sponsor.

Sponsor submitted pharmacology and pharmacokinetic studies with Vivitrex® in rats demonstrated that the formulation produced stable, pharmacologically relevant plasma levels of naltrexone for approximately a month following either subcutaneous or intramuscular injections.

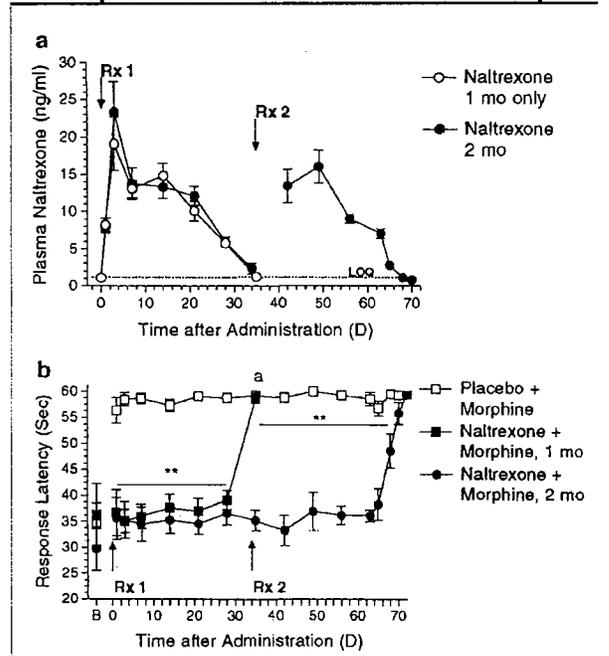
**a. Plasma levels of naltrexone in rats following a single, sc, injection of extended-release naltrexone microspheres (50 mg/kg naltrexone). (b) Pharmacodynamic effects of a single s.c. injection of extended-release naltrexone microspheres.**



B: baseline conditions.

Male Sprague –Dawley rats were subjected to ‘hot plate’ assay for determining their analgesic response after Vivitrex. Plasma levels of naltrexone in rats following a single, sc, and injection of extended-release naltrexone microspheres (50 mg/kg naltrexone) were analysed. Blood was sampled from the tail vein immediately after the hot-plate test. The plasma levels of naltrexone were noted to be maintained for 21 days and were above the LOQs for at least 28 days. Each point represents the mean ± SEM of plasma naltrexone concentrations (ng/ml) from eight rats. From the same experiment the pharmacodynamic effects of a single SC injection of extended-release naltrexone microspheres formulation was measured. This was assessed by testing naltrexone (circles) or placebo formulation (squares)-treated rats on the ‘hot plate’ 30 min after an injection of morphine (1 mg/kg IP, closed symbols) or saline (open symbols). Rats receiving placebo microspheres manifested a pronounced analgesic response to morphine that consistently approached the maximum latency of 60 sec. In contrast, animals pretreated with naltrexone microspheres showed substantial block of morphine analgesia, responding at or near the level of saline-treated animals. Data represent the mean ± SEM of the latency to lick a hind paw measured in eight rats.

**(a) Plasma levels of naltrexone in rats following either a single i.m. injection of extended-release microspheres (open circles) or a second, identical injection 34 days following the first treatment (closed circles). (b) Analgesic actions of morphine (1 mg/kg i.p.) following either one or two i.m. injections of extended-release naltrexone microspheres in rats as tested on the hot plate**



B: Baseline conditions.  
 Rx 1, 2: Times of first and second naltrexone injections.

Plasma levels of naltrexone in rats are following either a single IM injection of extended-release microspheres (open circles) or a second, identical injection 34 days following the first treatment (closed circles) were analyzed. Plasma levels of naltrexone were maintained for approximately 21 days following a single injection, an effect that was repeated with a second injection after an additional 34 days. Each point represents the mean ± SEM naltrexone plasma concentration (ng/ml) from nine rats. LOQ: lower limit of quantization (< 1 ng/ml). Analgesic actions of morphine (1 mg/kg IP) following either one or two IM injections of extended-release naltrexone microspheres in rats as tested on the hot plate were also determined. Naltrexone, when administered for 1 or 2 months IM, was capable of antagonizing morphine-induced analgesia, with responses equivalent to those observed under baseline conditions. The analgesic actions of morphine in rats treated once with naltrexone increased to levels observed in the placebo + morphine by 41 days. In contrast, two naltrexone treatments consistently suppressed morphine-induced analgesia for a total of 68 days. Data represent the mean ± SEM of latency to lick a hind paw by nine rats.

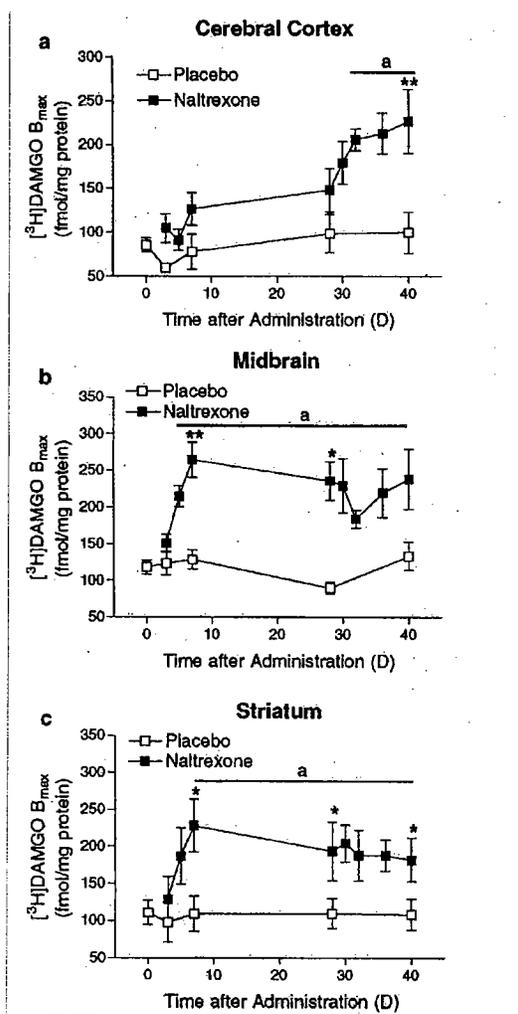
The above-mentioned studies show that the route of administration (IM or SC) had no significant effect on either the plasma naltrexone levels ( $P = 0.72$ , two-way ANOVA, or the area under the curves (332 vs 360 ng. Day/ml, IM vs S.C., respectively). However, plasma naltrexone concentrations changed significantly with time ( $P < 0.01$ , Two-way ANOVA), increasing to approximately one-half of the maximum within 24 h of injection, with maximum levels ( $15 \pm 1.4$  and  $19 \pm 3.6$  ng/ml, SC and IM, respectively) observed by 3 days. Plasma concentrations of naltrexone did not differ significantly from each other between 3 and 14 days (IM) or 21 days (SC) post injection, with detectable levels of naltrexone maintained to 35 days. A similar pattern was observed in animals that received a second i.m. injection of extended-release naltrexone microspheres. There were no significant differences in plasma naltrexone levels during the plateau phase between the first and second injections. Moreover, naltrexone was no longer quantifiable in the plasma ( $< 1$  ng/ml) 35 days after the second injection.

The pharmacodynamic effects of extended-release naltrexone corresponded well with the pharmacokinetic profile derived from the same animals. Extended-release naltrexone significantly suppressed the analgesia produced by morphine, independent of the route of microsphere administration (Treatment Effect,  $P < 0.0$  Route Effect,  $P = 0.35$ , Multiway ANOVA). Morphine induced a profound analgesia in rats receiving placebo microspheres, as evidenced by hot-plate times approaching the maximum duration ( $57 \pm 0.60$  sec). In contrast, the analgesic effects of morphine were suppressed in rats previously administered extended-release naltrexone. Over a 21-day period, the rats receiving extended-release naltrexone + morphine showed hot-plate response times ( $40 \pm 0.54$  sec) that were approximately 70% of the level of those that received extended release placebo + saline ( $34 \pm 0.80$  s). After 28 days, the morphine-associated response latencies of the extended-release naltrexone-treated rats increased to the level of those rats receiving placebo microspheres ( $59 \pm 0.84$  vs  $57 \pm 1.8$  sec, placebo + morphine vs naltrexone + morphine). Rats receiving extended-release naltrexone IM had hot-plate response times after morphine treatment ( $36 \pm 0.40$  sec) that were statistically indistinguishable from saline-treated animals (eg placebo+saline= $31 \pm 5.1$  sec; naltrexone+saline= $34 \pm 3.5$  sec). Animals receiving a second IM injection of extended-release naltrexone on day 34 continued to exhibit complete antagonism of the analgesic effects of morphine throughout the second month (36 sec). The analgesic effects of morphine on naltrexone-treated rats reverted to the level of the placebo-treated rats ( $59 \pm 0.48$  vs  $59 \pm 0.58$  sec, placebo + morphine vs naltrexone + morphine) by 35 days after treatment (Figure 2b).

Opioid receptor changes following Vivitrex in rats were assayed by  $^3\text{H}$ DAMGO radioligand binding. Saturation binding assays revealed that the  $B_{\text{max}}$  for binding to the midbrain and the striatum was significantly increased (110 and 110% vs placebo treatment,  $P < 0.01$ , 0.05, respectively, by 1 week after administration of extended-release naltrexone. Evidence of increased  $\mu$ -opioid receptor density was observed as early as 5 days after administration. These increases in receptor density were sustained through out the subsequent 33 days, at least 1 week after the significant decline in pharmacodynamic effectiveness of the extended-release preparation. Interestingly, the density of cortical  $\mu$  opioid receptors did not begin to increase until 30 days after extended-release naltrexone administration, reaching significance at 40 days (120% increase vs placebo,  $P < 0.01$ ). No

significant changes in radioligand affinity for the receptors were observed in any brain region at any time, regardless of treatment (cortex:  $7.1 \pm 0.40$ ; midbrain:  $4.2 \pm 0.30$ ; striatum:  $3.1 \pm 0.10$  nM).

**Regional changes in the Bmax of [<sup>3</sup>H]DAMGO binding to  $\mu$ -opioid receptors in the brain following a single IM dose of extended-release naltrexone.**



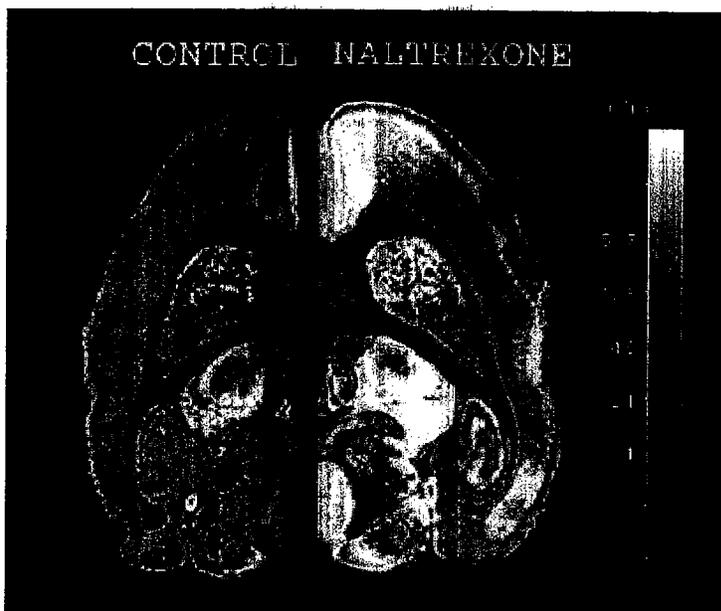
Data represent the mean  $\pm$ SEM of data from eight rats (panels a, b) or eight sets of striata pooled from 16 rats (panel c). Significant increases in the density of  $\mu$  receptors in the cerebral cortex were not observed until 32 (relative to control) to 40

(relative to placebo control) days after naltrexone administration (panel a). In contrast  $\mu$ -opioid receptor density in the midbrain (panel b) and striatum (panel c) was significantly increased by 7 days (relative to placebo) after naltrexone administration. (a) Significantly different from to control,  $P < 0.05$ ; \*, \*\*significantly different from the placebo control,  $P < 0.05$ . Significant increases in the density of  $\mu$  receptors in the cerebral cortex were not observed until 32 (relative to control) to 40 (relative to placebo control) days after naltrexone administration (panel a). In contrast  $\mu$ -opioid receptor density in the midbrain (panel b) and striatum (panel c) was significantly increased by 7 days (relative to placebo) after naltrexone administration. (a) Significantly different from to control,  $P < 0.05$ ; \*, \*\*significantly different from placebo control,  $P < 0.05$ . 0.01, two-way ANOVA from eight rats (panels a, b) or eight sets of striata pooled from 16 rats (panel c). Significant increases in the density of  $\mu$  receptors in the cerebral cortex were not observed until 32 (relative to to control) to 40 (relative to placebo control) days after naltrexone administration (panel a). In contrast  $\mu$ -opioid receptor density in the midbrain (panel b) and striatum (panel c) was significantly increased by 7 days (relative to placebo) after naltrexone administration. (a) Significantly different from to control,  $P < 0.05$ ; \*, \*\*significantly different from placebo control.

Similar results, were obtained using radioligand binding autoradiography. In this study, rats received either one or two injections of extended-release naltrexone spaced 34 days apart, and the changes in  $\mu$ -opioid receptor density quantified at 1 month and 24h after the antagonism of morphine's analgesic effects had dissipated (ie 2 months from initial injection). Autoradiography revealed that radioligand binding to  $\mu$  opioid receptors was significantly increased above control in all brain regions examined, ranging from 90% in the habenular nucleus to 160% in the dorsal raphe nucleus after 1 month. In most regions, these densities continued to increase at 2 months, from 100% in the subiculum to 220% in the dorsal raphe.

Immunohistochemistry using brain sections adjacent to those used in the radioligand autoradiography also revealed significantly increased  $\mu$  opioid receptor immunoreactivity. After 1 month of treatment with extended-release naltrexone, immunoreactivity was significantly increased above control levels in only two of 15 brain regions studied, including the nucleus accumbens (20%) and the substantia nigra (20%). Following 2 months of treatment, increased immunoreactivity over placebo controls was observed in 14 of 15 brain regions examined. However, the magnitude of these increases was lower than those observed with radioligand receptor binding, ranging from 10% in the perfrontal cortex to 40% in the substantia nigra.

**Representative photomicrograph of brain sections incubated with [<sup>3</sup>H]DAMGO from rats receiving IM. injections of either naltrexone containing or placebo microspheres for approximately 2 months.**



**Figure 4** Representative photomicrographs of brain sections incubated with [<sup>3</sup>H]DAMGO from rats receiving i.m. injections of either naltrexone-containing or placebo microspheres for approximately 2 months (see text for details). Note the marked increase in the density of  $\mu$ -opioid receptor binding in the prefrontal cortex, striatum, thalamus, hippocampus, and superior colliculus in those animals receiving extended-release naltrexone relative to rats receiving placebo microspheres. See Table 1 for quantitative data.

The marked increase in the density of  $\mu$ -opioid receptor binding in the prefrontal cortex, striatum, thalamus, hippocampus, and superior colliculus in those animals receiving extended-release naltrexone relative to rats receiving placebo microspheres was observed.

