

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 140-874

B. Sponsor

Wildlife Laboratories
Incorporated 1401 Duff Drive, Suite 600
Fort Collins, Colorado 80534

C. Proprietary Name

Antagonil

D. Established Name

yohimbine hydrochloride

E. Dosage Form, Route of Administration and Recommended Dosage

The product is supplied as a sterile solution for intravenous administration at a dose rate of 0.20 to 0.30 mg/kg body weight.

F. Indication

For the antagonism of xylazine sedation in free-ranging and confined members of the family *Cervidae* (deer and elk).

II. EFFECTIVENESS

Due to the nature of the species in which the efficacy of yohimbine HCL to reverse xylazine sedation was to be demonstrated, and humane concerns for the safety and welfare of these animals as well as the fact that these animals are wild and free-ranging and under the jurisdiction of federal and state wildlife agencies, or, in the case of the exotic members of the family *Cervidae* in zoos under the jurisdiction of either state or municipal entities, it was deemed inappropriate and inhumane to immobilize deer with xylazine and leave them unreversed by yohimbine as controls in these trials.

Immobilization of deer with xylazine without reversal puts them at risk to complications common to ruminants after xylazine sedation such as bloat, regurgitation of rumen contents and aspiration into the lungs, and self-induced trauma as a result of incoordination during the recovery phases. Furthermore, the published, peer-reviewed scientific literature contains sufficient controlled studies documenting the recovery times of deer following xylazine sedation. It was determined that this scientific base of information could be relied upon to adequately establish control values and that these trials could be conducted without putting additional animals at unnecessary and inhumane risk as control animals in these trials to establish efficacy of yohimbine HCL to reverse xylazine sedation in the deer family.

In these efficacy trials, over 400 members of the family *Cervidae*, represented by seven different species were administered yohimbine HCL following xylazine sedation. Following

yohimbine HCL administration, the recumbency time was reduced to 4.37 +/- 0.13 (SE) minutes. The expected recumbency times established in well controlled trials in the scientific literature for these animals would have been in excess of 100 minutes. In accordance with 21 CFR 514.111(a)(5)(ii), the effectiveness of yohimbine HCL as an antagonist to xylazine in *Cervidae* is conclusively established by the alternative procedure utilized in the clinical field trials. Therefore a waiver of the criteria defining control trials was granted.

The following parameters were recorded in these studies: 1) dosage of xylazine, 2) time to sternal and/or lateral recumbency after treatment with xylazine, 3) time between xylazine administration and yohimbine HCL administration, 4) dosage of yohimbine HCL, 5) time to initial effect and time to standing after treatment with yohimbine HCL and 6) adverse effects. a) The pivotal efficacy study was conducted in elk demonstrating the efficacy of yohimbine HCL to reverse xylazine sedation in elk (*Cervus elaphus*) as a representative of the family *Cervidae*.

A. Type of Study: Field Efficacy

1. Name and Address of Investigator:

Dr. Terry Hofstra
Redwood National Park
1125 16th Street Arcata, CA 95211

2. Study Design:

i. Purpose: Demonstrate efficacy to reverse xylazine sedation in freeranging elk.

ii. Test Animals:

1. Species: Elk (*Cervus elaphus*)
2. Number: 25
3. Age and Sex: Adult, subadult, male and female

3. Type of Control: A waiver of the criteria defining adequate and well controlled trials was granted under 514.111(8)(5)(ii). (copy attached)

4. Diagnosis: N/A

5. Dose Form: Sterile Injectable Liquid

6. Route of Administration: Intravenous

7. Dose Used: Average dose was 0.22 mg/kg body weight

8. Parameters Measured:

- i. Dosage of Xylazine in mg/kg
- ii. Time to Immobilization
- iii. Interval Between Xylazine Administration and Yohimbine HCL Administration
- iv. Amount of Yohimbine HCL in mg/kg

- v. Time to Recovery
- vi. Adverse Effects

9. Results: Sedation was produced in these elk by an average intramuscular dose rate of 3.85 mg/kg of xylazine. The average time between the administration of xylazine and the administration of yohimbine HCL in 25 elk was 33 minutes, with a range of 16-54 minutes. Total recumbency time was 36.5 minutes. The xylazine was effectively reversed with an average of 0.22 mg/kg intravenous yohimbine HCL administration that resulted in an average standing time of 3 and one-half minutes. The recovery time of elk from xylazine sedation documented in well controlled studies published in the scientific literature is in excess of 100 minutes (10, 11, 13).

10. Statistical Analysis: None

11. Conclusion: Yohimbine HCL administered to these elk within the 0.2 to 0.3 mg/kg dose range was effective in reversing xylazine sedation in these elk in less than six minutes after yohimbine HCL administration.

12. Adverse Reactions: None was observed.

13. Special Issues:

- i. A waiver of the criteria defining adequate and well controlled trials in accordance with provisions of 514.111 (a)(5)(ii) has been granted.
- ii. First corroborative study demonstrating the efficacy of yohimbine HCL in reversing the effects of xylazine in elk as a representative member of the family *Cervidae*.

