Date of Index Listing: June 16, 2016

FREEDOM OF INFORMATION SUMMARY

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

MIF 900-000

THIANIL

(thiafentanil oxalate)

Captive non-food-producing minor species hoof stock

"For immobilization of captive minor species hoof stock excluding any member of a food-producing minor species such as 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:

A. File Number:	MIF 900-000
B. Requestor:	Wildlife Pharmaceuticals, Inc. 1230 W. Ash Street, Suite D Windsor, CO 80550
C. Proprietary Name(s):	THIANIL
D. Established Name(s):	Thiafentanil oxalate
E. Pharmacological Category:	Opioid agonist
F. Dosage Form(s):	Injectable solution
G. Amount of Active Ingredient(s):	10 mg thiafentanil oxalate/mL
H. How Supplied:	10 mL clear glass vials
I. How Dispensed:	By prescription (Rx) as a Schedule II controlled substance
J. Dosage(s):	Dependent on species, weight, and condition of the animal. Dose range is 1 mg to 15 mg total dose.
K. Route(s) of Administration:	Intramuscular
L. Species/Class(es):	Captive non-food-producing minor species hoof stock
M. Indication(s):	For immobilization of captive minor species hoof stock excluding any member of a food-producing minor species such as 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 THIANIL, for immobilization of captive minor species hoof stock excluding any member of a food-producing minor species such as 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 THIANIL 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, review of clinical studies, and their own personal experience, the qualified expert panel concluded that the benefits of using THIANIL for immobilization of captive minor species hoof stock excluding any member of a food-producing minor species such as 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 opioids are the preferred class of drug for immobilization of minor species hoof stock. Thiafentanil, 4-(methoxycarbonyl)-4-(N-phenmethoxyacetamido)-1-[2-(thienyl)ethyl]piperidium, is a synthetic derivative of fentanyl and is structurally related to sufentanil and carfentanil. Thiafentanil is registered in South Africa and has been widely used in that country as an immobilization agent for captive and wild hoof stock. Also, each of the qualified expert panel members has extensive experience with the immobilization of minor species hoof stock and has successfully used THIANIL in multiple species. Based on the literature and their own personal experience, the qualified expert panel states that thiafentanil has a shortened induction time while retaining equivalent agonist activity when compared to carfentanil citrate and etorphine HCl (Alcantar *et al*, 2007; Citino *et al*, 2002; Cooper *et al*, 2005; Kreeger and Arnemo, 2007; Fowler and Miller, 2008; Stanley *et al*, 1989; Tranquilli *et al*, 2007). Thiafentanil appears to not only be more rapidly absorbed, but also more rapidly metabolized, reducing the incidence of opioid renarcotization (McJames *et al*, 1993).

The qualified expert panel reviewed the findings of five clinical studies to assess the target animal safety and effectiveness of thiafentanil oxalate as an immobilization agent in minor species hoof stock. A brief summary of the findings of each study are provided below:

Study 1: In this study, 44 impala were immobilized with thiafentanil oxalate in Kruger National Park, South Africa to determine the effective dose range and to evaluate the physiologic effects of the drug. Nine impala were immobilized with carfentanil citrate as a positive control. Heart rate, respiratory rate, blood pressure, and relative blood oxygen saturation were measured during immobilization. Mild hypertension and initial, mild tachycardia were noted with thiafentanil immobilization. The effective dose of thiafentanil oxalate to immobilize 90% of the impala (ED_{90}) within 3 minutes was 80.7 µg/kg bodyweight, similar to the ED_{90} for carfentanil citrate of 68.8 µg/kg bodyweight and with no significant differences in the observed outcomes. The study animals were reversed with either diprenorphine or naltrexone hydrochloride, recognized mu opioid antagonists. Both antagonists provided rapid reversal of thiafentanil oxalate and no renarcotization occurred within 24 hours of reversal.