**Regional Changes in  $\mu$ -Opioid Receptor Density Following Extended-Release Naltrexone**

Brain region	Treatment				
	Control	Naltrexone (1 month)	% Increase	Naltrexone (2 months)	% Increase
Central grey	7.5 ± 0.27	18 ± 0.74*	140	20 ± 0.62*	160
Dentate gyrus	7.1 ± 0.39	16 ± 0.82*	125	17 ± 0.89*	140
Dorsal raphe nucleus	7.2 ± 0.86	19 ± 2.3*	160	23 ± 1.1*	220
Habenular nucleus	19 ± 1.4	36 ± 2.5*	90	41 ± 2.4*	120
Hippocampus CA1	4.8 ± 0.29	12 ± 0.79*	150	14 ± 0.75*	190
Inferior colliculus	10 ± 1.7	23 ± 1.9*	130	27 ± 1.5*	170
Lateral orbital cortex	8.8 ± 0.72	20 ± 0.81*	120	24 ± 1.3*	170
Nucleus accumbens	13 ± 1.1	25 ± 2.2*	90	22 ± 1.3*	70
Perirhinal cortex	6.4 ± 0.24	13 ± 0.51*	100	15 ± 0.57*	130
Striatum	8.0 ± 0.67	15 ± 0.79*	80	14 ± 0.38*	75
Subiculum	20 ± 1.6	34 ± 2.3*	70	40 ± 1.8*	100
Substantia nigra	8.7 ± 0.77	18 ± 0.68*	100	21 ± 1.5*	140
Superior colliculus	8.9 ± 1.2	20 ± 1.6*	120	24 ± 1.4*	120
Taenia tecta	9.2 ± 1.1	23 ± 1.3*	150	29 ± 1.7*	215
Thalamus	11 ± 1.5	22 ± 1.4*	100	21 ± 1.1*	90

Brains from animals treated with extended-release naltrexone (50 mg/kg) were processed for [<sup>3</sup>H]DAMGO autoradiography of  $\mu$ -opioid receptors. One group of animals was killed 29 days after administration when the behavioral effects of naltrexone were maximal. The remaining animals received a second treatment with extended-release naltrexone at 34 days and were killed after an additional 29 days. Significant increases in radioligand binding to the  $\mu$  opioid receptor were observed in all brain regions by 1 month, with only the subiculum and taenia tecta showing further changes following 2 months of naltrexone. Data represent the mean  $\pm$  SEM  $\mu$ Ci/g, n = 8 (1 month) or 9 (2 months). \*Significantly different, naltrexone vs control groups ( $P < 0.05$ ).

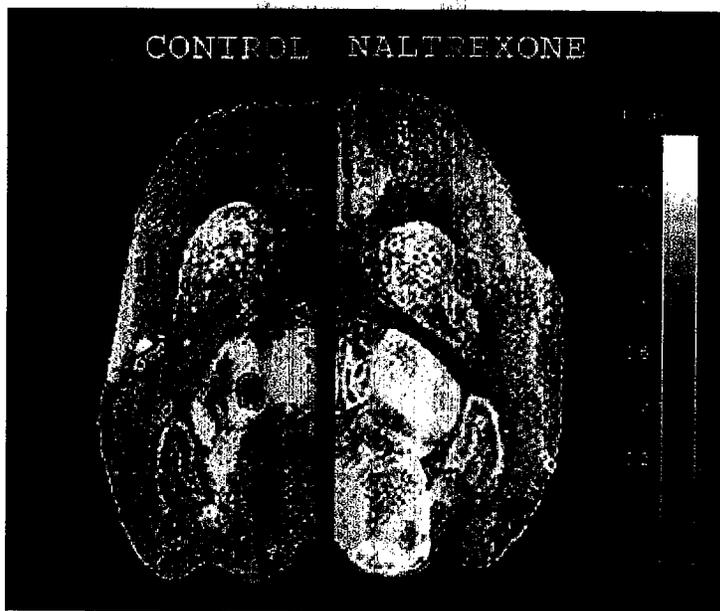
**Regional Changes in  $\mu$ -Opioid Receptor Immunoreactivity following Extended-Release Naltrexone**

Brain region	Treatment				
	Control	Naltrexone (1 month)	% Increase	Naltrexone (2 months)	% Increase
Central grey	2.9 ± 0.19	3.2 ± 0.33	10	4.0 ± 0.25**	40
Dentate gyrus	2.6 ± 0.18	2.9 ± 0.17	10	3.2 ± 0.17*	20
Dorsal raphe nucleus	2.4 ± 0.13	2.9 ± 0.17	20	3.1 ± 0.21*	30
Habenular nucleus	2.9 ± 0.17	3.3 ± 0.18	10	3.9 ± 0.24*	30
Hippocampus CA1	2.6 ± 0.18	2.6 ± 0.13	0	3.0 ± 0.18	15
Inferior colliculus	3.0 ± 0.16	3.3 ± 0.17	10	3.7 ± 0.13*	20
Lateral orbital cortex	2.8 ± 0.18	3.1 ± 0.24	10	3.4 ± 0.13*	20
Nucleus accumbens	2.9 ± 0.20	3.5 ± 0.24*	20	3.8 ± 0.11*	30
Perirhinal cortex	2.5 ± 0.13	2.5 ± 0.18	0	2.7 ± 0.07	10
Striatum	2.8 ± 0.15	3.3 ± 0.20	30	3.6 ± 0.20*	30
Subiculum	3.3 ± 0.13	3.8 ± 0.25	15	4.3 ± 0.21*	30
Substantia nigra	2.5 ± 0.15	3.1 ± 0.16*	20	3.5 ± 0.17*	40
Superior colliculus	2.6 ± 0.10	2.7 ± 0.14	0	3.2 ± 0.12	20
Taenia tecta	2.8 ± 0.12	3.0 ± 0.14	10	3.3 ± 0.08	20
Thalamus	2.8 ± 0.16	3.3 ± 0.16	20	3.8 ± 0.16*	40

Brain sections adjacent to those used for  $\mu$ -opioid receptor radioligand binding (Table 1) were processed for immunohistochemical visualization of  $\mu$ -opioid receptors using a radiolabeled secondary antibody. The changes in opioid receptor immunoreactivity following extended-release naltrexone administration were restricted to select brain regions and were lower in amplitude than the changes in radioligand binding (Table 1). In contrast with the increases in radioligand binding, which were relatively constant between 1 and 2 months, the majority of brain regions examined showed increases in immunoreactivity only after 2 months of extended-release naltrexone treatment. Data are presented as mean  $\pm$  SEM nCi/g, n = 8. \*, \*\*Significantly different, naltrexone vs control ( $P < 0.05$ ), 1 vs 2 months naltrexone administration ( $P < 0.05$ ), respectively.

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**Representative photomicrographs of brain sections processed for immunohistochemical visualization of opioid receptors using a radiolabeled secondary antibody for autoradiographic quantitation.**



**Figure 5** Representative photomicrographs of brain sections processed for immunohistochemical visualization of opioid receptors using a radiolabeled secondary antibody for autoradiographic quantitation. Brain sections adjacent to those described above for binding studies (Figure 4) were used. The regions showing increased opioid receptor immunoreactivity following naltrexone treatment (ie striatum, hypothalamus, hippocampus, and superior colliculus) were similar to those observed using radioligand autoradiography. However, the amplitude of the elevations was less robust than the increases in receptor density determined by radioligand binding assays. See Table 2 for quantitative data.

Brain sections adjacent to those described above were used for binding studies. The regions showing increased opioid receptor immunoreactivity following naltrexone treatment (ie striatum, hypothalamus, hippocampus, and superior colliculus) were similar to those observed using radioligand autoradiography. However, the amplitude of the elevations was less robust than the increases in receptor density determined by radioligand binding assays.

As a surrogate model of the opioid system's involvement in substance abuse and dependency, the Sponsor evaluated the ability of Vivitrex microspheres to suppress the analgesic properties of morphine administered periodically to rats.

Male Sprague-Dawley rats ( $450 \pm 50$  grams; Taconic Farms, Germantown, NY) were used in all studies. Rats were pair-housed in polypropylene cages with free access to food and water. Naltrexone-containing microspheres (Vivitrex) were fabricated from PLG polymer to provide loading densities of approximately 35% (w/w) naltrexone base.

Placebo (non-loaded) microspheres were prepared in an identical manner except that naltrexone was omitted. The microspheres were suspended in 0.75 ml of an aqueous diluent ← saline, Tween-20 and carboxymethyl cellulose) and injected IM using a 22 G needle to provide a total of 50 mg/kg naltrexone, or a comparable mass of placebo microspheres.

One week after this injection, and every week thereafter for 4 weeks, the potency of morphine to induce analgesia, as measured by the hotplate test, was determined. Animals received an intraperitoneal (IP) injection of morphine (0.25, 0.5, 1, 5, 10, 15, 25, 30, or 50 mg/kg in 0.5 ml saline) or saline alone, and were tested on the hotplate at least 20 minutes later.

Analgesia was monitored using a commercially available hotplate apparatus. Rats were individually placed on the hotplate (surface temperature = 48°C) and the latency (Criterion time: 120 second maximum) to lick either hind paw was recorded. Animals received 2 baseline trials on the hotplate test before administration of Vivitrex/placebo, and were then randomly assigned to treatment groups.

The latency to lick the hindpaw was normalized to both the minimum time observed following saline administration, and the maximum, criterion time (120 sec) using the following equation:

$$\% \text{ Maximum Possible Effect} = \frac{\text{Morphine Latency} - \text{Saline Latency}}{\text{Maximum Latency (120 sec)} - \text{Saline Latency}} (\% \text{MPE})$$

This normalization allows the amount of interest variability, associated with daily changes in animal perception of thermal stimuli, to be reduced, by taking into account the non-drug associated sensitivity and the maximum range of responses. Sigmoidal curves were fitted to the resulting dose-response curves using non-linear regression techniques, with the curve bottom constrained to zero and the top to 100%. Values for the ED were then provided, along with the 95% confidence intervals for the value.

### Experimental Design:

GROUP #	TREATMENT MATERIAL	CHALLENGE MATERIAL (DOSE, mg/kg)	CHALLENGE DAYS
1	Vivitrex: Medisorb Naltrexone, (50 mg/kg)	Morphine Sulfate, (0.5, 1, 10, 15, 25, 30, 50)	7, 14, 21, 28.
2	Medisorb Placebo	Morphine Sulfate, (0.25, 0.5, 1, 5, 10, 15)	7, 14, 21, 28.

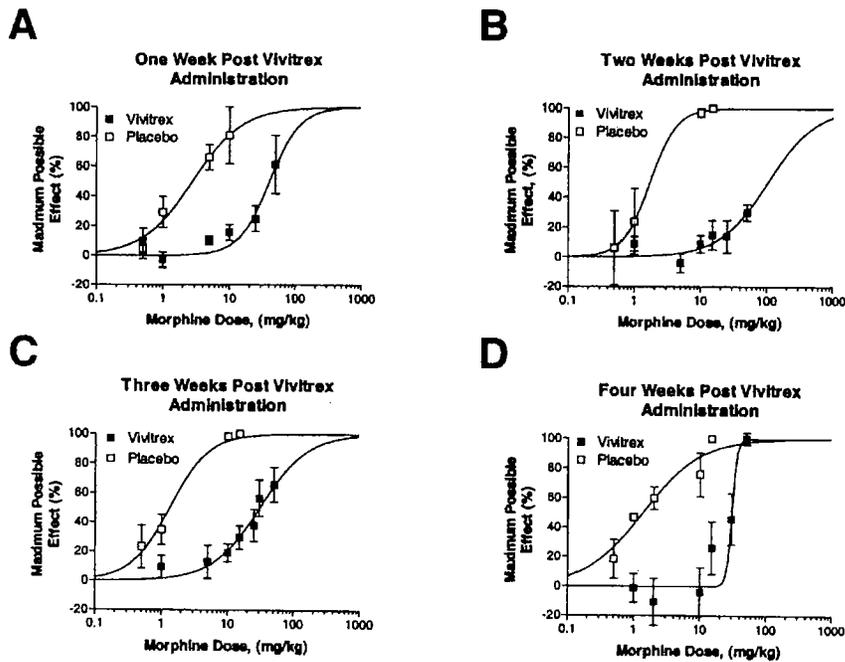
Vivitrex-treated rats appeared to tolerate the drug well, as evidenced by no significant differences between the groups in weight or physical appearance. The ability of Vivitrex

to effectively suppress the analgesic properties of morphine was readily apparent at the first testing, 1 week after administration. While placebo-treated rats demonstrated full analgesia (as defined by the parameters of the hotplate test) after the administration of 10 mg/kg morphine, the administration of 50 mg/kg morphine to the Vivitrex-treated rats was not sufficient to cause full analgesia. Analysis of the dose-response curve indicated a 14.6 fold reduction in the analgesic potency of morphine in Vivitrex-treated subjects, relative to the placebo group.

Morphine analgesia was consistently suppressed throughout the 4 week testing period, with 59-, 24- and 21-fold decreases in the analgesic potency of morphine as measured in the hotplate test 2, 3 and 4 weeks respectively, after Vivitrex administration. The ED<sub>50</sub> values between the Vivitrex and placebo groups were significantly different at all time points, as indicated by the lack of overlap of the 95% confidence intervals. The ED<sub>50</sub> values for morphine analgesia over the 4 time points were not significantly different within the placebo group. Similarly, the ED<sub>50</sub> values for morphine analgesia at different timepoints within the Vivitrex group were not significantly different. However, there was a strong tendency towards a greater degree of suppression of morphine potency 2 weeks post administration of Vivitrex. Only by 4 weeks after the initiation of treatment was the 50 mg/kg dose of morphine capable of inducing full analgesia in the Vivitrex-treated group.

**Temporal Shift In the Analgesic Potency of Morphine In Vivitrex and Placebo-Treated Rats: Dose Response Curves:**

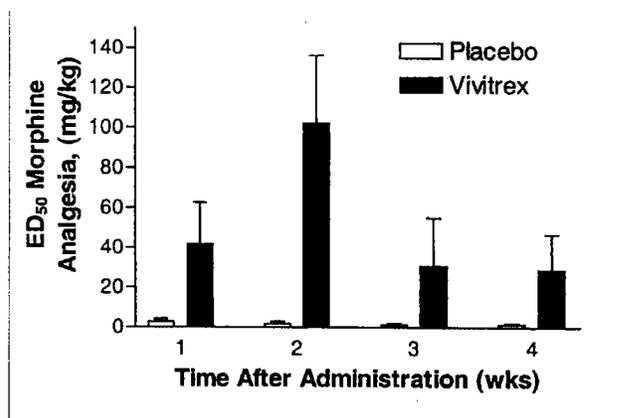
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ED<sub>50</sub> Values for Morphine Analgesia In Vivitrex and Placebo-Treated Rats:

TIME AFTER FORMULATION ADMINISTRATION (WKS)	PLACEBO (ED <sub>50</sub> , MG/KG, 95% CI)	VIVITREX (ED <sub>50</sub> , MG/KG, 95% CI)
1	2.8 (1.5, 5.4)	41 (31, 54)
2	1.7 (1.4, 2.1)	100 (34, 307)
3	1.3 (0.7, 2.7)	31 (24, 39)
4	1.4 (0.7, 2.8)	30 (27, 35)

Summary of the Shift in ED values for Morphine Analgesia in Vivitrex and Placebo-Treated Rats:



These non-GLP nonclinical studies indicated that a single dose of Vivitrex microspheres (50 mg/kg of naltrexone) completely blocked the analgesic actions of morphine (1 mg/kg, IP) for approximately 1 month, simultaneous with a sustained elevation in plasma naltrexone concentrations.

### 2.6.2.3 Secondary pharmacodynamics

No secondary pharmacokinetics study have been submitted by the sponsor or reported in the literature with Vivitrex. However, Naltrexone is known to have an endocrine effect, specifically, naltrexone alters the function of hypothalamic-pituitary adrenal cortical axis (HPA). Naltrexone and naloxone increase adrenocorticotrophic hormone (ACTH) levels in rhesus monkeys.