B. Type of Study: Field Efficacy

1. Name and Address of Investigator:

Dr. Michael Cranfield
Baltimore Zoo
Druid Park
Baltimore, MD 21217

2. Study Design:

- i. Purpose: Demonstrate efficacy of yohimbine HCL to reverse xylazine sedation in elk as a representative member of the family *Cervidae*.

3. Test Animals:

- i. Species: (*Cervus elaphus*)
- ii. Number: 17
- iii. Age and Sex: Subadult, adult, male and female

4. Type of Control: A waiver of the criteria defining adequate and well controlled trials was granted under 514.111(a)(5)(ii).
5. Diagnosis: N/A
6. Dose Form: Sterile Injectable Liquid
7. Route of Administration: Intravenous
8. Dose Used: Average 0.15 mg/kg body weight
9. Parameters Measured:
 - i. Dosage of Xylazine in mg/kg
 - ii. Time to Immobilization
 - iii. Amount of Yohimbine HCL in mg/kg
 - iv. Time to Recovery
 - v. Adverse Effects
10. Results: In 17 immobilizations the elk had an average time to effect of less than one minute. The time to standing after administration of yohimbine HCL averaged nine minutes. Two of the 17 gave a first effect response in two and five minutes but did not stand until 60 minutes after yohimbine HCL administration.
11. Statistical Analysis: None
12. Conclusion: The field efficacy study conducted by Dr. Cranfield provides data that supports the efficacy of yohimbine HCL at an average dose rate of 0.15 mg/kg, but that resulted in an average standing time of 9 minutes. The recovery time of elk from xylazine sedation documented in well controlled studies published in the scientific literature is in excess of 100 minutes (10, 11, 13).
13. Adverse Reactions: None was observed.
14. Special Issues:
 - i. A waiver of the criteria defining adequate and well controlled trials was granted under 514.111 (a)(5)(ii).
 - ii. Second corroborative study demonstrating the efficacy of yohimbine HCL to reverse xylazine sedation in elk as a representative of the family *Cervidae*.

C. Type of Study: Field Efficacy

1. Dr. Ed Doornebal
Barrhead Veterinary Services
Box 858, Barrhead, Alberta
Canada TOG OEO

2. Study Design:

- i. Purpose: Demonstrate efficacy of yohimbine HCL to reverse xylazine sedation in free-ranging elk.

3. Test Animals:

- i. Species: Elk (*Cervus elaphus*)
- ii. Number: 66
- iii. Age and Sex: Animals ranged in age from one to eight years and an average body weight of 341 kg. Sixty-four were females and two were males.

4. Type of Control: A waiver of the criteria defining adequate and well controlled trials was granted under 514. 111(a)(5)(ii).

5. Diagnosis: N/A

6. Dose Form: Sterile Injectable Liquid

7. Route of Administration: Intravenous

8. Dose Used: Average dose used 0.15 mg/kg body weight

9. Parameters Measured:

- i. Dosage of Xylazine in mg/kg
- ii. Time to Immobilization
- iii. Amount of Yohimbine HCL in mg/kg
- iv. Time to Recovery
- v. Adverse Effects

10. Results: This group of elk was effectively immobilized with xylazine at an average intramuscular dose of 0.9 mg/kg body weight. The average time to lateral recumbency was 16 minutes. This level of xylazine sedation was effectively reversed with an average intravenous dose of 0.15 mg/kg of yohimbine HCL. The average time to first effect following yohimbine HCL administration was two minutes and the average time to standing was four minutes in this group of elk.

11. Statistical Analysis: None

12. Conclusion: This field efficacy study demonstrates the efficacy of yohimbine HCL at a dose rate 0.15 mg/kg to produce reversal of xylazine sedation in elk four minutes following yohimbine HCL administration. The recovery time of elk from xylazine sedation documented in well controlled studies published in the scientific literature studies is in excess of 100 minutes (10, 11, 13).

13. Adverse Reactions: None was observed.

14. Special Issues: A waiver of the criteria defining adequate and well controlled trials was granted under 514.111 (a)(5)(ii).

D. Additional Corroborative Studies in Elk:

1. Summary: Nine additional investigators reversed xylazine sedation in 39 elk at various locations throughout the United States and Canada with yohimbine HCL. The elk were sedated with intramuscular xylazine dose rates ranging from 0.7 to 3.9 mg/kg body weight. The effective levels of yohimbine HCL administered ranged from 0.12 to 0.4 mg/kg body weight. All elk in these studies had an average time to standing of nine minutes or less. These additional studies substantiate the wide range of efficacy of yohimbine HCL to reverse xylazine sedation in elk.

The following table summarizes the investigator's name, address, number of animals treated, average dose of xylazine used, average dose of yohimbine HCL used, average time to effect and standing.

