

Date of Index Listing: November 3, 2016

FREEDOM OF INFORMATION SUMMARY

ORIGINAL REQUEST FOR ADDITION TO THE INDEX OF LEGALLY MARKETED UNAPPROVED NEW ANIMAL  
DRUGS FOR MINOR SPECIES

MIF 900-003

TREXONIL

(naltrexone hydrochloride)

Captive non-food-producing minor species hoof stock

"For use as an antagonist to THIANIL (thiafentanil oxalate) immobilization of captive minor species hoof stock excluding any member of a food-producing minor species such as mule deer, elk, or bison and any minor species animal that may become eligible for consumption by humans or food-producing animals."

Requested by:

Wildlife Pharmaceuticals, Inc.

**TABLE OF CONTENTS**

I. GENERAL INFORMATION: .....1

II. EFFECTIVENESS AND TARGET ANIMAL SAFETY: .....1

    A. Findings of the Qualified Expert Panel: .....2

    B. Literature Considered by the Qualified Expert Panel: .....3

III. USER SAFETY: .....5

IV. AGENCY CONCLUSIONS: .....5

    A. Determination of Eligibility for Indexing: .....5

    B. Qualified Expert Panel: .....6

    C. Marketing Status: .....6

    D. Exclusivity: .....6

    E. Attachments: .....6

**I. GENERAL INFORMATION:**

<b>A. File Number:</b>	MIF 900-003
<b>B. Requestor:</b>	Wildlife Pharmaceuticals, Inc. 1230 W. Ash Street, Suite D Windsor, CO 80550
<b>C. Proprietary Name(s):</b>	TREXONIL
<b>D. Established Name(s):</b>	Naltrexone hydrochloride
<b>E. Pharmacological Category:</b>	Opioid antagonist
<b>F. Dosage Form(s):</b>	Injectable solution
<b>G. Amount of Active Ingredient(s):</b>	50 mg naltrexone hydrochloride/mL
<b>H. How Supplied:</b>	20 mL clear glass vials
<b>I. How Dispensed:</b>	By prescription (Rx)
<b>J. Dosage(s):</b>	10 mg TREXONIL for each mg of THIANIL (thiafentanil oxalate) previously administered
<b>K. Route(s) of Administration:</b>	Intramuscular (IM) injection; or ¼ dose by intravenous injection (IV) and ¾ dose by IM injection
<b>L. Species/Class(es):</b>	Captive non-food-producing minor species hoof stock
<b>M. Indication(s):</b>	For use as an antagonist to THIANIL (thiafentanil oxalate) immobilization of captive minor species hoof stock excluding any member of a food-producing minor species such as mule deer, elk, or bison and any minor species animal that may become eligible for consumption by humans or food- producing animals.

**II. EFFECTIVENESS AND TARGET ANIMAL SAFETY:**

In accordance with 21 CFR part 516, a qualified expert panel evaluated the target animal safety and effectiveness of TREXONIL, for use as an antagonist to THIANIL (thiafentanil oxalate) immobilization of captive minor species hoof stock excluding any member of a food-producing minor species such as mule deer, elk, or bison and any minor species animal that may become eligible for consumption by humans or food-producing animals, to determine whether the benefits of using TREXONIL for the proposed use outweigh the risks to the target animals. The members of the qualified expert panel were:

Scott Citino, DVM, Diplomate, ACZM (Panel Leader), White Oak Conservation Center;  
David Kenny, VMD, Denver Zoological Foundation;  
David Jessup, DVM, Diplomate, ACZM, California Department of Fish and Game, The Marine Wildlife Veterinary and Research Center.

**A. FINDINGS OF THE QUALIFIED EXPERT PANEL:**

Based on a thorough review of the literature and their own personal experience, the qualified expert panel concluded that the benefits of using TREXONIL, for use as an antagonist to THIANIL (thiafentanil oxalate) immobilization of captive minor species hoof stock excluding any member of a food-producing minor species such as mule deer, elk, or bison and any minor species animal that may become eligible for consumption by humans or food-producing animals, outweigh the risks to the target animals.