Naltrexone is reported to increase plasma ACTH and cortisol levels. Animals and humans have shown that ethanol stimulates the hypothalamic-pituitary-adrenal (HPA) axis as demonstrated by increases in plasma levels of adrenocorticotropin hormone (ACTH) and corticosterone or cortisol. While it has been suggested that the HPA response to ethanol is related to both the reinforcing effect of ethanol and the ability of naltrexone to decrease ethanol consumption, it is still not clear how ethanol and naltrexone interact on the HPA axis, reviewer agree with the conclusion.

Naltrexone is known to increase plasma concentrations of luteinizing hormone (LH) and follicle stimulating hormone (FSH). Increases in LH concentrations are believed to result from blockade of endogenous opioid inhibition of luteinizing hormone-releasing hormone (LHRH) release. Increases in testosterone and estrogen/progesterone secretion during the luteal phase do not appear to accompany naltrexone treatment. Naltrexone has seen limited use in the treatment of certain clinical endocrinopathies including hyperprolactinemic amenorrhea, and hypothalamic ovarian failure. In these cases naltrexone produced at least a partial normalization of menstrual cycling. In a study of naltrexone in obese women with polycystic ovarian syndrome, body mass index significantly decreased and menstrual cyclicity improved in most patients. Blockade of the tonic opioid inhibition of HPA axis activity also appears to result in release of

proopiomelanocortin-derived hormones in the pituitary and cortisol from the adrenal gland. Reviewer concurs with the above discussion noted by the Sponsor.

Naltrexone reversed the decrease in plasma thyroid stimulating hormone concentrations usually observed with exposure to acute or chronic stress in rats. Naltrexone indirectly blocked the effect of thyrotropin releasing hormone (TRH) on gastrointestinal (GI) transit and fluid accumulation in rabbits and rats, presumably by blocking TRH-induced release of serotonin. Published reports reviewed are in agreement with these observations.

#### 2.6.2.4 Safety pharmacology

No safety pharmacology studies have been done with Vivitrex. Safety pharmacology studies reported for naltrexone in the scientific literature. The nonclinical and clinical experience with naltrexone indicates that secondary pharmacological effects of naltrexone affecting essential body functions are limited in the therapeutic dose range. Opioid antagonists do not have significant effects on cardiovascular responses, including heart rate and blood pressure in primates and humans. There is no evidence in the scientific literature of ECG abnormalities being induced by naltrexone. The literature does contain reports of pharmacologic effects, including increased systolic and/or diastolic blood pressure, respiratory depression, and decreased oral temperature, suggestive of opioid receptor agonist actions, occurring in occasional patients treated with naltrexone. However, the magnitude of these effects does not trigger safety concerns. Naltrexone administered to animals in shock appears to aid in the maintenance of cardiovascular tone, although the mechanism is not well characterized.

In chronic toxicity, a one-year monkey study no changes in respiratory rate, heart rate, or systolic pressure were noted in animals treated with oral naltrexone up to 20 mg/kg/day were observed. Similarly no clinical findings relating to disturbances of CNS, GI or urinary function were reported. Toxicology studies in other species (rat, dog, and rabbit) provided no basis for safety pharmacology concerns.

Sponsor noted that the bradycardia was reported following naltrexone administered IV at doses of 5-80 µg/kg in non-anesthetized dogs. However, respiratory rate, blood pressure, arterial blood gases, and EEG remained unchanged throughout the dose range. The relevance of this finding to IM dosing is not known. Reviewer concurs with this observation.

Sponsor provided the evidence from the published studies indicating LD<sub>50</sub> values for naltrexone in mouse range from 190 mg/kg for IV dosing to 1100 mg/kg for oral dosing, 117 mg/kg IV and 1450 mg/kg orally for the rat, and 117 mg/kg IV for the dog. Lethal oral doses in animals produce tonic and/or clonic convulsions while lethal IV doses are reported to be followed by respiratory failure. The cause of death and the mechanism(s) leading to the development of convulsions or respiratory failure has not been investigated. No reports regarding the pathological findings involving target organs in animals killed by naltrexone overdose have been obtained.

### 2.6.2.5 Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were conducted by the Sponsor.

Patients receiving naltrexone may not benefit therapeutically from opiate-containing preparations, including those used for the management of cough, diarrhea, and pain. Use of these preparations should generally be avoided during naltrexone therapy if an alternative, non-opioid therapy is available. Because naltrexone can precipitate potentially severe opiate withdrawal, naltrexone should not be used in patients receiving opiates or in nondetoxified patients physically dependent on opiates. Special consideration must also be made regarding the sustained release characteristics of Vivitrex microspheres. Use of Vivitrex microspheres should be avoided if there is an anticipated need for opioid therapy during the period of naltrexone release from the depot. Naltrexone has been administered concurrently with non-opiate drugs (e.g., disulfiram, tricyclic antidepressants, and lithium) frequently used in the treatment of drug dependence without evidence of unusual adverse effects. However, these drug interactions have not been examined closely in a controlled clinical environment.

### 2.6.3 PHARMACOLOGY TABULATED SUMMARY

#### 2.6.4 PHARMACOKINETICS/TOXICOKINETICS

##### 2.6.4.1 Brief summary

Vivitrex 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 postdose concentrations slowly decline, with measurable levels for greater than 1 month. Maximum plasma concentration (C<sub>max</sub>) and area under the curve (AUC) for naltrexone and 6β-naltrexol (the major metabolite) following Vivitrex administration are dose proportional. Steady state is reached at the end of the dosing interval following the first injection. There is minimal accumulation (<15%) of naltrexone or 6β-naltrexol upon repeat administration of Vivitrex.

In vitro data demonstrate that naltrexone plasma protein binding is low (21%). Naltrexone is extensively metabolized in humans. Production of the primary metabolite, 6β-naltrexol, is mediated by dihydrodiol dehydrogenase, a cytosolic family of enzymes. The cytochrome P450 system is not involved in naltrexone metabolism. Two other minor metabolites are 2-hydroxy-3-methoxy-6 and 2-hydroxy-3-methoxy-naltrexone. Naltrexone and its metabolites are also conjugated to form glucuronide products. 6β-naltrexol generated following IM administration of Vivitrex compared to administration of oral naltrexone due to a reduction in first-pass hepatic metabolism is

claimed to be less in human PK studies. The major human metabolite of naltrexone, 6 $\beta$ -naltrexol, is significantly less potent as an opioid receptor antagonist than naltrexone, but due to its longer elimination half-life (Myer et al 1984), it may contribute to the overall duration of receptor blockade. This metabolite is not produced in significant amounts in rodents and dogs and is found at only low levels in non-human primates (Dayton et al 1976, Garrett et al 1985). Elimination of naltrexone and its metabolites occurs primarily via urine, with minimal excretion of unchanged naltrexone.

The elimination half-life of 6 $\beta$ -naltrexol following Vivitrex administration is 5 to 10 days. In vitro drug metabolism studies indicate that naltrexone does not inhibit cytochrome P450 (CYP) enzymes at clinically relevant concentrations.

#### 2.6.4.2 Methods of Analysis

Concentrations of naltrexone and 6 $\beta$ -naltrexol (primary human metabolite) in beagle dog and rhesus monkey plasma were determined using validated LC-MS-MS methods. Pharmacokinetic parameters for naltrexone and 6 $\beta$ -naltrexol were determined by standard noncompartmental methods.

#### Summary of Bioanalytical Methods Used in Nonclinical Pharmacokinetic Studies

SPECIES	METHOD TYPE	MATRIX	ANALYTE	LINEAR RANGE (NG/ML)	ACCURACY	PRECISION
Beagle dog	LC-MS-MS	Plasma	Naltrexone	0.200 to 100	≤ 2.5%	≤ 9.2%
			6 $\beta$ -naltrexol	0.200 to 100	≤ 6.0%	≤ 9.4%
Rhesus monkey	LC-MS-MS	Plasma	Naltrexone	0.200 to 100	≤ 3.7%	≤ 9.1%
			6 $\beta$ -naltrexol	0.211 to 105	≤ 3.8%	≤ 11.3%

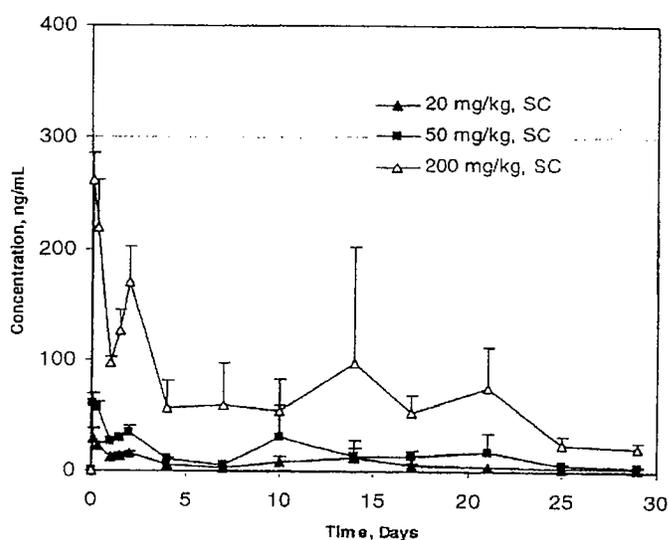
#### 2.6.4.3 Absorption

Pharmacokinetic properties of Vivitrex were analysed by the Sponsor along with the toxicity studies in different species after various routes of administration.

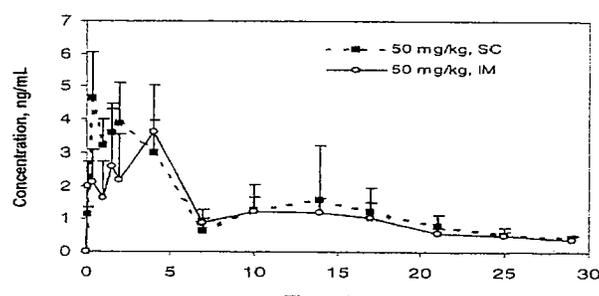
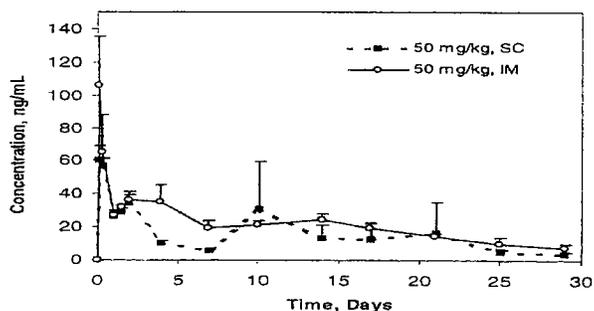
The linearity of release of naltrexone from Medisorb Naltrexone microspheres at three dose levels (20, 50 and 200 mg/kg) in monkeys following SC administration, was evaluated.  $C_{max}$ ,  $AUC_{0-1d}$ ,  $AUC_{0-7d}$  and  $AUC_{0-29d}$  were dose proportional suggesting linear pharmacokinetics of Medisorb Naltrexone within the dose range tested. The mean  $\pm$  SD  $C_{max}$  values were  $32 \pm 8.4$ ,  $64 \pm 6.4$ , and  $265 \pm 25$  ng/mL for the 20, 50, and 200 mg/kg doses, respectively. The corresponding SC  $AUC_{0-29days}$  were  $187 \pm 46$ ,  $449 \pm 155$  and  $2115 \pm 645$  ng\*d/mL, respectively. In this primate study, the data suggests that there is no marked difference in these release profiles between SC and IM routes. The IM route had higher naltrexons  $C_{max}$  ( $106 \pm 30.0$  ng/mL) and  $AUC$  ( $609 \pm 21$  ng\*d/mL)

values compared to SC dosing. The plasma profiles of 6 $\beta$ -naltrexol for all groups were parallel to the naltrexone profiles. The mean 6 $\beta$ -naltrexol concentrations were about 10 to 20 times lower than the mean naltrexone values. The day 29, naltrexone concentrations were dose related with values of  $2.86 \pm 1.06$ ,  $4.06 \pm 1.04$  and  $21.3 \pm 5.03$  ng/mL for the 20, 50, and 200 mg/kg groups respectively. The day 29 value for the 50 mg/kg IM group was  $7.60 \pm 2.66$  ng/mL which was somewhat greater than the SC value. The two recovery animals (200 mg/kg, SC) maintained naltrexone plasma concentrations of approximately 4 ng/mL for 59 days post-dose.

**Plasma Naltrexone Profiles of Medisorb Naltrexone Microsphere Formulation at Three Subcutaneous Dose Levels in Monkeys:**



**SC and IM Plasma Naltrexone and 6 $\beta$ -Naltrexol Profiles of Medisorb Naltrexone Microsphere Formulation at 50 mg/kg in Monkeys: Mean (n = 4)  $\pm$ SD**



In order to assess the effect of multiple doses on the pharmacokinetics of the naltrexone and  $\beta$ -naltrexol, Medisorb Naltrexone was administered subcutaneously to monkeys at naltrexone doses of 20, 50 and 75 mg/kg. Each animal received three doses at 28-day intervals. Naltrexone  $C_{max}$  and  $AUC_{0-last}$  values increased with increasing dose, although inter animal variability was large.

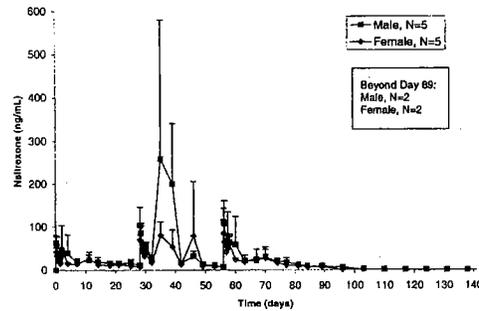
$C_{max}$  and AUC values tended to be larger in male monkeys compared to female monkeys. The small number of animals involved in the study prevented meaningful statistical comparisons, however; there was no evidence of a substantial gender difference.

Assessment of accumulation is somewhat complicated by the large variability observed between dose cycles. For naltrexone, there was no consistent evidence of accumulation based on  $C_{max}$ , and  $AUC_{0-last}$  values. The 75 mg/kg dose group was the only group where mean  $C_{max}$ , and  $AUC_{0-last}$  values increased from Cycle 1 to Cycle 3. For  $6\beta$ -naltrexol,  $C_{max}$  and  $AUC_{0-last}$  did not change from Cycle 1 to Cycle 3 at the 20 and 50 mg/kg doses. A small increase was observed in  $C_{max}$ , and  $AUC_{0-last}$  in the 75 mg/kg group.

Due to the large variability between animals and dose cycles, examination of pre-dose concentrations provides a better assessment of accumulation. On Day 28 (prior to the second injection), all 22 animals had reportable naltrexone plasma concentrations and 20 of 22 had reportable  $6\beta$ -naltrexol, concentrations. On Day 56 (prior to the third injection), 20 out of 22 and 15 out of 22 reported naltrexone and  $6\beta$ -naltrexol concentrations, respectively. The presence of naltrexone prior to the second and third

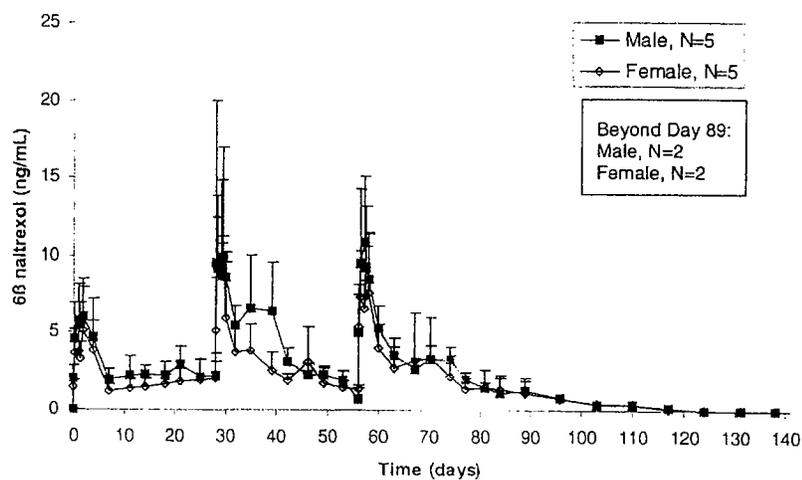
injections indicates some degree of accumulation was present. The majority of pre-dose concentrations were <10% of the following C<sub>max</sub>. Pre-dose concentrations increased with increasing dose, but did not increase with successive doses, signaling accumulation did not occur beyond the second dose.