Investigator Location	# of Animals	Avg. Dose of Xylazine (mg/kg)	Avg. Dose of Yohimbine (mg/kg)	Avg. Time to Effect (min.)	Avg. Time to Standing (min.)
1. Rich Harris WA State U Dept. Fish & Range Mgmt	3	1.0	.011	NR*	2.7
2. Dr. Doug Coffman Colorado	7	2.8	0.14	NR	45
3. Dr. Morgan McArthur Kinghorn Vet Clinic	5	0.78	0.12	2.0	7.0
4. Dr. Scott B. Citino Miami Zoo	1	2.36	0.12	NR	NR
5. Dr. David Jenkins Catskill Animal Hospital	2	0.65	0.12	NR	4.0
6. Dr. Stephen Kerr Midtown Animal Hosp Nebraska	1	2.2	0.4	4.0	6.0
7. Dr. Lisa Jensen Burnet Park Zoo	1	1.1	0.3	1.0	3.75
8. Chris Reynolds Lester Eberhardt Battelle Northwest Washington	3	1.0	0.12	4.0	6.0
9. Dr. Carol Lee Wallace Burnet Park Zoo	1	0.06	0.1	2.0	3.0

*Not recorded

E. The pivotal efficacy field study in deer as a representative of the family *Cervidae* to demonstrate efficacy of yohimbine HCL to reverse xylazine sedation in deer.

1. Type of Study: Field Efficacy

2. Name and Address of Investigator:

Mr. Wally Haussaman
New Mexico Department of Fish & Game
Santa Fe, NM 87503

3. Study Design:

i. Purpose: Demonstrate efficacy of yohimbine HCL to antagonize xylazine sedation in free-ranging mule deer.

ii. Test Animals:

1. Species: Mule deer (*Odocoileus hemionus*)
2. Number: 215
3. Age and Sex: Adult, subadult, male and female

iii. Type of Control: A waiver of the criteria defining adequate and well controlled trials was granted under 514.111 (a)(5)(ii). (copy attached)

iv. Diagnosis: N/A

v. Dose Form: Sterile Injectable Liquid

vi. Route of Administration: Intravenous

vii. Dose Used: Average dose was 0.2 mg/kg body weight

viii. Parameters Measured:

1. Dosage of Xylazine in mg/kg
2. Time to Immobilization
3. Interval Between Xylazine Administration and Yohimbine HCL Administration
4. Amount of Yohimbine HCL in mg/kg
5. Time to Recovery
6. Adverse Effects

4. Results: This group of 215 wild, free-ranging mule deer trapped at various locations in New Mexico were sedated with an average intramuscular dose of xylazine of 4.33 mg/kg body weight. This dose level of xylazine produced lateral recumbency within an average time of 3.5 minutes. Average time between xylazine administration and yohimbine HCL administration in 192 deer was 17 minutes with a range of 7-77 minutes. Total recumbency time was 20.5 minutes. Yohimbine HCL was administered intravenously at an average dose rate of 0.2 mg/kg body

weight. In this group of deer, the average time to effect and time to standing following yohimbine administration was less than one minute. One animal in this group of 215 did require five minutes to stand following yohimbine administration.

5. Statistical Analysis: None
 6. Conclusion: The results obtained by Mr. Haussaman document the efficacy of yohimbine HCL to reverse xylazine sedation of wild, free- ranging mule deer at a yohimbine HCL dose rate of 0.2 mg/kg at an average of less than one minute. The published scientific literature contains well-controlled studies establishing the recovery time of deer from xylazine sedation to be in excess of 200 minutes (6, 15).
 7. Adverse Reactions: None was observed.
 8. Special Issues: A waiver of the criteria defining adequate and well controlled trials was granted under 514.111 (a)(5)(ii).
- F.** The first corroborative study in deer as a representative of the family *Cervidae* was conducted by Dr. Stephen Schmitt, Michigan Department of Natural Resources.
1. Type of Study: Field Efficacy
 2. Name and Address of Investigator:

Dr. Stephen Schmitt
Wildlife Pathology & Physiology Lab
8562 East State Road
East Lansing, MI 48823
 3. Study Design:
 - i. Purpose: Demonstrate efficacy of yohimbine HCL to reverse xylazine sedation in white-tailed deer.
 - ii. Test Animals:
 1. Species: White-tailed deer (*Odocoileus virginianus*)
 2. Number: 8
 3. Age and Sex: Adult, males
 - iii. Type of Control: A waiver of the criteria defining adequate and well controlled trials was granted under 514.111 (a)(5)(ii).
 - iv. Diagnosis: N/A
 - v. Dose Form: Sterile injectable liquid
 - vi. Route of Administration: Intravenous

vii. Dose Used: Average dose rate 0.32 mg/kg body weight

viii. Parameters Measured:

1. Dosage of Xylazine in mg/kg
2. Time to Immobilization
3. Amount of Yohimbine HCL in mg/kg
4. Time to Recovery
5. Adverse Effects

4. Results: The eight male white-tailed deer were immobilized with an intramuscular dose of 0.38 mg/kg body weight of xylazine. These deer became sternally recumbent within an average of six minutes. Yohimbine HCL was administered intravenously at an average dose rate of 0.32 mg/kg body weight. The average time to first effect following yohimbine HCL administration was seven minutes and the average time to standing was nine minutes.