Study 2: This study involved multiple wild hoof stock species and was conducted in Kruger National Park, South Africa. All animals were immobilized with thiafentanil oxalate by dart. Species included in the study were: African buffalo, waterbuck, kudu, eland, African elephant, and rhinoceros. Once recumbent, body temperature,

mean arterial pressure, respiratory rate, heart rate, and blood oxygen saturation were measured every 5 minutes. After 20 minutes of immobilization and monitoring, the animals were reversed with naltrexone hydrochloride and observed until standing. The following dosages of thiafentanil oxalate and induction times were recorded: African buffalo 17-37 µg/kg bodyweight, mean induction time 3.6 ± 0.5 minutes; kudu 37-120 µg/kg bodyweight, mean induction time 3.6 ± 1.6 minutes; eland 37-110 µg/kg bodyweight, mean induction time 4.1 ± 2.3 minutes; waterbuck 34-43 µg/kg bodyweight, mean induction time 2.4 ± 1.6 minutes; rhinoceros 4 mg total dose, mean induction time 5.6 ± 1.4 minutes; and African elephant 15-40 mg total dose, mean induction time 6.4 ± 2.1 minutes. A mild increase in body temperature was noted in the study animals, but no treatment was necessary. The heart rates and respiratory rates of the study animals remained within acceptable limits. Blood oxygen saturation levels remained at acceptable levels, except for the rhinoceros which had lower levels of oxygen saturation. However, this is a common finding when immobilizing this species with a potent mu opioid. In two of the species, rhinoceros and kudu, mean arterial pressure was high, but no treatment to reduce the blood pressure was indicated. All animals recovered after being given the reversal agent and no renarcotization occurred.

Study 3: This study was conducted in several parks in South Africa and included multiple species of wild hoof stock. All animals were immobilized with thiafentanil by dart and reversed with naltrexone hydrochloride. Species included in the study were: Nile lechwe, nyala, sable antelope, white rhinoceros, waterbuck, African buffalo, and roan antelope. Once recumbent, body temperature, heart rate, respiratory rate, and blood oxygen saturation were measured approximately every 5 minutes. Body weight was also measured for the smaller animals (less than 100 kg) and estimated for the larger animals. The following dosages of thiafentanil oxalate and induction times were recorded: Nile lechwe 47.85 ± 7 µg/kg bodyweight, mean induction time 2 minutes 35 seconds ± 17 seconds; nyala 115.88 ± 13.47 µg/kg bodyweight, mean induction time 3 minutes 14 seconds ± 1 minute; sable antelope 29.38 ± 2.5 µg/kg bodyweight, mean induction time 2 minutes 40 seconds ± 32 seconds; white rhinoceros 2-3 µg/kg bodyweight , mean induction time 4 minutes 45 seconds ± 1.4 minutes; waterbuck 24.41 µg/kg bodyweight, mean induction time 2 minutes 12 seconds ± 49 seconds; African buffalo 11-14 µg/kg bodyweight, mean induction time 3 minutes ± 1 minute; roan antelope 26.27 µg/kg bodyweight, mean induction time 2 minutes 45 seconds ± 1 minute 7 seconds. A mild increase in heart rate was noted in the Nile lechwe while a progressive decrease in heart rate was seen in the sable and African buffalo, however the heart rate remained within acceptable limits in all study animals. The body temperature and respiratory rate remained within acceptable limits for each species of study animal. Blood oxygen saturation levels were consistent and remained within acceptable levels, except in the rhinoceros which had lower oxygen saturation levels. All study animals recovered after reversal and no renarcotization occurred.