**Mean ± SD Dose-normalized Naltrexone Plasma Concentrations in Male and Female Rhesus Monkeys Following Three 75 mg/kg Subcutaneous Injections of Medisorb Naltrexone at 28-day Intervals**

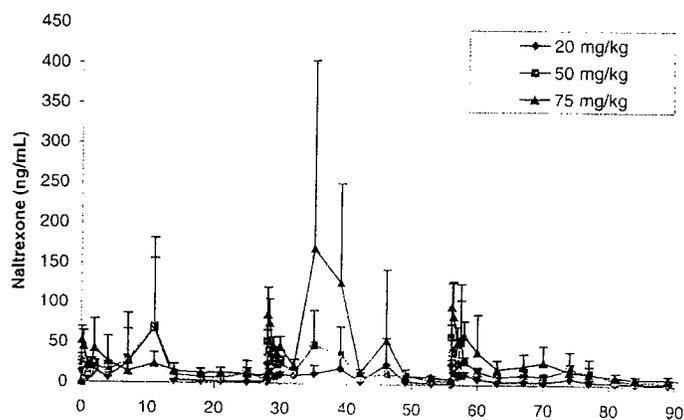


**Mean ± SD Dose-normalized 60-naltrexol Plasma Concentrations in Male and Female Rhesus Monkeys Following Three 75 mg/kg Subcutaneous Injections of Medisorb Naltrexone at 28-day Intervals**

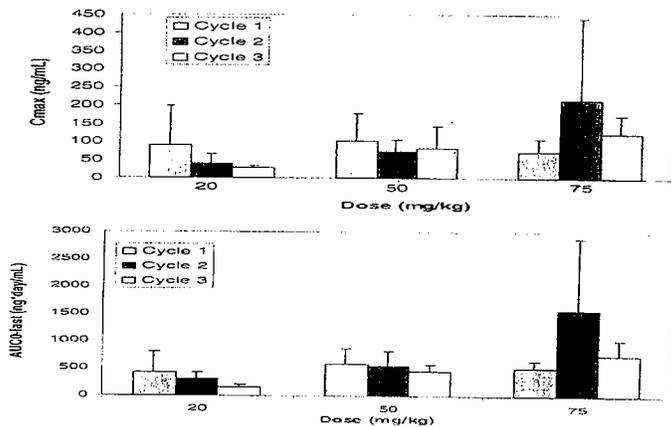
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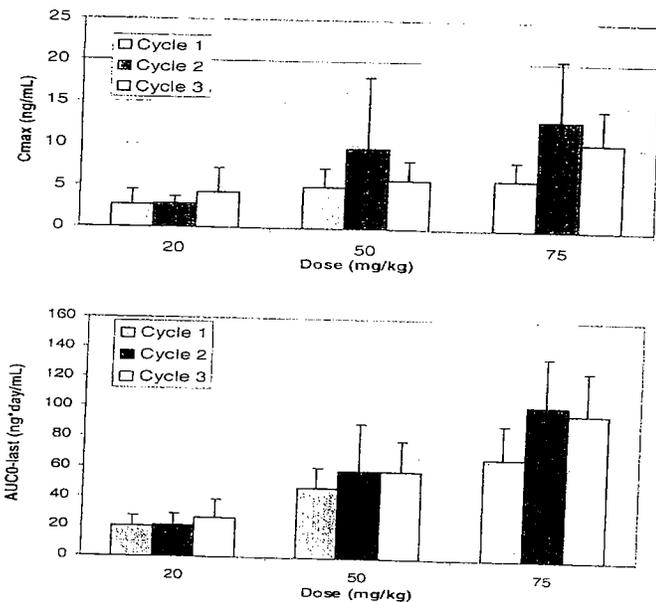
**Mean + SD Dose-normalized Naltrexone Plasma Concentrations in Rhesus Monkeys Following 3 Subcutaneous Injections of Medisorb Naltrexone at 28-day Intervals**



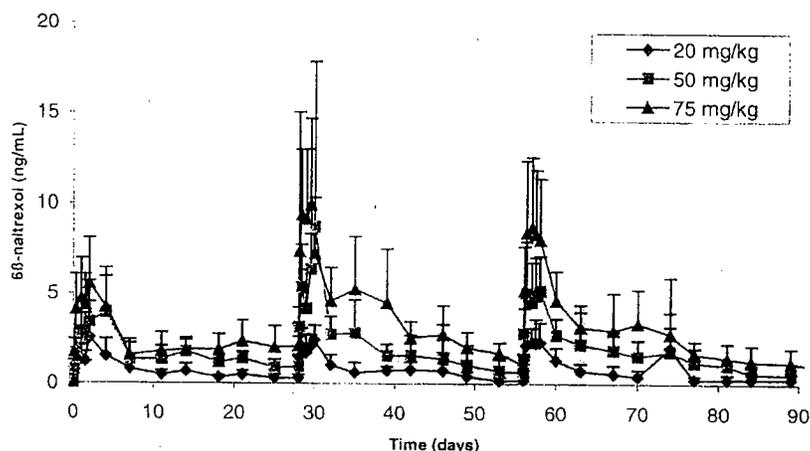
**Mean ± SD Dose-normalized Naltrexone Toxicokinetic Parameters by Dosing Cycle Following 3 Subcutaneous Injections of Medisorb Naltrexone at 28-day Intervals (C<sub>max</sub> top panel, AUC<sub>0-last</sub> bottom panel)**



**Mean ± SD Dose-normalized 6p-naltrexol Toxicokinetic Parameters by Dosing Cycle Following 3 Subcutaneous Injections of Medisorb Naltrexone at 28-day Intervals (C<sub>max</sub> top panel, AUC<sub>0-last</sub> bottom panel)**



**Mean  $\pm$  SD Dose-normalized 6 $\beta$ -naltrexol Plasma Concentrations in Rhesus Monkeys Following 3 Subcutaneous Injections of Medisorb Naltrexone at 28 day Intervals**



The pharmacokinetics of naltrexone was studied in dogs after two 394 mg IM injections of naltrexone, administered as the Medisorbo Naltrexone sustained-release injectable formulation. The two doses were injected 30 days apart, either in opposite legs (Group 1) or in the same site (Group 2).

There were no measurable 6 $\beta$ -naltrexol concentrations (LLOQ = 0.200 ng/mL) in any of the animals except for two plasma samples for Dog 38449 in Group 2 on Study Day 32 and 34. These values were low and close to the limit of detection of 6 $\beta$ -naltrexol.

For naltrexone, plasma concentrations seem to increase immediately (2 hour time point) after dosing, followed by a secondary peak 2 to 4 days later. The data are consistent across the doses and groups as can be seen in Figure I which shows an overlay of the naltrexone plasma profile following both doses for Group 1 and Group 2.

Plasma concentrations declined relatively slowly with low levels of naltrexone still being detected on Study Day 30 prior to administration of the second dose in 6 out of the 12 samples collected. Note that the Study Day 30 sample is also the pre-dose sample for the subsequent dose. However, these concentrations were considered to be sufficiently low

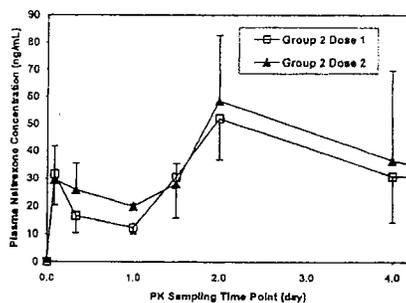
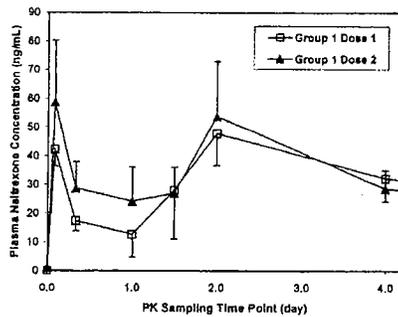
(less than 1.3 ng/mL) not to interfere with the pharmacokinetic analysis and interpretation of the data for the repeat dose.

Following the second dose, measurable concentrations of naltrexone were noted in 5 out of the 6 dogs remaining in the study by Study Day 67. All naltrexone levels fell below the detection limit of the assay (LLOQ < 0.200 ng/mL) by Study Day 102.

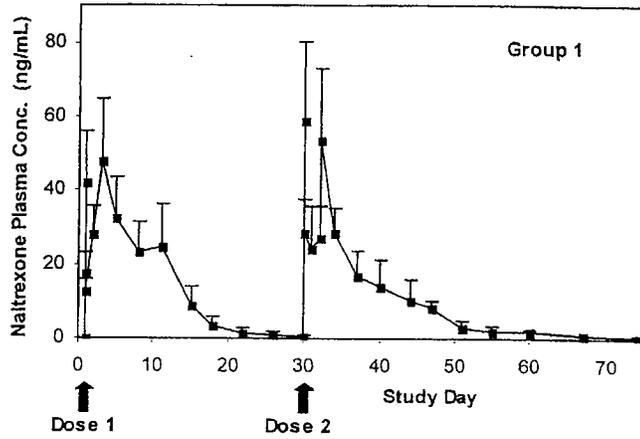
T<sub>max</sub> occurred either 2 hours or 2 days post-dose in all animals except 38449 following Dose 2. Though T<sub>max</sub> was variable, C<sub>max</sub> values were comparable across doses. Mean AUC values over all time intervals were comparable following Dose 1 and Dose 2. No trend (increase or decrease) in the data following the second naltrexone injection was noted for either group.

The C<sub>max</sub> and AUC values in Group 1 (opposite leg) and Group 2 (same site) following Dose 2 were comparable indicating that repeated dosing at the same or different injection site has no effect on the exposure to naltrexone.

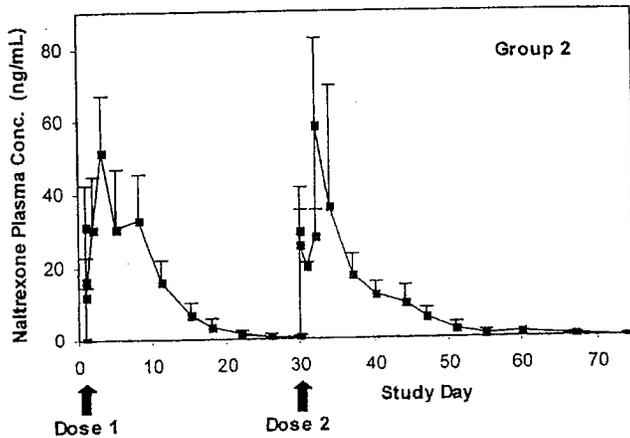
**Overlay Plot of Naltrexons Plasma Concentration-Time Profile for Dose 1 and Dose 2 from Madisorb: Immediately following IM Injection in Group 1 (Opposite Leg) and Group 2 (Same Site) Beagle Dogs. Values shown are Mean: ±SD (N=7).**



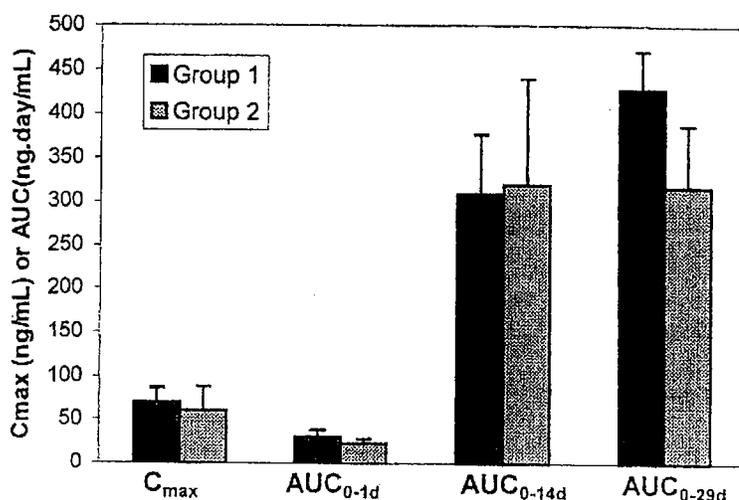
**Mean  $\pm$ SD Plasma Levels of Naltrexone in Beagle Dogs Following Two 394 mg Intramuscular Injections of Medisorb on Study Day 1 and 30 For Group 1 (Opposite Leg)**



**Mean  $\pm$ SD Plasma Levels of Naltrexone in Beagle Dogs Following Two 394 mg intramuscular Injections of Medisorb on Study Day 1 and 30 For Group 2**



**Comparison of C<sub>max</sub> and AUC Following the Second 394 mg Intramuscular Injection of Medisorb For Group 1 (Opposite Leg) and Group 2**



**2.6.4.4 Distribution**

The protein binding of [<sup>3</sup>H]-naltrexone was evaluated in mouse, rat, guinea pig, dog, monkey and human plasma using equilibrium dialysis at 37°C over a concentration range of 0.1-500 ng/mL. The concentration range used included concentrations typically encountered with clinical dosing of Vivitrex (mean C<sub>max</sub>- 25-28 ng/mL).

The extent of binding was independent of the naltrexone concentration over the studied range. Plasma binding was similar in all species ranging from approximately 20% in rats and humans to 27% in beagle dogs. These data suggest that naltrexone drug interactions due to protein displacement are unlikely.

**Plasma Protein Binding of Naltrexone in Various Species\***

SPECIES	% NALTREXONE BOUND
Mouse	21.9 (2.25)
Rat	19.9 (1.35)
Guinea Pig	20.9 (2.43)
Dog (beagle)	26.8 (2.12)
Monkey	21.3 (2.86)
Human	20.7 (0.47)

Values represent the mean ± (SD)  
 \* Data from Ludden et al 1976 (8)

Partitioning of naltrexone and its metabolites 6 $\beta$ -naltrexol and 2-hydroxy-3-methoxy- 6 $\beta$ -naltrexol (HM-naltrexol, a minor human metabolite) in human blood (plasma and RBC) was determined from samples collected 16-24 hours after dosing from subjects taking oral naltrexone 200 mg twice daily. Saliva and spot urine samples were also collected at the same time. The concentrations of metabolites exceeded that of naltrexone levels in all body fluids. 6 $\beta$ -naltrexol was the predominant metabolite. Concentrations of naltrexone in plasma and RBC were comparable indicating a uniform distribution of naltrexone in the blood. In contrast, 6 $\beta$ -naltrexol was predominantly associated with plasma, while HM-naltrexol was predominantly associated with the RBC fraction.