5. Statistical Analysis: None

6. Conclusions: Results of Dr. Schmitt's corroborative field efficacy study demonstrates yohimbine HCL effectively reverses xylazine sedation in whitetailed deer and significantly reduces time in recumbency. This published scientific literature contains well controlled studies establishing the recovery time of deer from xylazine sedation to be in excess of 200 minutes (6).

7. Adverse Reactions: None

8. Special Issues: A waiver of the criteria defining adequate and well controlled trials was granted under 514.111 (a)(5)(ii).

G. The second corroborative study in deer supporting the efficacy of yohimbine HCL to reverse xylazine sedation in deer as representatives of the family *Cervidae*.

1. Summary: Twelve additional investigators located in the United States used yohimbine HCL to antagonize xylazine sedation in 45 white- tailed deer of various ages and sex under a variety of field situations. Results of these investigations substantiates efficacy of yohimbine HCL to antagonize xylazine sedation in white-tailed deer. The results of these investigators are summarized in the following table.

Investigator Location	# of Animals	Avg. Dose of Xylazine (mg / kg)	Avg. Dose of Yohimbine (mg / kg)	Avg. Time to Effect (min.)	Avg. Time to Standing (min.)
1. Keith Hinshaw Philadelphia Zoo	1	5.3	0.2	7.0	10.0

Investigator Location	# of Animals	Avg. Dose of Xylazine (mg / kg)	Avg. Dose of Yohimbine (mg / kg)	Avg. Time to Effect (min.)	Avg. Time to Standing (min.)
2. Chris Chase Michigan	2	1.5	0.1	11.0	13.0
3. Dr. Barbara Thomas Baker Riverbanks Zoo	8	1.72	0.17	2.0	2.0
4. Dr. Lisa Jensen Burnet Park Zoo	3	2.93	.054	1.0	3.0
5. Dr. Chris Brooks Texas	3	0.17	0.16	10.0	12.0
6. Dr. Frank Grasse California	1	0.87	0.13	8.0	8.0
7. Dr. Connie Hodges Texas A&M	4	0.95	0.13	5.0	0.0
8. David Whitehouse Texas	16	3.81	0.19	6.0	7.0
9. Dr. Mark Lerman All Creatures Great & Small	6	0.52	0.37	4.0	5.0
10. Terry Wolfe Lion Country Safari	1	0.75	0.1	10.0	10.0
11. Dr. George Lillard Texas	3	5.21	0.26	4.0	4.0
12. Steven Dobbs Stone Mountain Park	3.	1.64	0.18	6.0	15.0
13. Dr. Michael Briggs Wildlife Safari, Oregon	1	2.0	0.125	60.0	120.0

14. Dr. Tom Thorne Wyoming Fish & Game	4	0.7	0.38	5.0	8.0
15. Dr. Ben Gonzales	6	2.3	0.5	27.0	31.0

H. The third corroborative study in deer supporting the efficacy of yohimbine HCL to reverse xylazine sedation in deer as representatives of the family *Cervidae*.

1. Three additional investigators used yohimbine HCL to antagonize xylazine in mule deer with varied results. The results obtained by Dr. Briggs in one deer illustrated in the following table could not be explained. The results of these investigators are summarized in the following table.

Investigator Location	Number of Animals	Average Dose of Xylazine (mg / kg)	Average Dose of Yohimbine (mg / kg)	Avg. Time to Effect (min)	Avg. Time to standing (min)
Dr. Michael Briggs Wildlife Safari, Oregon	1	3.0	0.125	60.0	120.0
Dr. Tom Thorne Wyoming Fish & Game	4	0.7	0.38	5.0	8.0
Dr. Ben Gonzales	6	2.3	0.5	27.0	31.0

I. Additional Corroborative Studies in Other Members of *Cervidae*:

1. Summary: Data from six additional species in the family *Cervidae* were collected under field conditions. These were Caribou (16), Sika deer (7), Fallow deer (1), Axis deer (1) and Muntjac (1).
2. Caribou: Four investigators immobilized a total of 16 caribou with an average body weight from 102 to 133 kg. The average dose of xylazine ranged from 0.2 to 2.21 mg/kg body weight. Lateral recumbency was achieved within an average of less than 11 minutes in these animals. The response of these 16 caribou to yohimbine HCL antagonism of xylazine sedation at intravenous dose rates of 0.1 to 0.25 mg/kg was similar to the data in other *Cervidae*. The data from these investigators are summarized on the following table.