Studies 4 and 5: Two studies were conducted in captive elk in Utah. Even though use of THIANIL, as an indexed product, is prohibited in food-producing species such as elk, the qualified expert panel reviewed the results of these two studies to support the determination of safety and effectiveness of the product in non-food species. The first study was conducted at two locations and included 21 elk immobilized with thiafentanil oxalate and 21 elk immobilized with carfentanil citrate as a positive control group. At the first location, two groups of 10 elk were administered either 15 mg thiafentanil oxalate or 4 mg carfentanil citrate by dart. The mean induction time for thiafentanil oxalate was 2 minutes ± 0.8 minutes as compared to a mean induction time of 2.7 minutes ± 0.8 minutes or carfentanil citrate. At the second location, two groups of 11

elk were administered either 15 mg of thiafentanil oxalate or 2 mg carfentanil citrate by dart. The mean induction time was 1.2 minutes ± 0.4 minutes for thiafentanil oxalate compared to 3.4 minutes ± 1 minute for carfentanil citrate. Once recumbent, heart rate, respiratory rate, and body temperature were measured every 5 minutes for 15 minutes. The study animals were reversed with nalmefene hydrochloride (a mu opioid antagonist). All study animals recovered after reversal and no renarcotization occurred. Two animals died during the study. The first animal was in the carfentanil citrate dose group and was found dead 4 hours after immobilization. Physical symptoms and necropsy findings suggest acute capture myopathy as the cause of death. The second animal was in the thiafentanil oxalate dose group and was found dead two days after immobilization. A necropsy could not be performed due to predation, but the animal was observed to be normal at 4 hours and 24 hours after immobilization.

The objective of the second study was to determine an effective dose (ED_{90}) of thiafentanil oxalate for immobilization in elk. Over 100 elk were included in the study and animals were dosed by both syringe and dart. Optimal immobilization was defined as an induction time of less than three minutes. Successful immobilization was defined as an induction time of less than five minutes. The ED_{90} for syringe injection was between 4 and 8 µg/kg bodyweight for optimal immobilization and 2.55 µg/kg bodyweight for successful immobilization. For dart injection, the ED_{90} was 40.88 µg/kg bodyweight for optimal immobilization and 29.65 µg/kg bodyweight for successful immobilization. All study animals recovered after immobilization and no renarcotization occurred.

The result of the qualified expert panel's risk-benefit analysis was a unanimous conclusion that THIANIL is safe and effective for use for immobilization of captive minor species hoof stock excluding any member of a food-producing minor species such as 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 THIANIL be marketed by prescription.

B. LITERATURE CONSIDERED BY THE QUALIFIED EXPERT PANEL:

1. Alcantar BE, McLean M, Chirife AD, Lohe T, Bennett JP, Oritz 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. 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.
3. 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.
4. 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 cameloparadalis*). *Proc. Conf. Amer. Assoc. Zoo Vet*. 2006, 211-212.
5. 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.

6. 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.

7. 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.

8. Janssen DL, Allen JL, Raath JP, de Vos V, Swan GE, Jessup D, Stanley TH. Field studies with the narcotic immobilizing agent A3080. *Proc. Conf. Amer. Assoc. Zoo Vet*. 1991, 340-342.

9. 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.

10. Kock MD, Meltzer D, and Burrows R, eds. *Chemical and Physical Restraint of Wild Animals: A Training and Field Manual for African Species*, 1st ed. IWVS (Africa), PO Box 106, Greyton 7233, South Africa, 2009. Print.

11. Kreeger TJ, Cook WE, Picho CA, Smith T. Anesthesia of pronghorns using thiafentanil or thiafentanil plus xylazine. *J. Wildl. Mgmt*. 2001, 65(1): 25-28.

12. Kreeger TJ, Analyses of immobilizing dart characteristics. *Wildl. Soc. Bull*. 2002, 30(30): 968-970.

13. Kreeger, TJ and Arnemo JM. *Handbook of Wildlife Chemical Immobilization*, 3rd ed. tkreeger@starbrand.net or Amazon.com, 2009. Print.

14. Lance WR. Attachment C: Recommended Dosages for Adult Animals of South Africa and North America. Wildlife Pharmaceuticals, Inc., Windsor, CO. 9-10.