**Relative Abundance of Naltrexone and its Metabolites in Plasma, Red Blood Cells (RBC), Saliva, and Urine Collected from Human Subjects 16- 24 hours Following Oral Naltrexone 200 mg Twice Daily\***

BODY FLUID	CONCENTRATION (ng/mL) [MEAN (SD); N= 8]			RELATIVE ABUNDANCE EXPRESSED AS PERCENTAGE OF TOTAL BASE <sup>†</sup> FOR EACH SAMPLE		
	NALTREXONE	6 $\beta$ - NALTREXOL	HM- NALTREXOL	NALTREXONE	6 $\beta$ - NALTREXOL	HM- NALTREXOL
Plasma	9.4 (5.2)	200.6 (39.1)	62.9 (14.4)	3.4	73.5	23.1
RBC	6.8 (1.9)	ND	166.5 (47.1)	3.9	ND	96.1
Saliva	13.9 (17.1)	166.7 (184)	ND	7.7	92.3	ND
Urine <sup>‡</sup>	14.3 (13.0)	122.4 (74.8)	23.0 (16.8)	9.0	76.6	14.4

ND: Not determined

<sup>†</sup>: Data from Vereby et al, 1980 (9)

<sup>‡</sup>: Sum of all components

<sup>‡</sup>: Single spot sample

Naltrexone tissue distribution in male albino CF1 mice (Ludden 1976) and male New Zealand rabbits (Taylor 1980) was studied following IV administration of [<sup>3</sup>H]-naltrexone. Results indicated that the radioactivity is rapidly and extensively distributed to the body tissues in both species.

In mice, less than 4% of the administered radioactivity remained in the plasma after one minute following a 1 mg/kg [<sup>3</sup>H]-naltrexone IV dose. By 15 minutes, most of the administered radioactivity was localized in the major organs of elimination: kidneys (5% of [<sup>3</sup>H]-dose), liver (-23%) and GI tract (-18%). Less than 1% of the dose could be found in the brain, heart and spleen. Recovery of the total radioactive dose was essentially complete with approximately 98% of the radioactivity being accounted for in tissues and organs plus carcass within 15 minutes.

Similar results were observed in rabbits. Tissue distribution studies were undertaken following IV injection of 5 mg/kg of [<sup>3</sup>H]-naltrexone. Total radioactivity was measured in various tissues 90 minutes following dosing. In addition, the concentration of

naltrexone and 6 $\beta$ -naltrexol was measured simultaneously in each tissue. Within 3 minutes only 5% of the administered radioactivity remained in plasma. Tissue distribution at 90 minutes indicated that the concentration of total radioactivity in all tissues was higher than in plasma, except for fat and liver. The submaxillary glands had the highest concentration of total radioactivity followed by the stomach, spleen, large intestine, kidney and lung; naltrexone accounted for most of the radioactivity present. Measurable levels of 6 $\beta$ -naltrexol were also found in most tissues including brain, spleen, heart, testes, and kidneys. In the majority of tissues, levels of 6 $\beta$ -naltrexol were lower than those of naltrexone, except in fat, liver, and urine where levels of 6 $\beta$ -naltrexol exceeded those of naltrexone. Radioactivity in the seminal vesicles of rabbits was higher than in plasma. This latter finding was corroborated in a separate set of experiments where plasma and semen were collected from rabbits given a single IV bolus injection (1 and 5 mg/kg) of naltrexone.

**Distribution of Naltrexone and 6P-Naltrexol in Select Rabbit Tissues 90 minutes after Administration of 5 mg/kg IV [<sup>3</sup>H]-Naltrexone\***

TISSUE	<sup>3</sup> H-NALTREXONE EQUIVALENT <sup>†</sup> (μg/g)	6 $\beta$ -NALTREXOL/ NALTREXONE RATIO	NALTREXONE TISSUE/PLASMA RATIO
Plasma	0.32 (0.04)	0.15	1
Brain	1.50 (0.42)	0.42	3.2
Fat	0.47 (0.05)	1.81	0.5
Heart	1.38 (0.37)	0.34	3.5
Kidney	3.60 (0.28)	0.32	8.7
Large intestine	3.24 (1.52)	ND	9.6
Liver	0.17 (0.08)	3.0	0.2
Lung	2.73 (0.74)	ND	8.2
Seminal vesicle	2.03; 2.20	0.26	5.5
Spleen	6.64 (0.93)	0.16	18.0
Stomach content	8.90 (0.66)	0.05	24.2
Submaxillary glands	15.51 (5.01)	0.05	40.4
Testis	2.22 (0.04)	0.34	6.2
Urine	1.61 (0.18)	1.32	2.2

ND: Not determined

\*: Data from Taylor et al., 1980 (3)

†: Mean  $\pm$  SD (n=3), except for seminal vesicle

The disposition of [<sup>3</sup>H]-naltrexone in the brain was evaluated in male Wistar rats following a single 10 mg/kg SC dose of a naltrexone solution. Blood and brain tissues

were collected up to 96 hours. The brain-to-plasma ratio of naltrexone was 1.78 and 1.26 at 0.5 and 1.0 hour post-dosing, respectively, indicating that naltrexone crosses the blood brain barrier. After one hour, the brain-to-plasma ratio quickly declined to less than 1.0, though concentrations of naltrexone in the brain were still measurable up to 48 hours postdose. The reported half-life of naltrexone in the rat brain was 8 hours. 6 $\beta$ -Naltrexol was detected in very small amounts in rat brain but not in plasma.

Placental transfer of naltrexone was studied in pregnant female Sprague Dawley rats (Zagon et al 1997). On gestation day 20, female rats were assigned to a control or treatment group and injected intraperitoneally with 50 mg/kg naltrexone or saline (control). One hour later the animals were sacrificed and the brain, heart, and liver of the fetuses were removed for analysis. Naltrexone was detected in the fetal brain, heart, and liver, suggesting that transplacental passage of naltrexone can occur in the rat.

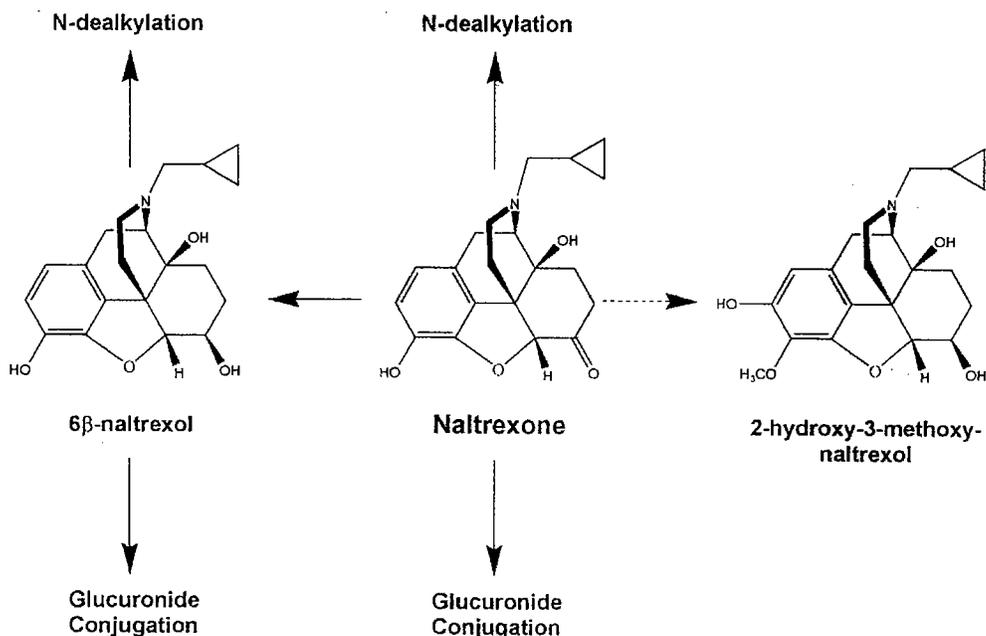
In summary, naltrexone protein binding is low (20-27%) in all species evaluated. Overall, animal studies have demonstrated rapid and extensive distribution of naltrexone in rodents and rabbits following SC, IV, and IP administration. In pregnant rats, naltrexone was found to pass the placental barrier and appeared in measurable quantities in the brain, heart and liver of the fetus. Tissue distribution in mice and rabbits following IV administration indicated the highest concentrations were present in the gastrointestinal region and kidneys.

#### **2.6.4.5 Metabolism**

The in vitro and in vivo metabolism of naltrexone has been studied in several animal species and humans. Data presented below indicate that the route of elimination of naltrexone and its metabolites, as well as the extent of formation of the various metabolites, is species-dependent. Within an individual species, the same qualitative metabolic profile is observed regardless of the route of administration, although the metabolites are generated in varying proportions. Therefore evaluation of naltrexone metabolism in preclinical species is based on available literature data. In addition, in vitro drug interaction studies were conducted by Alkermes to assess the potential for metabolic-based drug interactions.

The main pathways are: reduction of the 6-keto group to 6 $\beta$ -naltrexol; glucuronidation of naltrexone and naltrexol; N-dealkylation to nor-compounds of naltrexone and naltrexol; and 3-O- methylation and 2-hydroxylation.

#### **Major metabolic pathways of naltrexone**



6β-Naltrexol is recognized as the major human metabolite. Recent studies investigating the enzyme(s) involved in its formation have been reported in the literature. Using purified enzyme preparations from human liver samples, naltrexone was shown to be a substrate of dihydrodiol dehydrogenases (DDs), a cytosolic polymorphic family of enzymes. Reduction of naltrexone was stereospecific resulting in the formation of 6β-naltrexol; 6α-naltrexol was not detected.

The formation kinetics of 6β-naltrexol in human liver cytosolic and microsomal preparations from eight patients (4 females and 4 males) was evaluated. Results showed that cytochrome P450 enzymes are not involved in the formation of 6β-naltrexol in microsomal preparations. Additionally, naltrexone was not produced when 6β-naltrexol was incubated with microsomes and NADPH-generating enzymes indicating that the reverse oxidation of 6β-naltrexol to naltrexone does not occur.

Hepatic enzymatic formation of 6β-naltrexol appears to be confined to the cytosolic fraction only. The  $V_{max}$ ,  $K_m$  and intrinsic clearance in human liver cytosol were calculated and showed considerable intersubject variability. The high degree of inter-individual variability may be due to differences in enzymatic activity or genetic polymorphisms of the DDs in the different liver samples.

### **Enzyme Kinetics of 6 $\beta$ -naltrexol Formation from Naltrexone Using Human Liver Cytosol Preparations\***

	$V_{MAX}$ (nmol·hr <sup>-1</sup> ·mg <sup>-1</sup> protein)	$K_M$ ( $\mu$ M)	$CL_{INT}^{\dagger}$ (mL·hr <sup>-1</sup> ·mg <sup>-1</sup> protein)
Mean	26.5	34.4	1.03
Range	15.8 - 45.6	17.1 - 55.1	0.29 - 2.23
%CV (n=8)	42.6	49.1	70.0

\*: Data from Porter et al., 2000 (13)

†:  $Cl_{int} = V_{max} / K_m$

In several animal species including human, a common route of biotransformation of naltrexone and 6 $\beta$ -naltrexol is through direct glucuronide conjugation of the phenolic group. The glucuronide conjugates are formed enzymatically by the transfer of the glucuronyl group from uridine 5'- diphosphoglucuronate (UDPGA) by glucuronyl transferases (UGTS) found in microsomes of liver and other tissues. Coffman et al showed that UGT2B7, a UGT isoenzyme, plays a major role in the glucuronidation of a large number of clinically important opioids including morphine and naltrexone.

Naltrexone is extensively metabolized by the liver. First-pass hepatic metabolism substantially limits the amount of unchanged naltrexone that reaches the systemic circulation. The most commonly observed metabolites in plasma, urine, bile and feces are 6 $\beta$ -naltrexol and its conjugates (glucuronides), conjugated naltrexone, and 2-hydroxy-3-methoxy naltrexol (HM-naltrexol). These are formed in varying proportions depending on the species and route of naltrexone administration.

In rats, naltrexone metabolites 7,8-dihydro-14-hydroxynormorphinone (N-dealkylated naltrexone) and 7,8-dihydro-14-hydroxynormorphine were identified in addition to naltrexone and its conjugate in plasma. 6 $\beta$ -Naltrexol was not present in detectable quantities in the rat plasma, though small amounts of 6 $\beta$ -naltrexol were present in the brain. Following chronic oral dosing of naltrexone (100 mg/kg daily for 365 days), small amounts of naltrexone (free and conjugated) and 6 $\beta$ -naltrexol (free and conjugated) were detected in the urine. Female rats appeared to excrete twice as much free drug in the urine compared with male rats. In this experiment, less than 1% of the dose was accounted for in the 24-hour urine sample in chronically treated rats, in contrast to the 40% recovery reported in the rat urine following a single IM or IV dose. Traces of two other metabolites, HM- naltrexol and 2-hydroxy-3-methoxy naltrexone (HM-naltrexone) have also been identified in the 24-hour urine of rats following oral administration of a single 25 mg naltrexone dose. Feces were not collected in these studies.

In New Zealand rabbits, levels of conjugated metabolites exceeded those of naltrexone within 5 minutes of administering [<sup>3</sup>H]-naltrexone 5 mg/kg intravenously. The plasma-conjugated metabolites were not identified further. By 240 minutes postdose, the concentration of free drug represented only 5% of the radioactivity in plasma. The major

urinary metabolite was conjugated naltrexone, 6 $\beta$ -naltrexol was also detected in trace amounts.

In mongrel dogs, naltrexone and its conjugate were the major analytes in plasma, urine, and bile following IV administration of 0.5 and 5 mg/kg naltrexone. 6 $\beta$ -Naltrexol was not detected in the bile, plasma, or urine of the dog.

In rhesus monkeys, conjugated naltrexone is the major plasma metabolite following both oral and IV administration of a single 10 mg/kg naltrexone dose. 6 $\beta$ -Naltrexol and its conjugates were also present in plasma. Conjugated naltrexone and conjugated 6 $\beta$ -naltrexol were the major urinary metabolites. The urinary excretion pattern in monkeys was similar following a single oral or IV dose and chronic oral dosing. Urinary excretion in female monkeys was approximately twice that of male monkeys. Fecal elimination consisted predominantly of free 6 $\beta$ -naltrexol.

In humans, 6 $\beta$ -naltrexol is the major metabolite in plasma. A minor metabolite, 2-hydroxy-3-methoxy 6 $\beta$ -naltrexol (HM-naltrexol), was also detected. Approximately 60% of the total dose was excreted in the urine within 48-72 hours following oral or IV administration and 76% following SC administration. The urinary excretion profile shows 6 $\beta$ -naltrexol and conjugated 6 $\beta$ -naltrexol as the major metabolites. Minor metabolites HM-naltrexol and conjugated naltrexone were also identified in urine in addition to small amounts of naltrexone. Trace amounts of HM-naltrexone have also been reported in human urine following oral naltrexone administration. Naltrexone fecal excretion is minimal with <6% of the dose recovered within 48 hours following oral administration.