The qualified expert panel report states that naltrexone has been the drug of choice for antagonizing the opioid effects of etorphine hydrochloride, carfentanil citrate, and fentanyl citrate, all potent opioids similar to thiafentanil, in minor species hoof stock for many years. Naltrexone is a cyclopropyl derivative of oxymorphone with the chemical name 17-(cyclopropylmethyl)-4,5-epoxy-3,14 dihydroxy-morphinan-6-one hydrochloride. It is structurally similar to naloxone and nalorphine and is metabolized by the liver. The qualified expert panel notes that naltrexone has minimal to undetectable agonist properties which supports its safe use as an opioid reversal agent. It is reported to be 2 to 3 times more potent than naloxone and 40 times more potent than nalorphine. (Kreeger and Arnemo, 2007; Raath).

Renarcotization is a safety concern when immobilizing animals with a potent opioid. The qualified expert panel states that they have not observed renarcotization following reversal of thiafentanil with naltrexone and it has also not been reported in the literature. The lack of renarcotization has been attributed to the antagonist activity of the liver metabolite 6beta-naltrexol (Porter *et al*, 2002). The qualified expert panel believes that this may explain the excellent reversal results seen in species such as eland and rhinoceros which are prone to renarcotization. Naltrexone was used to reverse opioid immobilization in 166 minor species hoof stock at the San Diego Zoo Wild Animal Park with no incidences of renarcotization, while the rates for renarcotization for nalmefene were 10.6% and 5.3% for diprenorphine (Allen, 1989). The qualified expert panel states that using naltrexone to reverse thiafentanil immobilization provides an added safety margin because renarcotization can be fatal in animals that cannot be observed for the entire recovery period.

The qualified expert panel agrees with the proposed dosage of 10 mg naltrexone for each milligram of thiafentanil previously administered. Based on personal experience and literature, the qualified expert panel states that the entire calculated dose can be safely administered by intramuscular injection. Dysphoria, hyperexcitation, and extrapyramidal effects have been observed by members of the qualified expert panel when opioid antagonists, such as naltrexone, are administered intravenously. These adverse effects have not been observed after intramuscular injection. In the case of an anesthetic emergency (extreme respiratory depression or cardiac arrest), the qualified expert panel states that a portion of the calculated dose may be given intravenously to shorten recovery time. To reduce the risk of adverse effects while

still allowing for faster recovery, the qualified expert panel recommends that  $\frac{1}{4}$  of the dose of naltrexone be administered intravenously and  $\frac{3}{4}$  of the dose be administered intramuscularly. Recovery time after thiafentanil immobilization ranged from 0.8 to 1.7 minutes when using a  $\frac{1}{4}$  intravenous to  $\frac{3}{4}$  intramuscular administration of naltrexone in multiple species of hoof stock in Kruger National Park, South Africa (Raath). In the experience of the qualified expert panel, recovery following intramuscular administration of naltrexone should take 3 to 5 minutes.

The qualified expert panel reviewed literature reporting successful reversal of thiafentanil immobilization with naltrexone when thiafentanil was administered as a single agent and when thiafentanil was administered concurrently with other sedatives, tranquilizers, or neuroleptics. They state that opioid reversals with naltrexone have been described in the literature as: rapid, effective, controlled, complete, stable, alert, no complications, no obvious stress, no recovery hyperthermia, and no reanarcotizations. Animal species reported in the literature include: elk, pronghorn, impala, African buffalo, eland, greater kudu, white rhino, African elephant, waterbuck, warthog, lechwe, and nyala. Each of the qualified expert panel members has extensive experience successfully using naltrexone to reverse immobilization induced by thiafentanil and similar potent opioids. In addition, all of the panel members consider it to be the drug of choice for reversing the opioid effects of thiafentanil.

The qualified expert panel concluded their report by stating that there is a critical shortage of safe and efficacious immobilization agents for minor species hoof stock, and for safe, long-lasting reversal agents. The rapid reversal provided by naltrexone when given intramuscularly means that immobilized animals can be recovered safely and quickly. This is also a benefit if there is an anesthetic emergency requiring rapid recovery of the patient. Intramuscular injection results in increased respiratory rate within 1 to 2 minutes and arousal shortly thereafter. Intravenous administration can result in almost instantaneous arousal and, in the opinion of the qualified expert panel, should be reserved for life-threatening conditions (respiratory or cardiac arrest).

The result of the qualified expert panel's risk-benefit analysis was a unanimous conclusion that TREXONIL is safe and effective for use as an antagonist to THIANIL (thiafentanil oxalate) immobilization of captive minor species hoof stock excluding any member of a food-producing minor species such as mule deer, elk, or bison and any minor species animal that may become eligible for consumption by humans or food-producing animals. The qualified expert panel also recommended that TREXONIL be marketed by prescription of a licensed veterinarian.