Investigator Location	# of Animals	Avg. Dose of Xylazine (mg / kg)	Avg. Dose of Yohimbine (mg / kg)	Avg. Time to Effect (min.)	Avg. Time to Standing (min.)
1. Dr. Lisa Jensen Burnet Park Zoo	3	0.7	0.25	2.0	10.0
2. Dr. Nadine Richter Detroit Zoo	9	0.2	0.10	12.0	12.0
3. Gregg Servheen Idaho	3	2.21	0.23	8.0	17.0
4. William Carlton Indiana	1	0.9	0.11	3.0	10.0

3. Sika Deer: Two investigators immobilized seven sika deer in zoological collections with an average dose rate of 2.9 and 3.0 mg/kg body weight. Times to lateral recumbency were within two minutes or less. Yohimbine HCL at doses ranging from 0.15 to 0.34 mg/kg body weight, produced a time to standing in these individuals averaging four minutes or less. The results indicate that sika deer have a response to yohimbine HCL antagonism of xylazine sedation similar to other members of the family *Cervidae*. These results are summarized in the following table.

Investigator Location	# of Animals	Avg. Dose of Xylazine (mg / kg)	Avg. Dose of Yohimbine (mg / kg)	Avg. Time to Effect (min.)	Avg. Time to Standing (min.)
1. Dr. Mike Cranfield Baltimore Zoo	4	2.9	34	2.0	3.0
2. Philip Robinson San Diego Zoo	3	3.0	15	1.0	4.0

4. Fallow Deer, Axis Deer and Muntjac Deer: Three investigators (Christian, Peddie, Leifeste) submitted data on single immobilizations of fallow deer, axis deer, muntjac deer with xylazine. Although statistically insignificant the individual animals all exhibited a response to yohimbine HCL

antagonism of xylazine similar to other members of the family *Cervidae*.
Data are summarized in the following table.

Investigator Location	# of Animals	Avg. Dose of Xylazine (mg / kg)	Avg. Dose of Yohimbine (mg / kg)	Avg. Time to Effect (min.)	Avg. Time to Standing (min.)
Fallow deer 1. Dr. David L. Christian Oregon	1	2.34	0.17	3.0	3.0
Fallow deer Dr. James Peddie Conejo Valley Vet Clinic	1	2.05	0.1	2.5	6.0
Axis deer 1. Dr. Lloyd Leifeste Texas	1	0.9	0.13	15.0	20.0
Muntjac deer 1. Jim Peddie Conejo Valley Vet Clinic	1	1.3	0.08	2.5	2.5

J. First Corroborative Study from Peer-reviewed Scientific Literature:

1. Name and Address of Investigator:

- i. Walter Hsu, DVM PhD
Department of Veterinary Physiology & Pharmacology
Iowa State University
Ames, IA 50011
- ii. William P. Shulaw, DVM
Amanda Animal Hospital
Rural Route 2, Box 8650
Spencerville, OH 45887

2. Test Animals:

- i. Species: White-tailed deer (*Odocoileus virginianus*)
- ii. Number per Group: 5 Control, 20 Treated

3. Study Design:

- i. The study was well controlled with five white-tailed deer that were administered xylazine and the time to standing following sedation recorded.
 - ii. Dose Rate: 0.1 mg/kg
 - iii. Route of Administration: Intravenous
- 4. Results and Conclusions: The five control deer, with an average time to standing of 268 +/- 76 minutes following a xylazine dosage of 3.7 +/- 1.2 mg/kg xylazine. Twenty treated deer, given an average of 2.8 +/- 1.0 mg/kg xylazine had a time to standing after administration of yohimbine HCL at a rate of 0.1 mg/kg of 4 +/- 5 minutes in 19 of 20 deer. The yohimbine HCL also reversed the bradycardia and respiratory depression induced by xylazine(6).

K. Second Corroborative Study from Peer-reviewed Scientific Literature:

- 1. Name and Address of the Investigators
 - i. C.G. MacKintosh
Invermay Agricultural Research Center
Mosgiel, New Zealand
 - ii. B) Gilbert Van Reenen
Aspiring Veterinary Service
Box 223
Wanak, New Zealand
- 2. Test Animals:
 - i. Species: Elk (*Cervus elaphus*)
 - ii. Number per Group: 13 Control, 34 Treated
- 3. Study Design:
 - i. The study was well controlled. The type of control was a non-treated control (xylazine sedation with no reversal).
 - ii. Dose Form: Sterile injectable liquid at dose rates of 0.625 mg/kg to 0.25 mg/kg. Two unsedated elk received 1.0 mg/kg intravenously.
- 4. Other Relevant Information: The publication cited refers to *Cervus elaphus* as deer as they commonly are termed in New Zealand. Genus and species is the same as North American elk.
- 5. Results and Conclusions: Trials were conducted to test the ability of yohimbine HCL, 4-aminopyridine and doxapram given by intravenous injection to antagonize xylazine sedation in red deer (*Cervus elaphus*). Yohimbine HCL produced the best and most consistent results. The mean

time taken for 34 animals to stand spontaneously after receiving yohimbine HCL at a dose rate of 0.2 to 0.25 mg/kg was 2.50 minutes. This occurred on an average of 34 minutes after the initial dose of xylazine. Control animals took 67 and 147 minutes on average, to standing after receiving intravenous (0.64 to 0.96 mg/kg) and intramuscular (1.0 to 1.5 mg/kg) injection of xylazine respectively. Two deer given high intravenous doses of yohimbine HCL (1.0 mg/kg) became mildly nervous and anxious, but returned to normal within one hour. The authors concluded that yohimbine HCL administered by intravenous injection at a dose rate of 0.2 to 0.25 mg/kg appears to be a safe and reliable drug for the reversal of xylazine sedation in deer (elk)(10).