### Overview of Naltrexone Metabolic Pattern in Plasma in Various Animal Species and Human

SPECIES (STRAIN)	PLASMA METABOLITE				REFERENCE
	CONJUGATED NALTREXONE	6 $\beta$ -NALTREXOL	CONJUGATED 6 $\beta$ -NALTREXOL	OTHER	
Rat (Wistar)	Present	ND	ND	N-dealkylated naltrexone and N-dealkylated 6 $\beta$ -naltrexol	(10)
Dog (mongrel)	Major	ND	ND	--	(1)
Monkey (rhesus)	Major	Minor	Minor	--	(2)
Human	Major	Major	Major	HM-naltrexol <sup>†</sup>	(6)

ND: none detected

--: not reported

: 7,8-dihydro-14-hydroxynormorphine and normorphine

†: 2-hydroxy-3-methoxy 6 $\beta$ -naltrexol

**Metabolic Pattern of Naltrexone and its Metabolites in Urine and Feces (0-24 hour) in Various Animal Species and Human**

SPECIES (STRAIN)	GENDER (N)	DOSE/ ROUTE	DOSAGE SCHEDULE	PERCENTAGE OF ADMINISTERED DOSE RECOVERED				TOTAL BASE <sup>1</sup>	REFERENCE
				NALTREXONE		6β-NALTREXOL			
				FREE	CONJ.	FREE	CONJ.		
Urine									
Rat (Holtzman)	Male (3)	100 mg/kg Oral	Daily for 12 months	0.1	0.2	0.1	0.1	0.5 (0.1)	(15)
	Female (3)	100 mg/kg Oral	Daily for 12 months	0.2	0.2	0.3	0.1	0.8 (0.1)	
Guinea Pig (Camm)	Male (3)	1 mg/kg IM	Single dose	0.709 (0.515)	57.1 (6.9)	6.96 (1.06)	4.28 (1.44)	— <sup>1</sup>	(7)
Rabbit (New Zealand)	Male (3)	30 mg/kg IP	Daily for 8 days	0.2	14.5	0.1	3.3	18.2 (8.4)	(15)
Dog (mongrel)	Male (6 to 7)	0.5 or 5 mg/kg IV	Single dose	7.4 <sup>1,2</sup> (1.0)	58.9 <sup>1,2</sup> (3.3)	BDL	BDL	—	(1)
Monkey (rhesus)	Male (3)	12 mg/kg Oral	Daily for 8 months	0.1	8.1	0.3	8.0	16.5 (0.4)	(15)
	Female (2)	12 mg/kg Oral	Daily for 8 months	1.3	21.0	0.9	15.0	38.2 (0.9)	
	Female (5)	10 mg/kg Oral	Single dose	0.398 (0.142)	28.8 (5.0)	0.414 (0.125)	17.3 (4.7)	46.9 <sup>1</sup> (8.9)	(2)
	Female (5)	10 mg/kg IV	Single dose	2.28 (1.37)	37.5 (3.1)	0.453 (0.129)	12.1 (3.3)	52.4 (5.3)	
Human	Male (6)	50 mg Oral	Single dose	1.2 <sup>1</sup> (0.2)	9.7	26.3 <sup>1</sup> (2.2)	16.4	53.4 <sup>1†</sup>	(16)
	Male (3)	125 mg/kg Oral	3x/wk for one month	0.8	7.6	16.8	11.8	37.0 (9.6)	(15)
	Male (4 to 5)	1 mg IV	Single dose	1.9 <sup>2†</sup>	7.8 <sup>2†</sup>	17.8 <sup>2†</sup>	13.0 <sup>2†</sup>	43 (4) <sup>1,††</sup>	(6)
	Male (4 to 6)	5 mg SC	Single dose	3.3	6.6	22.5	9.8	63	(18)
Feces									
Guinea Pig (Camm)	Male (3)	1 mg/kg IM	Single dose	5.11 (2.36)	—	5.45 (0.84)	—	— <sup>1†</sup>	(7)
Dog (mongrel)	Male (1)	0.5 or 5 mg/kg IV	Single dose	—	19 <sup>2†</sup> / 36	—	—	—	(1)

SPECIES (STRAIN)	GENDER (N)	DOSE/ ROUTE	DOSAGE SCHEDULE	PERCENTAGE OF ADMINISTERED DOSE RECOVERED				TOTAL BASE <sup>1</sup>	REFERENCE
				NALTREXONE		6β-NALTREXOL			
				FREE	CONJ.	FREE	CONJ.		
Monkey (rhesus)	Male (3)	12 mg/kg Oral	Daily for 8 months	1.7	0.5	4.4	BDL	6.6 (0.8)	(15)
	Female (3)	12 mg/kg Oral	Daily for 8 months	0.6	1.2	6.2	BDL	8.0 (2.9)	
Human	Male (5)	50 mg Oral	Single	0.35 <sup>2†</sup>	—	—	—	5.4 <sup>2†</sup>	(6)

Values are reported as Mean (SD) except where noted  
 — Not reported  
 BDL: Below the detection limit of the assay  
 n: number of subjects  
 1: Represents the sum of the four compounds listed or total radioactivity excreted  
 2: About 1.4% of dose was attributed to α-naltrexol and its conjugate in urine  
 †: Mean (SEM)  
 ††: Percentage excreted over the duration of the study  
 †††: Percentage excreted over 0-48 hours  
 ††††: Percentage excreted over 6 days  
 †††††: Percentage of individual analytes calculated from data in Table 6 m reference  
 ††††††: Includes HM-naltrexol (2.2%) and its conjugate (1.4%)  
 †††††††: Fecal excretion also includes 0.7% attributed to α-naltrexol and 0.5% as unidentified material  
 ††††††††: Collected from one bile-cannulated dog over 12 hours

Microsomal enzymes such as cytochrome P450 (CYP 450) enzymes are not involved in the metabolism of naltrexone or 6 $\beta$ -naltrexol. Consequently, metabolic CYP 450-based drug interaction studies evaluating the impact of other drugs on naltrexone and 6 $\beta$ -naltrexol were not undertaken since neither compound is a CYP 450 substrate.

The potential for drug interactions due to naltrexone or 6 $\beta$ -naltrexol inhibition of the CYP 450 enzymes was evaluated. Results indicate that the potential for CYP 450- based drug interactions due to naltrexone or 6 $\beta$ -naltrexol inhibition of major drug- metabolizing enzymes is remote.

Naltrexone and 6 $\beta$ -naltrexol were assessed for their inhibitory potential toward the ten major human CYP 450 drug metabolizing isozymes using individually cDNA-expressed human enzymes in microsomes prepared from baculovirus infected insect cells. In vitro incubations were carried out using individual human CYP 450 enzymes and isozyme specific substrates in the presence and absence of varying concentrations of naltrexone and 6 $\beta$ -naltrexol. Formation of the substrate metabolites was followed by fluorescence. Appropriate controls were included for each assay. The final concentrations of the substrates were at or below the apparent Km value of their respective enzymes. Concentrations of naltrexone and 6 $\beta$ -naltrexol ranged from 0 to 100  $\mu$ M, and included the maximum naltrexone plasma concentrations observed in humans following the proposed therapeutic dose.

The concentrations of naltrexone and 6 $\beta$ -naltrexol required to inhibit 50% of the catalytic activities (IC<sub>50</sub>) were determined. Naltrexone and 6 $\beta$ -naltrexol inhibited CYP2D6 catalytic activity with IC<sub>50</sub> values of 3.1 and 33  $\mu$ M, respectively. Naltrexone, but not 6 $\mu$ -naltrexol, inhibited the catalytic activity of CYP2C19 with an IC<sub>50</sub> value of 47  $\mu$ M. All other enzymes were either not inhibited or weakly inhibited (< 50%) by naltrexone or 6 $\beta$ - naltrexol.

In vitro inhibition data may be used to assess the clinical implications of potential drug interactions. It is generally accepted that drug interactions are remote if the ratio of C<sub>max</sub>/K<sub>i</sub> is below 0.1. Based on such an analysis, and assuming IC<sub>50</sub> K<sub>i</sub>, drug interactions due to inhibition of CYP2D6 or CYP2C19 are remote. At the proposed therapeutic dose of 380 mg, the highest observed individual naltrexone C<sub>max</sub> value (0.15  $\mu$ M, 50 ng/mL) relative to its CYP2D6 and CYP2C19 K<sub>i</sub> values are 0.05 and 0.003, respectively. Similarly the highest individual C<sub>max</sub> concentration of 6 $\beta$ -naltrexol (0.19  $\mu$ M, 64 ng/mL) relative to its CYP2D6 IC<sub>50</sub> value is approximately 0.006.

The effect of inhibition of dihydrodiol dehydrogenases (DD) on metabolism of naltrexone was reported by Porter et al. A variety of inhibitors were evaluated for their potential to inhibit 6 $\beta$ -naltrexol formation. The inhibitors were selected on the basis that they are general reductase inhibitors or because they are often co- administered with naltrexone. Results of the inhibition studies showed that testosterone and dihydrotestosterone were potent inhibitors of 6 $\beta$ -naltrexol formation. Testosterone inhibited 6 $\beta$ -naltrexone formation (K<sub>i</sub> = 280 nM) at concentrations approximately 10-fold the upper limit of normal for circulating testosterone concentrations in males; therefore

this interaction is unlikely to be of clinical significance. Naloxone, menadione, corticosterone, testosterone and dihydrotestosterone produced > 50% inhibition at a concentration of 100  $\mu$ M. The opioid agonists morphine, oxycodone, oxymorphone, and hydromorphone as well as a range of benzodiazepines showed less than 20% inhibition at 100  $\mu$ M.

These interactions were weak and the likelihood for in vivo drug-drug interaction occurring between naltrexone and these drugs is very low.

Formal enzyme induction studies have not been conducted because human data indicate that naltrexone does not induce its own metabolism. Clinical studies following acute and chronic oral naltrexone administration (100 mg dose) showed no changes in the disposition of naltrexone and its metabolite from the acute to the chronic state.

#### 2.6.4.6 Excretion

The excretion of naltrexone has been reported in several animal species and humans following IM, oral and/or IV administration. The excretion profile varied across species, the profile within a species was independent of dose and route of administration of naltrexone. Consequently, studies evaluating the excretion of naltrexone following IM administration of Vivitrex have not been conducted by the sponsor

Excretion of naltrexone following IM administration has been reported for rats and guinea pigs. In addition, excretion studies have been conducted in rats, guinea pigs, rabbits and dogs following IV administration, and in monkeys and humans following both oral and IV administration. The dosing formulation consisted of naltrexone and/or [ $^3$ H]-naltrexone in an aqueous solution in all studies except for human oral administration where the drug solution was administered in gel capsules.

In all animal studies, 50% or more of the radio-labeled dose was excreted in the urine and feces within 48-96 hours. Excretion of [ $^3$ H]-naltrexone and its metabolites in male rats was determined following IM or IV administration of 1 mg/kg. Approximately 50 - 60% of the radioactive dose was excreted in the feces, while the remainder of the dose (~40%) was recovered in the urine. The pattern of elimination was similar regardless of the route of naltrexone administration.

In contrast to rats, only 10 - 20% of the radioactive dose was recovered in the feces of guinea pigs following IM (1 and 20 mg/kg) or IV (1 mg/kg) administration of [ $^3$ H]-naltrexone; the remainder of the dose (80%) was recovered in urine. The pattern of elimination was similar regardless of the dose and route of administration.

In rabbits, analysis of urine collected over 24 hours following IV administration of 5 mg/kg [ $^3$ H]-naltrexone showed the presence of 59% of the administered dose, indicating that naltrexone metabolites are quickly excreted into the urine. Feces were not collected in this study.

Following IV administration of 0.72 mg/kg naltrexone in dogs, approximately 37% of the dose was excreted in the urine within 24 hours. Up to 36% of the dose was collected in the bile of bile-cannulated dogs, with 66% of the dose recovered in the urine over the study duration.

Urinary excretion was the primary route of elimination in the monkey with 52% and 47% of the dose recovered in the urine over a 48-hr period following IV (10 mg/kg) or oral (10 mg/kg) administration of naltrexone, respectively. Recovery in the feces was minimal.

In humans, urinary excretion is also the predominant route of naltrexone elimination. Approximately 51 and 43% of the dose are recovered in the urine within the first 24 hours following oral (50 mg) and IV [<sup>3</sup>H]-naltrexone 1 mg/kg administration respectively. Approximately 60% of the dose was recovered in the urine and 5% in the feces in 48 to 72 hours. Though urinary excretion of radioactivity between 24 and 48 hours post-dose was appreciable (9% of the dose) following oral administration, samples were not collected beyond 48 hours. Approximately 5% of the dose is recovered in the feces following oral administration of a 50 mg oral [<sup>3</sup>H] - naltrexone dose.

In order to facilitate comparisons, 0-24 hour data are presented in where possible, though sample collection continued beyond 24 hours in some studies.

Naltrexone appears to undergo enterohepatic recycling both in animals and humans. The pronounced biliary excretion of conjugated naltrexone in dogs and guinea pigs and the presence of secondary peaks in the plasma concentration-time profile in addition to the prolonged elimination phase for naltrexone and its conjugates in dogs, monkeys, and humans support this assumption.

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**Summary of the 24-Hour Radioactivity Excretion Profile Following Naltrexone Administration\* to Various Species**

SPECIES (STRAIN)	GENDER (N)	DOSE/ ROUTE	PERCENTAGE OF ADMINISTERED DOSE			REFERENCE
			URINE	FECES	TOTAL	
Rat (Cox-SD)	Male (1)	1 mg/kg IM	36.9	44.1	81	(7)
	Male (3)	1 mg/kg IV	41.7 (14.8)	47.4 (11.9)	89.1 --	
Guinea Pig (Camm)	Male (3)	1 mg/kg IM	79.7 (5.4)	13.5 (3.0)	93.2 --	(7)
	Male (6)	20 mg/kg IM	82.4 (10.6)	8.7 (4.2)	91.1 ----	
	Male (4)	1 mg/kg IV	80.1 (2.3)	10.4 (3.0)	90.5 --	
Rabbit (New Zealand)	Male (1)	5 mg/kg IV	59	--	--	(3)
Dog (foxhound)	Male (2)	0.72 mg/kg IV <sup>†</sup>	36.6, 37.9	--	--	(4)
Dog (mongrel)	Male (6 to 7)	0.5 and 5 mg/kg IV <sup>†</sup>	66.3 <sup>‡</sup>	19 <sup>§</sup> , 36 <sup>  </sup>	--	(1)
Monkey (rhesus)	Female (5)	10 mg/kg Oral	46.9 <sup>¶</sup> (8.9)	2.1 <sup>¶</sup> , **	--	(2)
	Female (5)	10 mg/kg IV	52.4 <sup>¶</sup> (5.3)	1.2 <sup>¶</sup> , **	--	
Human	Male (5 to 6)	50 mg Oral	51 (2)	5.4 <sup>††</sup>	--	(6)
	Male (4 to 5)	1 mg IV	43 (4)	--	--	
	Male (4 to 6)	5 mg SC	63	--	--	(18)

Values are reported as Mean (SD) except for human where values are Mean (SEM)

--: Not reported

: Formulation used in all animal studies consisted of a naltrexone solution in aqueous buffer. For oral dosing in human, the [<sup>3</sup>H]-naltrexone dose was dissolved in 1 mL water:ethanol solution (1:1,v/v) in 2 gelatin capsules.

†: Studies with non-radiolabeled naltrexone

‡: Value was calculated from data in Table III in reference by adding the overall average fraction of dose excreted over duration of study in dog urine as naltrexone (0.074±0.010, n=6) and conjugated naltrexone (0.589 ± 0.033, n=7) then multiplying by 100.

§: Collected over 12 hours from a single bile-cannulated dog administered 0.5 or 5 mg/kg

¶: Data for 0-48hr

\*\*: Data from one animal

††: Feces data for 0-48 hr. Urinary excretion during the same interval was 60 ± 3% and 54± 5% of dose following

Naltrexone and 6 $\beta$ -naltrexol are reported to be excreted in the milk of lactating rats and sheep (Chan et al 2001) dosed with naltrexone. Transfer of naltrexone and 6 $\beta$ -naltrexol into human milk has been reported in one breastfeeding woman undergoing naltrexone pharmacotherapy (50 mg/day). In milk and plasma, 6 $\beta$ -naltrexol concentrations were consistently higher than naltrexone. Using the mean of 2 single point measurements obtained approximately 3.7 and 5 hours following the naltrexone dose, the milk:plasma ratio was 1.9 for naltrexone and 3.4 for 6 $\beta$ -naltrexol. Over the time period of 3.7 to 23 hours following the naltrexone dose, the total relative infant dose due to both compounds was 0.86% of the weight-adjusted maternal dose. Naltrexone was not detected in infant plasma collected at 9.5 hours after the maternal dose, but 6 $\beta$ -naltrexol was present at 1.1 ng/mL (marginally above the 1 ng/mL lower limit of detection for the assay). The 1.5

month-old breastfed infant was in good health, had achieved expected milestones and showed no drug- related effects.