15. McJames SW, Smith IL, Stanley TH, Painter G. Elk immobilization with potent opioids: A3080 vs. Carfentanil. *Proc. Conf. Amer. Zoo Vet*. 1993: 418-419.

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 Thiafentanil Oxalate (A3080) as an Immobilising Agent in Non-Domestic Species. First Study, 1-11.

18. Raath JP. Clinical Expert Report: The Use of Thiafentanil Oxalate (A3080) as an Immobilising Agent in Non-Domestic Species. Second Study, 11-22.

19. Raath JP. Clinical Expert Report: The Use of Thiafentanil Oxalate (A3080) as an Immobilising Agent in Non-Domestic Species. 1-38.

20. Fowler ME and Miller RE, eds. *Zoo and Wildlife Animal Medicine: Current Therapy*, 6th ed. Saunders Elsevier, St. Louis, Missouri, 2008. Print.

21. Smith IL, McJames SW, Natte R, Stanley TH, Kimball JF, Becker T, Hague B, Barrus B. A-3080 studies in elk: effective immobilizing doses by syringe and dart injections. *Proc. Conf. Amer. Assoc. Zoo Vet*. 1993: 420-421.

22. 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.

23. Stanley TH, McJames SW, Kimball J, Port JD, Pace NL. Immobilization of elk with A-3080. *J. Wildl. Mgmt*. 1988: 577-581.

24. Stanley TH, McJames SW, Kimball J, Port JD, Pace NL. Chemical immobilization for the capture and transportation of big game. *Proc. Conf. Amer. Assoc. Zoo Vet.* 1989: 13-14.

25. Tranquilli WJ, Thurmon JC, Grimm KA, eds. *Lumb & Jones, Veterinary Anesthesia and Analgesia*, 4th ed. Blackwell Publishing, Ames, Iowa, 2007. Print.

26. 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 THIANIL:

Human Warnings:

Not for use in humans. Keep out of the reach of children. THIANIL contains thiafentanil, a high concentration (10 mg/mL) opioid agonist and Schedule II controlled substance. THIANIL should be handled with extreme caution to avoid accidental exposure.

If accidental self-injection or ingestion occurs, seek immediate medical treatment and provide physician with the vial or package insert/product information. Symptoms of toxicity include dizziness, nausea, and constriction of pupils (pinpoint) followed by respiratory depression, lowered blood pressure, cyanosis, and in extreme cases, loss of consciousness and cardiac arrest. If necessary, apply CPR until medical help arrives.

The antidote for human exposure to THIANIL is an opioid antagonist such as naltrexone or naloxone.

If accidental skin exposure occurs, wash area with copious amounts of water and contact a physician. If accidental eye exposure occurs, flush with copious amounts of water for 15 minutes and contact a physician.

Because of the potential for adverse reactions associated with accidental exposure, THIANIL should only be administered by individuals experienced in handling immobilization agents in zoos, exotic animal and wildlife practices, wildlife management programs, and biological research. It is advisable only to handle THIANIL when accompanied by another person. Wear gloves and eye protection when handling THIANIL. The handler should be paired with a second person also knowledgeable about the hazards of working with potent opioids. All personnel involved in an immobilization should be informed that potent opioids are being utilized. Needles and syringes should be secured and safely disposed of as a biohazard following use.

IV. AGENCY CONCLUSIONS:

The information submitted in support of this request for THIANIL 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 for immobilization of captive minor species hoof stock excluding any member of a food-producing minor species such as 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 THIANIL 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 THIANIL for use for immobilization of captive minor species hoof stock excluding any member of a food-producing minor species such as deer, elk, or bison and any minor species animal that may become eligible for consumption by humans or food-producing animals.

C. MARKETING STATUS:

THIANIL will be marketed by prescription as a Schedule II controlled substance.

D. EXCLUSIVITY:

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

E. ATTACHMENTS:

Facsimile Labeling:

10 mL bottle