III. ANIMAL SAFETY

Conventional safety studies were not conducted with yohimbine HCL due to the nature of the target species. Since these animals are not confined and are governed by state or municipal entities, it was not necessary or reasonable to conduct conventional/classical pre-clinical laboratory toxicity studies in this family of animals. Nevertheless, under actual use conditions, dose rates for yohimbine HCL approached six to 10 times the recommended level in deer without causing adverse reactions or side effects. Over 400 members of the family *Cervidae* were administered yohimbine HCL at the approximate recommended dose with individual animals receiving higher doses, with no report of toxicity or adverse reactions. Additionally, the published literature contains studies which further substantiate the safety of this product. The effects of yohimbine HCL in reversing xylazine have been examined in several species and reports of its effects have been published for cats (4, 5), cattle (9, 17), deer (6, 7, 8, 12, 14) and dogs (1, 2, 3). In these studies the effects of yohimbine HCL on mean arousal time, mean standing time and mean walking time were recorded and compared to control animals that received xylazine alone.

The rationale for developing the drug for use in *Cervidae* is based on the fact that if left in a position of prolonged lateral recumbency following immobilization, members of the family *Cervidae* like other ruminants would be highly susceptible to bloat and/or aspiration pneumonia. The use of yohimbine HCL allows the effects of xylazine to be rapidly reversed, thus enabling the animals to rapidly and safely return to their natural environment.

The data filed in support of the product include field data gathered under actual conditions of use under free-ranging conditions, in zoos or in wildlife parks. Members of the family *Cervidae* for which data have been provided include several species of deer, elk, and caribou. The following parameters were recorded in these studies: 1) time to sternal and/or lateral recumbency after treatment with xylazine, 2) time to initial effect and time to standing after treatment with yohimbine HCL and, 3) adverse reactions.

The field trials in members of the deer family (*Cervidae*) referenced in the efficacy trials contain individual animals which received doses higher than the recommended dose range. Additionally, the published scientific literature contains studies that further substantiate the safety of this product.

1. Safety Trial One:

a. Type of Study: Field Safety

b. Name and Address of Investigator:

Dr. Lisa Jensen
Burnet Park Zoo
P.O. Box 146
Liverpool, NY 13088

c. Study Design:

- i. Purpose: Demonstrate efficacy and safety of yohimbine HCL to reverse xylazine in white-tailed deer.
- ii. Test Animals:
 1. Species: White-tailed deer (*Odocoileus virginianus*)
 2. Number: 1
 3. Age and Sex: Subadult, male
- iii. Type of Control: A waiver of the criteria defining adequate and well controlled trials was granted under 514.111(a)(5)(ii).
- iv. Diagnosis: N/A
- v. Dose Form: Sterile Injectable Liquid
- vi. Route of Administration: Intravenous
- vii. Dose Used: 1.14, mg/kg
- viii. Parameters Measured:
 1. Dosage of Xylazine in mg/kg
 2. Time to Immobilization
 3. Amount of Yohimbine HCL in mg/kg
 4. Time to Recovery
 5. Adverse Effects
- d. Results: This deer was given a total of 1.14 mg/kg in three doses of intravenous yohimbine HCL at a dose rate of 0.38 mg/kg per dose over a period of 12 minutes following a dose of xylazine of 3.8 mg/kg. No adverse effects were observed by Dr. Jensen.
- e. Statistical Analysis: None
- f. Conclusion: A total dose of 1.1 mg/kg (366% of the upper recommended dose) in this deer produced no adverse effects indicating safety at this dose level.
- g. Adverse Reactions: None

- h. Special Issues: A waiver of the criteria defining adequate and well controlled trials was granted under 514.111 (a)(5)(ii).

2. Safety Trial Two

- a. Type of Study: Field Safety

- b. Name and Address of Investigator:

Dr. Mark Lerman
381 Route 306
Monsey, NY 10952

- c. Study Design:

- i. Purpose: Determine safety of yohimbine HCL to reverse xylazine sedation in white-tailed deer.

- ii. Test Animals:

- 1. Species: White tailed deer (*Odocoileus virginianus*)
 - 2. Number: 2
 - 3. Age and Sex: Fawn male and female

- iii. Type of Control: A waiver of the criteria defining adequate and well controlled trials was granted under 514.111 (a) (5) (ii).