In summary, urinary excretion is the primary route of elimination for naltrexone and its metabolites in guinea pigs, rabbits, dogs, monkeys, and humans, while the fecal route of elimination predominates in rats. The excretion profile varies among species; however, the excretion pattern within a species is independent of dose and route of administration of naltrexone. In all studies where both urine and feces were collected, essentially complete recovery of the radioactivity dose was observed within 48-96 hours post-dosing with most of the dose being excreted in the urine and feces in the first 24 hours.

#### **2.6.4.7 Pharmacokinetic drug interaction**

In vivo drug interaction studies were not conducted in animals with Vivitrex as several factors suggest that pharmacokinetic drug interactions would not occur frequently with naltrexone. These factors include its proven clinical safety profile, In vivo drug interaction studies were not conducted in animals with Vivitrex as several factors suggest that pharmacokinetic drug interactions would not occur frequently with naltrexone. These factors include its proven clinical safety profile, and reduction in the renal and bile flow are common pharmacodynamic effects of morphine. In this study, naltrexone reversed the pupillary constriction caused by morphine but did not antagonize the perturbations in renal and biliary processes.

#### **2.6.4.8 Other Pharmacokinetic Studies: None**

#### **2.6.4.9 Discussion and Conclusions**

The pharmacokinetics/toxicokinetics of naltrexone following Vivitrex administration was evaluated as part of tolerability study in beagle dogs and as part of one- and three-month toxicology evaluations in rhesus monkeys. The nonclinical pharmacokinetic studies focused on evaluating exposure to naltrexone and its major metabolite, 6p-naltrexol, following Vivitrex administration. Data pertaining to naltrexone distribution, metabolism and excretion were obtained from published scientific literature.

Naltrexone pharmacokinetics are characterized by rapid absorption and distribution, extensive metabolism and a high total body clearance that is independent of dose. Intravenous administration of naltrexone in rabbits resulted in rapid distribution from the plasma with a reported half-life of  $55 \pm 5$  and  $53 \pm 3$  minutes following 1 and 5 mg/kg doses, respectively. Similar results were obtained in mongrel dogs with a terminal plasma half-life of  $46.9 \pm 4.7$  min. In contrast, the half-life of naltrexone following intravenous administration to rhesus monkeys was determined to be 468 minutes, approximately 10-fold greater than that observed in the other two species. Naltrexone was extensively absorbed following oral administration in monkeys; however, naltrexone is subject to a high first-pass effect probably mediated by the liver resulting in a low systemic availability of 3.6%. Following oral administration in humans, naltrexone was rapidly absorbed from the gastrointestinal tract with peak concentrations occurring one-

hour postdose. The oral bioavailability of naltrexone was reported to be low and varies between 5 and 40% . The half-life of naltrexone was determined to be 2.7 to 8.9 hours following IV and oral administration.

**Comparative Pharmacokinetic Data and Systemic Exposure to Naltrexone following Oral and Intravenous Administration in Rabbit, Dog**

SPECIES	DOSE (mg/kg)	ROUTE	AUC (mg·hr/L)	CL <sub>TOT</sub> (mL/min/kg)	V <sub>D</sub> (L/kg)	T <sub>1/2</sub> (min)	F	REFERENCE
Rabbit (New Zealand)	5	IV	--	--	--	53 (3) <sup>*</sup> (n=5)	--	(3)
Dog (mongrel)	0.5 & 5	IV	--	52.8 <sup>†</sup> (12.1) (n= 9)	3.4 <sup>†</sup> (0.7) (n=9)	46.9 <sup>*</sup> (4.7) (n=9)	--	(1)
Monkey (rhesus)	10	PO	0.086 (0.049) (n=5)	--	--	--	0.036	(2)
	10	IV	2.9 (0.93) (n=5)	65.7 (22.9) (n=5)	5.06 (2.23) (n=5)	468 <sup>**</sup>	--	(2)
Human	50 mg	PO	0.0804 <sup>‡</sup>	--	--	533	0.4 <sup>§</sup>	(6)
	1 mg	IV	0.004 <sup>‡</sup>	47.9 <sup>  </sup>	--	161		(6)

Values represent the mean ± (SD) unless otherwise specified. Naltrexone was administered as an aqueous buffered aqueous solution in all studies

-- Not reported

<sup>\*</sup>: Values are mean ± SEM.

<sup>†</sup>: Mean value was calculated from data in original reference by dividing individual values [clearance values (mL/min) in Table II or Vd values (L) in Table III] by corresponding dog weight (kg) in Table I then calculating the overall mean for n=9.

<sup>‡</sup>: AUC value was calculated from dose-normalized AUC values of 96.5 min/mL (oral) and 240 min/mL (IV) reported in original reference [Table 7] by converting to hr/L and multiplying by dose.

<sup>||</sup>: Mean value was calculated from data in original reference [Table 7] assuming a body weight of 70 kg.

<sup>§</sup>: Obtained by dividing dose normalized AUC oral by AUC IV.

<sup>\*\*</sup>: Harmonic Mean (n=6) (6)

Exposure to naltrexone achieved over approximately one month with Vivitrex administration may be compared to that following daily oral administration in monkeys and humans. In both species, IM Vivitrex administration afforded increased naltrexone exposure relative to the oral route with a substantially lower monthly dose. Specifically, in humans, the proposed dose of Vivitrex 380 mg provided -4 times the exposure compared to 50 mg oral daily dosing, but with 1/3 of the monthly dose. In monkeys, 20 mg/kg/day oral naltrexone for one month produced an estimated naltrexone exposure of 201 ng-day/mL, slightly in excess of human exposure with 380 mg Vivitrex (160 ng-day/mL).

**Naltrexone Exposure Following Vivitrex or Oral Naltrexone Dosing**

SPECIES	DOSE	ROUTE	AUC (ng•day/mL)	SOURCE
Rhesus monkey	Vivitrex 75 mg/kg Q28d	SC	751	AT-21-03
	naltrexone 20 mg/kg/d*	PO	201 <sup>†</sup>	Estimated from (43) <sup>†</sup>
Human	Vivitrex 380 mg Q28d	IM	160	ALK21-005
	naltrexone 50 mg/d	PO	41	ALK21-005

\* Dose used in the chronic toxicology study for oral naltrexone [Trexan NDA 18-932]

<sup>†</sup> AUC following 10 mg/kg orally = 0.0861 mg•hr/mL, CL = 65.7 mL/min/kg and F = 0.036. Assuming linear kinetics, the aggregate exposure over 28 days following 20 mg/kg/d can be estimated.

Naltrexone is metabolized primarily by dihydrodiol dehydrogenase, a cytosolic polymorphic family of enzymes; CYP 450 enzymes are not involved. There is no evidence that naltrexone or 6 $\beta$ -naltrexol inhibit the activity of 10 major CYP 450 isozymes to a clinically meaningful degree. Drug-drug interactions with Vivitrex microspheres were not conducted, however; based on the metabolic pathway of naltrexone, its low protein binding and lack of effect on CYP 450 isozymes, the probability of drug-drug interactions with Vivitrex administration is low. Urinary excretion is the primary route of elimination for naltrexone and its metabolites in guinea pigs, rabbits, dogs, monkeys and humans, while the fecal route of elimination predominates in the rat.

#### 2.6.4.10 Tables and figures to include comparative TK summary

### 2.6.5 PHARMACOKINETICS TABULATED SUMMARY

### 2.6.6 TOXICOLOGY

#### 2.6.6.1 Overall toxicology summary

##### General toxicology:

**Study title: Oral Toxicity Screen with Glycolide - Lactide Copolymer by Capsule Administration in Rabbits. (Study Number: \_\_\_\_\_; Sponsor Reference No: AT-09-01):**

The purpose of this test was to estimate the potential oral toxicity of lycolide/ - Lactide Copolymer by determining if the 'Approximate Lethal Dose' (ALD); to find out whether ALD is greater or less than approximately 500 mg/kg body weight. Three female rabbits ranging in weight from 2.2 to 2.3 grams were each dosed with 1 to 3 capsules.

Approximately 0.55 to 0.59 grams of test material per gelatin capsule was used. The dosing day was test day one; postexposure day 14 was test day 15.

Due to an apparent obstruction of the trachea during dosing attempts, one rabbit was killed in extremis. In this study two rabbits were treated with approximately 500 or 648 mg/kg of the test material and observed for 14 days. The test rabbits were dosed with 2 and approximately 2 2/3 capsules, respectively. Both treated rabbits showed evidence of anorexia and one rabbit lost approximately 1% of its initial body weight one day after dosing. These responses were slight and were probably due to irritation off the throat incurred during balling gun dosing or were generalized reactions to stress. They are not considered to be toxicologically significant. Generally, rabbits continued to gain body weight throughout the recovery period. They showed no adverse clinical signs of toxicity and there was no mortality. On test day 6 the feces of one rabbit was white-coated and contained crystal appearing specks. From this observation, a small amount of test material was thought to be eliminated through the gastrointestinal tract

**Study title: 1-Month Toxicokinetic Study of Medisorb® Naltrexone in Rhesus Monkeys with a 1-Month Recovery. (Study Number: — 6403-117; Sponsor Reference No: AT-21-02)**

Under the conditions of this study, a single subcutaneous administration at doses up to 200 mg/kg and intramuscular administration at a dose of 50 mg/kg Medisorb® Naltrexone to male rhesus monkeys was well tolerated. Administration of the test material by either route did not produce alterations in body weights or clinical pathology parameters or any clinical signs of toxicity. No evidence for test material-related systemic toxicity was found based upon the macroscopic or microscopic evaluations. Subcutaneous and intramuscular administration of Medisorb® Naltrexone provided an initial release phase (during the first week) followed by a sustained-release phase. Subcutaneous and intramuscular administration of Medisorb® Naltrexone provided an initial release phase (during the first week) followed by a sustained-release phase. Dose proportional increases in C<sub>max</sub> and AUC were observed after subcutaneous administration of Medisorb® Naltrexone. The mean ± SD C<sub>max</sub> values were 32 ± 8.4, 64 ± 6.4, and 265 ± 25 ng/mL for the Medisorb® Naltrexone at doses of 20, 50, and 200 mg naltrexone/kg, respectively. The corresponding subcutaneous AUC (1-month) levels were 187 ± 46, 449 ± 155, and 2115 ± 645 ng\*d/mL, respectively. Naltrexone at 50 mg naltrexone/kg resulted in a similar plasma profile, although the initial naltrexone levels were generally somewhat higher during the first week. The intramuscular C<sub>max</sub> and AUC values were 106 ± 30.0 ng/mL and 609 ± 21 ng\*d/mL. The plasma profiles of 613-naltrexol for all groups tested were parallel to the naltrexone profiles but the levels were approximately 10 to 20 times lower than the mean naltrexone values. Circulating naltrexone levels were evident in a dose-related manner after 1-month. After 2 months at the high dose (recovery), naltrexone was present in the plasma.

Subcutaneous injection sites showed a localized enlargement attributed to the presence of test material depot from immediately following dosing, through the duration of the study. When measured, these enlargements varied in size among sites [to 28 x 27 mm (length x

width)]. Intramuscular injection sites were not visible clinically. Generally, the subcutaneous injection sites were largest immediately after dosing on Day 1 and gradually became smaller during the month; the greatest decrease in size occurred during the first 4 days following dosing. Clinically, Medisorb® Naltrexone sites were similar to the placebo microsphere sites. However, placebo microsphere sites were slightly smaller in size on Day 29 compared to Medisorb® Naltrexone sites. The subcutaneous injection site of one animal given 20 mg/kg and three of three subcutaneous injection sites of one animal given 50 mg/kg were softer and swollen in appearance compared to other sites during the third and fourth weeks (to Day 29). One subcutaneous injection site of one animal given 200 mg naltrexone/kg was softer on Day 25 compared with the other sites. Microscopically, the injection sites that were noted as clinically soft and swollen were not remarkably different from the other dose sites. There was little change in the size of the subcutaneous injection sites during recovery compared with Day 29 observations. Microscopically, at the terminal sacrifice, the subcutaneous injection sites with the test material (Medisorb® Naltrexone with 20, 50, or 200 mg naltrexone/kg) and the injection sites with the control material (Medisorb® Naltrexone Placebo microspheres) were essentially similar, except for the inflammatory response and fragmentation of the microspheres. Compared to the placebo sites, the test material sites had an increased incidence and severity of inflammatory response and more fragmentation of the microspheres. All subcutaneous injection sites (control and test material) had a minimal to moderately severe fibrous response enveloping the material. A granulomatous response (macrophages and foreign body multinucleated giant cells) was also present in all groups and varied in severity from minimal to moderately severe. The intramuscular sites (Medisorb® Naltrexone with 50 mg naltrexone/kg) had an inflammatory response of similar incidence and severity to that noted in the subcutaneous test material injection sites. The intramuscular injection sites also had minimal to slight lymphoplasmacytic inflammatory response and microsphere fragmentation. All of the animals treated by intramuscular injection had minimal skeletal muscle regeneration in one or more of the dose sites. Two of the intramuscular injection sites exhibited a minimal fibrous response enveloping the injected material where the material was between muscle bundles. All injection sites had residual material at the time of evaluation.

For recovery evaluation, two animals received the subcutaneous test material at a dose of 200 mg naltrexone/kg and were on study an additional 30 days. Macroscopically and microscopically, the injection sites appeared similar to the subcutaneous injection sites at the terminal sacrifice. The subcutaneous injection sites (test material) at the recovery sacrifice had a minimal to moderate fibrous response enveloping the material. A granulomatous response (macrophages and foreign body multinucleated giant cells) was also present in all injection sites. The granulomatous inflammation varied, between injection sites and the two animals, from minimal to moderately severe. The multinucleated giant cell response was variable but was still prominent in the recovery test material-treated animals. In the recovery animals, acute inflammatory cell response was minimal and present in only one injection site. The recovery test material sites also had a minimal to moderate lymphoplasmacytic inflammatory response. No test material-related systemic effects were found in the macroscopic evaluations nor in the microscopic evaluation of the liver.

**Study title: A 3-Month Repeated-Dose Toxicokinetic Study of Medisorb® Naltrexone Administered by Subcutaneous Injection to Rhesus Monkeys, with a 3-Month Recovery Period. (Study Number: — 0944-54; Sponsor Reference No: AT-21-03)**

The purpose of this study was to evaluate the toxicokinetic profile of Medisorbe Naltrexone, a sustained release formulation of naltrexone, following repeated subcutaneous injections (every 4 weeks) to rhesus monkeys, and to evaluate recovery from any effects of the test article over a 3-month treatment-free period. On Days 1, 29, and 57, each animal was given a dose by subcutaneous injection(s) in the dorsal region. Multiple injections were needed to achieve the required dose levels. Dosages used were 20, 50, 75 mg/kg. Repeated subcutaneous administration of Medisorbe Naltrexone every 4 weeks at naltrexone doses up to 75 mg/kg for 3 months was well tolerated in rhesus monkeys and no systemic effects were evident. There were no test article-related adverse effects in clinical signs and in body weight or clinical pathology parameters. Localized enlargements were noted at the injection sites following subcutaneous administration of placebo and Medisorbo Naltrexone and these enlargements were attributed to the depot materials (up to 1.5 mL volume). Grossly, nodules were present in the placebo and all test-article injection sites at the Day 90 sacrifice, and in all control animal injection sites on Day 180. In Group 4 animals on Day 180, injection site nodules were present in only 22 of 37 injection sites and those present were smaller than were the nodules in placebo injection sites at this time. Histological changes observed in Medisorbo Naltrexone and placebo injection sites were consistent with a classic foreign body response to an injected material. In the animals sacrificed on Days 90 and 93, comparable degrees of fibrous encapsulation and granulomatous inflammation for placebo and active formulations were apparent for the Day 29 and 57 injection sites. At the Day 1 sites the same changes were slightly more severe in the active group; however this was attributed to individual animal variation and not considered a test-article effect. In animals sacrificed on Day 180, the histologic responses in injection sites from each day of dose administration were similar to, but less severe than those in animals sacrificed on Days 90 and 93. This indicated that resolution of the tissue response was progressing but was not yet complete.