#### **B. LITERATURE CONSIDERED BY THE QUALIFIED EXPERT PANEL:**

1. Alcantar BE, McLean M, Chirife AD, Lohe T, Bennett JP, Ortiz JJ. Immobilization of Tibetan yak (*Bos gunnies*) using A3080 (Thiafentanil) and xylazine in a wildlife park. *Proc. Conf. Amer. Assoc. Zoo Vet.* 2007: 47-48.
2. Allen, JL. Renarcotization following carfentanil immobilization of nondomestic ungulates. *J. Zoo Wildl. Med.* 1989, 20(4): 423-426.
3. Citino SB, Bush M, Grobler D, and Lance W. Anaesthesia of roan antelope (*Hippotragus equinus*) with a combination of A3080, medetomidine and ketamine. *J. S. Afr. Vet. Assoc.* 2001, 72(1): 29-32.

4. Citino SB, Bush M, Grobler D, Lance W. Anesthesia of boma-captured Lichtenstein's hartebeest (*Simoceros lichtensteinii*) with a combination of thiafentanil, medetomidine, and ketamine. *J. Wildl. Dis.* 2002, 38(2): 457-462.
5. Citino SB, Bush M, Lance W, Hofmeyr M, Grobler D. Use of thiafentanil (A3080), medetomidine and ketamine for anesthesia of captive and free-ranging giraffe (*Giraffa camelopardalis*). *Proc. Conf. Amer. Assoc. Zoo Vet.* 2006, 211-212.
6. Cooper DV, Grobler D, Bush M, Jessup D, Lance W. Anesthesia of nyala (*Tragelaphus angasi*) with a combination of thiafentanil (A3080), medetomidine and ketamine. *J. S. Afr. Vet. Assoc.* 2005, 76(1): 18-21.
7. Fowler, ME, and RE Miller. *Zoo and Wild Animal Medicine: Current Therapy*, 6th ed. Saunders Elsevier, St. Louis, Missouri, 2008. Print.
8. Grobler D, Bush M, Jessup D, Lance W. Anaesthesia of gemsbok (*Oryx gazelle*) with a combination of A3080, medetomidine and ketamine. *J. S. Afr. Vet. Assoc.* 2001, 72(2): 81-83.
9. Heard, DJ, ed. *The Veterinary Clinics of North America, Exotic Animal Practice: Analgesia and Anesthesia*. W.B. Saunders, Co., Philadelphia, Pennsylvania, 2001. Print.
10. Herbert J, Lust A, Fuller A, Maloney SK, Mitchell D, Mitchell G. Thermoregulation in pronghorn antelope (*Antilocapra americana*) in winter. *J. Exper. Bio.* 2008, 211(5): 749-756.
11. Janssen DL, Swan GE, Raath JP, McJames SW, Allen JL, de Vos V, Williams KE, Anderson JM, Stanley TH. Immobilization and physiologic effects of the narcotic A-3080 in impala (*Aepyceros melampus*). *J. Zoo Wildl. Med.* 1993, 24: 11-18.
12. Jessup DA, Clark WE, Jones KR, Clark R, and Lance WR. Immobilization of free-ranging desert bighorn sheep, tule elk, and wild horses, using carfentanil and xylazine: reversal with naloxone, diprenorphine, and yohimbine. *J Amer. Vet. Med. Assoc.* 1985, 187(11): 1253-2154.
13. Kock MD, Meltzer D, and Burrows R, eds. *Chemical and Physical Restraint of Wild Animals: A Training and Field Manual for African Species*, 1<sup>st</sup> ed. IWVS (Africa), PO Box 106, Greyton 7233, South Africa, 2009. Print.
14. Kreeger, TJ and Arnemo JM. *Handbook of Wildlife Chemical Immobilization*, 3<sup>rd</sup> ed. [tkreeger@starbrand.net](mailto:tkreeger@starbrand.net) or Amazon.com, 2007. Print.
15. Porter SJ, Somogyi AA and White JM. In vivo and in vitro potency studies of 6beta-naltrexol, the major human metabolite of naltrexone. *Addiction Biology*, 7(2): 219-225.
16. Pye GW, Citino SB, Bush M, Klein L, Lance WR. Anesthesia of eastern giant eland (*Taurotragus derbianus gigas*) at White Oak Conservation Center. *Proc. Conf. Amer. Assoc. Zoo Vet.* 2001, 226-231.
17. Raath, JP. Clinical Expert Report: The Use of Naltrexone Hydrochloride (Trexonil) as a Reversal Agent for Morphine Derivative Anaesthesia in Non-Domestic Species.
18. Schmitt, SM, and WJ Dalton. Immobilization of moose by carfentanil and xylazine and reversal by naltrexone, a long-acting antagonist. *Alces*, 23: 195-219.
19. Smith KM, Powell DM, James SB, Calle P, Moore RP, Zurawka HS, Goscilo S, and Raphael BL. Anesthesia of male axis deer (*Axis axis*): evaluation of thiafentanil,