- iv. Diagnosis: N/A

- v. Dose Form: Sterile Injectable Liquid

- vi. Route of Administration: Intravenous

- vii. Dosages Used: 0.5 and 0.83 mg/kg

- viii. Parameters Measured:

- 1. Dosage of Xylazine in mg/kg
 - 2. Time to Immobilization
 - 3. Amount of Yohimbine HCL in mg/kg
 - 4. Time to Recovery
 - 5. Adverse Effects

- d. Results: Male fawn was immobilized with an intravenous dose of xylazine at 0.5 mg/kg that resulted in lateral recumbency in 8.32 minutes. This individual was reversed with yohimbine HCL at 0.5 mg/kg body weight and stood in 9 minutes. The female fawn was sedated with xylazine at 0.56 mg/kg and became laterally recumbent within 2.55 minutes. This level of sedation was reversed with 0.83 mg/kg of yohimbine HCL administered intravenously. The female fawn stood in 0.25 minutes.

- e. Statistical Analysis: None

- f. Conclusions: Yohimbine HCL administered at 166% and 276% of the highest recommended dose level in deer produced no adverse effects in these two individuals.
 - g. Adverse Reactions: None was observed at this excessive dose level.
 - h. Special Issues: A waiver of the criteria defining adequate and well controlled trials was granted under 514.111 (a)(5)(ii).
3. Safety Trial Three
- a. Type of Study: Field Safety
 - b. Name and Address of Investigator
 - Dr. T. Thorne
 - Wyoming Fish & Game Laboratory
 - University of Wyoming
 - Laramie, WY 82010
 - c. Study Design:
 - i. Purpose: Demonstrate safety and efficacy of yohimbine HCL to reverse xylazine.
 - ii. Test Animals
 - 1. Species: Mule deer (*Odocoileus hemionus*)
 - 2. Number: 2
 - 3. Age and Sex: Adult, male and female
 - 4. Facilities: Confined
 - iii. Type of Control: A waiver of the criteria defining adequate and well controlled trials was granted under 514.111 (a)(5)(ii).
 - iv. Diagnosis: N/A
 - v. Dose Form: Sterile Injectable Liquid
 - vi. Route of Administration: Intravenous
 - vii. Dosages Used: 0.44 and 0.48 mg/kg
 - viii. Parameters Measured:
 - 1. Dosage of Xylazine in mg/kg
 - 2. Time to Immobilization
 - 3. Amount of Yohimbine HCL in mg/kg
 - 4. Time to Recovery
 - 5. Adverse Effects

- d. Results: Two deer were immobilized with 0.7 mg/kg xylazine. The xylazine effects were antagonized with 0.48 and 0.44 mg/kg of yohimbine HCL intravenously with no adverse effects observed.
 - e. Statistical Analysis: None
 - f. Conclusions: Yohimbine HCL given at 0.48 and 0.44 mg/kg body weight (160% and 146% of upper recommended dose range) had no adverse effects on these deer.
 - g. Adverse Reactions: None
 - h. Special Issues: A waiver of the criteria defining adequate and well controlled trials was granted under 514.111 (a)(5)(ii).
4. Safety Trial Four
- a. Type of Study: Field Safety
 - b. Name and Address of Investigator:

Dr. Mike Cranfield
Baltimore Zoo
Druid Park Baltimore, MD 21217
 - c. Study Design:
 - i. Purpose: Demonstrate safety and efficacy of yohimbine HCL to reverse xylazine in sika deer.
 - ii. Test Animals:
 - 1. Species: Sika deer (*Cervus nippon*)
 - 2. Number: 4
 - 3. Age and Sex: Subadult, male and female
 - 4. Facilities: Confined in zoo exhibit
 - iii. Type of Control: A waiver of the criteria defining adequate and well controlled trials was granted under 514.111 (a)(5)(ii).
 - iv. Diagnosis: N/A
 - v. Dose Form: Sterile Injectable Liquid
 - vi. Route of Administration: Intravenous
 - vii. Dosages Used: Three of the four were dosed at 0.4 mg/kg yohimbine HCL following xylazine sedation at a range of 2.6 to 3.4 mg/kg. One sika deer received 0.14 mg/kg yohimbine HCL.
 - viii. Parameters Measured:

1. Dosage of Xylazine in mg/kg
2. Time to Immobilization
3. Amount of Yohimbine HCL in mg/kg
4. Time to Recovery
5. Adverse Effects

- d. Results: Three sika deer receiving 0.4 mg/kg yohimbine HCL did not exhibit any adverse effects. Xylazine sedation was effectively reversed at this dose as well as the 0.14 mg/kg dose level received by the fourth deer.
- e. Statistical Analysis: None
- f. Conclusions: The results in these sika deer demonstrate that yohimbine HCL at 0.4 mg/kg (130% of highest recommended dose level) produced no adverse effects in these deer.
- g. Adverse Reactions: None
- h. Special Issues: A waiver of the criteria defining adequate and well controlled trials was granted under 514. 111 (a)(5)(ii).