Seven of the 22 animals treated with Medisorb Naltrexone had at least one clinically apparent soft/swollen and/or ruptured injection site during one or more of the treatment cycles. In most cases the reactions did not involve all injection sites in an individual animal, but in three animals, all sites were affected. The incidence or severity of these changes was not dose-related and similar changes were not recorded in the placebo group. The absence of a local dose response effect can be explained by the dosing method in which dose progression was achieved by increasing the number of injection sites, while holding individual injection volume constant. It is notable that no animals were observed to rub or scratch injection sites during the study. The changes were generally reversible and by the time of scheduled necropsy (Days 90-93), there was no clear evidence of their presence by gross examination. Microscopic examination of these sites indicated that local reactions were less than or equivalent in severity to those at other Medisorb Naltrexone sites. Anti-naltrexone antibody was detected in one control animal prior to dosing and three Medisorbe Naltrexone treated animals developed

antibodies during the course of the study. Only one of the seven animals with swelling/rupture at injection sites had this response in conjunction with detectable anti-naltrexone antibody formation. It was therefore judged that injection site swelling/rupture was not precipitated by an immune response to the formulation. It was concluded that Medisorbe Naltrexone subcutaneous injection sites in monkeys were more susceptible to swell/rupture than placebo sites, and that mere presence of the formulation was not sufficient to produce the effect. The occurrence of anti-Naltrexone antibodies in 3 of 22 Medisorbe Naltrexone treated animals (13.6%) was not considered to have adversely impacted the study since toxicokinetic data did not indicate that antibody interfered with drug exposure. Dose- related increases were observed in AUC and C<sub>max</sub> for naltrexone and the metabolite, 6β-naltrexol. C<sub>max</sub>, and AUC values tended to be larger in male monkeys compared to female monkeys, however, the small number of animals involved in the study prevented meaningful statistical comparisons. Repeat dosing resulted in a slight accumulation of naltrexone. Predose concentrations were measurable in most animals prior to receiving the second dose on Day 28, however, concentrations collected prior to the third dose and 28 days after the third dose did not increase further. The shape of the plasma concentration-time profiles of 6β-naltrexol for all groups were similar to the naltrexone profiles but the mean concentrations of 6β-naltrexol were about 10-times lower than the mean naltrexone values. 6β-naltrexol exposure increased with increasing dose. As observed with naltrexone, slight accumulation of 6β-naltrexol was observed prior to the second dose, which did not increase further.

**Study title: 90-Day, Three Repeat Dose Subcutaneous-Toxicity Study of Medisorb® Naltrexone (VIVITREX) in Rats (Study Number: N103485; Sponsor Reference No: AT-21-08)**

The purpose of study was to evaluate the safety of Vivitrex microspheres following repeated subcutaneous administration to rats over a period of 90 days [3 monthly dosing, (0, 25, 100 mg/kg), cycles].

Three, once-per-month injections were well tolerated for all dose groups. One early death in animal #203 on Day 11 was due to a urinary tract obstruction. Clinical observations of swelling at each of the injections sites over the course of the study were attributed to the microspheres in the formulation and not naltrexone. No naltrexone-related changes were noted in body weight or clinical pathology parameters. Administration of Medisorb Naltrexone or placebo subcutaneously to groups of rats on Days 1, 30 and 58 did not result in any microscopic necropsy treatment-related systemic toxicity findings other than inflammation at the injection sites. This finding was observed in the Medisorb Naltrexone and placebo groups in approximately equal incidence and severity. Thus, inflammation at these injection sites was attributed to the polymer microspheres toxicity.

**Study title: An Acute Local Tolerance Study of Vehicles Administered Subcutaneously to Rabbits (Study Number: A 074-716 Sponsor Reference No: AT-03-09)**

The study was done to determine the local tolerability of two different formulations of \_\_\_\_\_ vehicle when administered subcutaneously to rabbits. The test articles were \_\_\_\_\_ vehicle 1 \_\_\_\_\_ Tween® 20, \_\_\_\_\_ NaCl) and \_\_\_\_\_ vehicle 2 ( \_\_\_\_\_ carboxymethyl cellulose, \_\_\_\_\_ Tween® 20, \_\_\_\_\_ NaCl. Administration of the \_\_\_\_\_ vehicles 1 and 2 by subcutaneous injection was well tolerated. The in-life observations included of injection site discoloration, occasional slight to mild erythema, and swelling which the Sponsor considered to be physically induced by the subcutaneous injection of a 2 ml volume and not to be related to the test materials. Histopathologically, both vehicles induced a relatively weak mixed local inflammatory cell response without necrosis or fibrosis, with slightly more marked inflammation being associated with \_\_\_\_\_ vehicle 2. The local inflammatory infiltration reached a maximum in each vehicle-treated group on Day 5 and sustained upto Day 8.

**Study title: An Acute Local Tolerance Study of \_\_\_\_\_ Formulations \_\_\_\_\_ and \_\_\_\_\_ Administered Subcutaneously to Rabbits. (Study Number: \_\_\_\_\_ A071-716; Sponsor Reference No: AT-07-01):**

Administration of the \_\_\_\_\_ formulations \_\_\_\_\_ and \_\_\_\_\_ by subcutaneous injection was well tolerated. No adverse effects on body weights or clinical observations were seen and no treatment-related erythema occurred. The in-life observations of local enlargement seen immediately following injection of \_\_\_\_\_ formulations and lasting through Day 8 of the study were considered to be due to the presence of the test material and not a local tissue reaction. When present, the grossly observable findings of red or white foci corresponded to hemorrhage or the presence of the \_\_\_\_\_ formulations, respectively. Microscopically, the two \_\_\_\_\_ formulations within the subcutaneous sites were indistinguishable. At Day 4, the local response consisted of heterophilic inflammation. However, by Day 8, it was compounded by granulomatous inflammation in which increased numbers of giant cells, focal/multifocal fibrosis and fibroblast proliferation were all present. With neither \_\_\_\_\_ formulation was there evidence of tissue necrosis. Compression of preexisting collagen seen in 11 of 12 sites at Day 4 persisted and was present in all 12 sites at Day 8. New collagen formation that was limited to 5 of 8 \_\_\_\_\_ formulation sites at Day 4 had progressed and was present in all 8 \_\_\_\_\_ formulation injection sites at Day 8. The degree of new collagen formation was indistinguishable between sites and never graded higher than mild. The conclusion of the study was that subcutaneous administration of \_\_\_\_\_ and \_\_\_\_\_ was well tolerated in rabbits. There was no clinically detectable local irritation at the injection sites. Macroscopic and microscopic responses at the subcutaneous injection sites appeared similar with both polymers.

**Study title: Development of Drug Delivery System (Study Number: \_\_\_\_\_ 89G-0102; Sponsor Reference No: AT-07-03):**

Sprague-Dawley male rats were given implants (1x5 mm disc) and subcutaneous injections (100 mg/ml and 0.3 ml was injected) of Test Article I ( \_\_\_\_\_ ) or Test Article II

The tissue responses such as chronic inflammation, layer of mild tissue granulation around implant sites and phagocytic response were common reactions observed in histopathology. Similarly, the histopathological examination of implants of the test article spheres of \_\_\_\_\_, exhibited granulation of tissues at implant sites, fibrosis, and inflammation of tissues similar to the earlier test article. The observed tissue reaction from test article disc of Poly \_\_\_\_\_ lactide-CO-glycolide and spheres of Poly \_\_\_\_\_ lactide -CO-glycolide) demonstrated similar tissue responses, as narrated earlier. The control implant sites for discs and spheres showed tissue responses similar to the test articles. The histopathology has indicated the presence of bland local responses to implantation and subcutaneous injection of both test articles with no evidence of undue necrosis or inflammation.

**Study title: Local Tolerance Study of Medisorb® Naltrexone in Rabbits Following Single Subcutaneous and Intramuscular Injections (Study Number: \_\_\_\_\_ 6403-118 Sponsor Reference No: AT-21-01)**

The study was done to assess the local tolerance for Medisorb® Naltrexone when administered as a single dose by subcutaneous and intramuscular injections to rabbits. Male Hra:(NZW)SPF rabbits (approximately 16 weeks old and weighing from 3.053 to 3.529 kg; were used for the study. The test material (Medisorb® Naltrexone; Lot No. 190-0292A) contained approximately 322 mg Medisorb® Naltrexone (approximately 114 mg naltrexone based on 35.5% drug load) and the control material (Medisorb®).

The subcutaneous injection of both the test material and the control material microspheres resulted in predominate microscopic findings of granulomatous inflammation and a fibrous response enveloping the residual test or control material and active fibroblast hyperplasia at Day 8 and at Day 30. At Day 30, the test material site had minimal to slight lymphoplasmacytic inflammation in four of five animals. The intramuscularly administered test and control materials were located in all of the microscopic sections with the exception of the control material section. The predominant finding was slight to moderately severe granulomatous inflammation and occasional minimal fibroblast hyperplasia. At Day 8, minimally to moderately severe muscle degeneration from necrosis (regeneration for a single control material site), minimal to slight edema, and minimal hemorrhage were also noted. At Day 30, the test material sites of all five animals had minimal to slight muscle regeneration and minimal to slight lymphoplasmacytic inflammation. Microscopically, the residual test and control material at both the subcutaneous and intramuscular sites consisted of spherical structures that sometimes contained refractile material in the processed section. The subcutaneous and intramuscular test material sites and one intramuscular control material site also had fragmentation of the spherical structures.

Under the conditions of this study, subcutaneous injections of Medisorb® Naltrexone, Medisorb® Placebo Microspheres, and \_\_\_\_\_ Diluent and the intramuscular injection of Medisorb® Naltrexone and Medisorb® Placebo Microspheres to male albino rabbits were well tolerated.

**Study title: Chronic Local Tolerance Study of Medisorb® Naltrexone in Rabbits Following Single Subcutaneous and Intramuscular Injections (Study Number: — 6403-119; Sponsor Reference No: AT-21-04)**

The purpose of this study was to assess the potential local tolerance of Medisorb Naltrexone following a single dose by subcutaneous and intramuscular injections to rabbits. Male rabbits were administered Medisorb Naltrexone at 195 and 293 mg/dose via the subcutaneous and intramuscular route of administration, respectively. Each animal received two subcutaneous treatments (A and B) at sites distant to each other and two intramuscular treatments, one on each leg. Five animals from each treatment regimen were sacrificed at each of the designated times (Days 8, 30, 89, 150, and 240).

All animals survived to the respective scheduled sacrifice interval. All clinical findings were considered incidental, unrelated to the test or control materials, and are commonly seen in animals of this age. During the in-life phase no erythematous reactions were observed at the — Diluent injection sites. Subcutaneous and intramuscular injection of Medisorb Naltrexone or Medisorb Naltrexone Placebo Microspheres resulted in a few instances of very slight erythematous reactions at the injection sites which were evident only during the first week. Local enlargements at the subcutaneous injection sites (due to the depot microspheres) were observed. These enlargements gradually decreased in size for animals sacrificed from Days 89 to 240. Local enlargements at the intramuscular injection sites were not observed except in occasional animals that received placebo microspheres. These enlargements occurred between Days 113 to 151, subsequently were not observed, and did not result in any treatment-related clinical effects.

The Medisorb Naltrexone sites had a similar macroscopic appearance to the placebo sites at all sacrifice intervals. The amount of residual test or placebo material at the treatment sites was noticeably less at the Day 240 sacrifice when compared to the earlier sacrifice intervals. This residual material generally had a light colored appearance (tan to white) at the subcutaneous and intramuscular injection sites. There were also instances of red, dark or mottled focal areas at the subcutaneous and intramuscular injection sites. The — Diluent subcutaneous and intramuscular injection sites had no treatment-related macroscopic findings. There were no macroscopic findings in the untreated skin and muscle tissues.

Microscopically, the subcutaneous and intramuscular injection sites for Medisorb Naltrexone had a similar appearance to those same sites treated with the placebo formulation. The Medisorb Naltrexone and Placebo Microspheres were readily identified at each sacrifice interval as refractile and occasionally fragmented spherical structures that were generally surrounded by a variable fibrous response and granulomatous inflammation. The severity grade of the local inflammatory response at the Medisorb Naltrexone and Placebo sites was initially low (minimal to moderate at 1 -week postdose) and exhibited a peak reaction at 1 and 3 months postdose (minimal to moderately severe). The inflammatory response gradually lessened after 3 to 5 months.

By 8 months, the inflammatory response was either not existent or significantly less than that present at 5 months. The residual materials were apparently degraded, in that, by the 8-month sacrifice, there was either no or very little microsphere material remaining (present as macrophage intracytoplasmic foreign material). The test and placebo subcutaneous injection sites often had some residual fibrous connective tissue present in close proximity to the remaining foreign material. At Day 240, other than minimal residual fibrous connective tissue at one placebo and one Medisorb Naltrexone intramuscular injection site, there was no fibrosis present in the intramuscular sites.

**Study title: Local Tolerance and Pharmacokinetic Evaluation of Medisorb® in Dogs Following Repeated Intramuscular Injections (Study Number: 6403-121; Sponsor Reference No: AT-21-05)**

The purpose of this study was to assess the local tolerance of Medisorb after repeated intramuscular administrations in dogs at a dose volume similar to the proposed clinical dose. Local tolerance was also evaluated when a series of up to three doses of Medisorb were administered at closely spaced sites in the same muscle mass.

Just prior to dosing, Medisorb microspheres were suspended in diluent at an approximate concentration of 286 mg/mL. Each dose site was uniquely identified. Animals in Group 1 received one dose on Day 1 in the right leg and the second dose on Day 30 in the left leg. Animals in Groups 2, 3 and 4 received their first dose in the right leg on Day 1 and each successive dose was delivered at, or in close proximity to, the first injection site in the right leg. Groups 2 and 3 received a second dose on Days 30 and 60, respectively. Group 4 received a second and third dose on Days 60 and 120, respectively.

The inlife observations and evaluations used to assess toxicity included mortality and moribundity checks, postdose clinical observations, body weights, and injection site observations. Plasma samples were collected for pharmacokinetic evaluation from animals in Groups 1 and 2 up to Day 120.

When unexpected injection site swelling occurred after the first injection, an additional interim sacrifice with pathologic evaluation was conducted on two animals on Day 18. All other sacrifices were conducted as scheduled on Day 14 and 6 months after the second or third dosing. Exposure to Medisorb was evident in Group 1 and 2 dogs following the first injection. No significant differences were observed for the C<sub>max</sub> and AUC values. On Day 30, prior to the second dose, naltrexone levels were either not detectable (<0.2 ng/mL) or not greater than 1.30 ng/mL. Following the second dose, naltrexone levels were generally not detectable after about 7 weeks post-dose. The concentrations of 6β-naltrexol were all below or near the limit of quantitation of the assay. Treatment-related findings consisted of an injection site reaction characterized primarily by a localized swelling that was clinically evident in all animals after each dosing. In addition, skin erythema was noted at some injection sites after each dosing. After a single dose, the injection site reactions were most severe between 1 to 3 weeks post-dose. The reactions gradually subsided in all cases. After 2 months, most injection