medetomidine, and ketamine versus medetomidine and ketamine. *J. Zoo Wildl. Med.* 2006, 37(4): 513-517.

20. Stanley TH, McJames SW, Kimball J, Port JD, Pace NL. Immobilization of elk with A-3080. *J. Wildl. Mgmt.* 1988: 577-581.
21. Tranquilli WJ, Thurmon JC, Grimm KA, eds. *Lumb & Jones, Veterinary Anesthesia and Analgesia*, 4<sup>th</sup> ed. Blackwell Publishing, Ames, Iowa, 2007. Print.
22. Wolfe LL, Lance, WR, Miller MW. Immobilization of mule deer with thiafentanil (A-3080) or thiafentanil plus xylazine. *J. Wildl. Dis.* 2004, 40(2): 282-287.

### **III. USER SAFETY:**

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to TREXONIL:

Not for use in humans. Keep out of the reach of children. Care should be taken to avoid accidental human exposure. If accidental self-injection occurs, call a physician immediately. A reaction may occur at the injection site which can be severe. If accidental ingestion occurs, contact a physician. Do not induce vomiting unless directed to do so by medical personnel. Avoid direct contact with skin and eyes. In cases of accidental skin exposure, wash area with soap and water and get medical attention if irritation develops. In cases of accidental eye exposure, flush with copious amounts of water for at least 15 minutes and get medical attention if irritation develops.

### **IV. AGENCY CONCLUSIONS:**

The information submitted in support of this request for TREXONIL for addition to the Index of Legally Marketed Unapproved New Animal Drugs for Minor Species (Index) for the following intended use satisfies the requirements of section 572 of the Federal Food, Drug, and Cosmetic Act and 21 CFR part 516:

For use as an antagonist to THIANIL (thiafentanil oxalate) immobilization of captive minor species hoof stock excluding any member of a food-producing minor species such as mule deer, elk, or bison and any minor species animal that may become eligible for consumption by humans or food-producing animals.

#### **A. DETERMINATION OF ELIGIBILITY FOR INDEXING:**

As part of the determination of eligibility for inclusion in the Index, FDA determined that the drug for this intended use was safe to the user, did not individually or cumulatively have a significant effect on the human environment, and that the description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of the new animal drug was sufficient to demonstrate that the requestor has established appropriate specifications for the manufacture of the new animal drug. Additionally, the requestor has committed to manufacture the drug in accordance with current good manufacturing practices (cGMP).

The Index is only available for new animal drugs intended for use in minor species for which there is a reasonable certainty that the animal or edible products from the animal will not be consumed by humans or food-producing animals and for new animal drugs intended for use only in a hatchery, tank, pond, or other similar contained man-

made structure in an early, non-food life stage of a food-producing minor species, where safety for humans is demonstrated in accordance with the standard of section 512(d) of the act. Because this new animal drug is not intended for use in food-producing animals, FDA did not require data pertaining to drug residues in food (i.e., human food safety) for granting this request for addition to the Index.

**B. QUALIFIED EXPERT PANEL:**

The qualified expert panel for TREXONIL met the selection criteria listed in 21 CFR 516.141(b). The panel satisfactorily completed its responsibilities in accordance with 21 CFR part 516 in determining the target animal safety and effectiveness of TREXONIL for use as an antagonist to THIANIL (thiafentanil oxalate) immobilization of captive minor species hoof stock excluding any member of a food-producing minor species such as mule deer, elk, or bison and any minor species animal that may become eligible for consumption by humans or food-producing animals.

**C. MARKETING STATUS:**

TREXONIL will be marketed by prescription.

**D. EXCLUSIVITY:**

Products listed in the Index do not qualify for exclusive marketing rights.

**E. ATTACHMENTS:**

Facsimile Labeling:

20 mL bottle