5. Safety Trial Five

- a. Type of Study: Field
- b. Name and Address of Investigator:

Dr. Ben Gonzales
Los Angeles Zoo
5333 Zoo Drive
Los Angeles, CA 90027

- c. Study Design:
 - i. Purpose: Demonstrate safety of yohimbine HCL as antagonist for xylazine sedation in white-tailed deer.
 - ii. Test Animals:
 1. Species: White-tailed deer (*Odocoileus virginianus*)
 2. Number: 1
 3. Age and Sex: Subadult, male
 - iii. Type of Control: A waiver of the criteria defining adequate and well controlled trials was granted under 514.111 (a)(5)(ii).
 - iv. Diagnosis: N/A
 - v. Dose Form: Sterile Injectable Liquid
 - vi. Route of Administration: Intravenous

vii. Dosages Used: 2.34 mg/kg

viii. Parameters Measured:

1. Dosage of Xylazine in mg/kg
2. Time to Immobilization
3. Amount of Yohimbine HCL in mg/kg
4. Time to Recovery
5. Adverse Effects

d. Results: This deer was sedated with xylazine and sedation was reversed with 2.34 mg/kg body weight of intravenous yohimbine HCL. Although the deer gave an abnormal response to the yohimbine HCL, as evidenced by extended time to effect, no adverse reactions were observed.

e. Statistical Analysis: None

f. Conclusions: Yohimbine HCL at 7.8 times (333%) of the upper recommended dose produced no toxic effects in this deer.

g. Adverse Reactions: None

h. Special Issues: A waiver of the criteria defining adequate and well controlled trials was granted under 514.111 (a) (5) (ii).

6. Data from published scientific literature to support safety of yohimbine HCL in *Cervidae* (deer):

- a. Data from the published referenced literature supports the safety of yohimbine HCL in the family *Cervidae*. In a study to compare the efficacy of yohimbine HCL with that of 4-aminopyridine and doxapram for the antagonism of xylazine, deer (*Cervus elaphus*) (North American elk) were given an intravenous dose of yohimbine HCL at a rate of 1.0 mg/kg. The only reaction was that these deer became mildly nervous and anxious, but returned to normal with one hour. These deer HAD NOT been treated with xylazine previously. This demonstrates the safety of yohimbine HCL, even without presedation with xylazine, at greater than 3 times the highest recommended dose level(1 C)).
- b. In a study to evaluate yohimbine HCL administration to reverse xylazine sedation in white-tailed deer and mule deer, six deer were given yohimbine HCL at an intramuscular dose rate up to 1.5 mg/kg body weight. Researchers noted that following the administration of yohimbine HCL, the deer remained calm but alert during one to two hours of remote observation. No adverse reactions were observed in any animal in this study(16).

IV. HUMAN SAFETY

Human Safety Relative to Food Consumption: Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this NADA. This product is labeled as a prescription drug not for use in domestic animals or animals to be

consumed for food. Use of this drug is also prohibited 30 days before or during a legal hunting season in free-ranging animals.

Human Safety Relative to Possession, Handling and Administration: Labeling contains adequate caution and warning statements

V. AGENCY CONCLUSIONS

The data submitted in support of this NADA comply with the requirements of Section 513 of the Act and Section 514.111 of the implementing regulations. The data demonstrated that Antagonil (yohimbine hydrochloride) Injection when used under the labeled conditions of use is safe and effective.

Under Section 512(C)(2)(F)(ii) of the Generic Animal Drug and Patent Term Restoration Act of 1988, this New Animal Drug Application qualifies for three years of marketing exclusivity because yohimbine hydrochloride is a previously approved drug for use in dogs and new clinical or field investigations were required for this NADA to provide for use in free ranging or confined members of the family (*Cervidae* (deer, elk)).

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is required to monitor critical signs of xylazine sedation, determine when the antidote yohimbine is indicated, and to then properly administer the drug intravenously.

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19. [See Waiver of Well Controlled Studies As Required By 514.111 (a)(5)(ii) dated July 20, 1990 (attached)]
20. Fletcher, J. 1974. Hypersensitivity of an isolated population of red deer (*Cervus elaphus*) to xylazine. Vet Rec 94:85-86. [See Waiver of Well Controlled Studies As Required By 514. 111(a)(5)(ii) dated July 20, 1990 (attached)]

WAIVER OF WELL-CONTROLLED STUDIES AS REQUIRED BY 514.111(a)(5)(ii)

A waiver of the requirements to perform adequate and well-controlled field investigations to demonstrate efficacy of this product for use as an antagonist to xylazine sedation in members of the family *Cervidae* (deer family) is granted. The waiver is based upon the following reasons:

1. The extensive length of sedation and recumbency produced by xylazine in members of the deer family is well documented in the scientific peer-reviewed literature. Studies of xylazine sedation in 49 white-tailed deer (*Odocoileus virginianus*) resulted in a mean recovery time of 197.9 +/- 101.5 (SD) minutes following intramuscular xylazine doses of +/- 1.91 mg/kg +/- 0.76 (SO) (Roughton, R.D. 1975. JAVMA 167(7):574-576). Studies of intramuscular xylazine sedation in 102 black-tailed deer (*Odocoileus hemionus*) demonstrated a mean duration of recumbency of 144 +/- 9.3 minutes (Jacobson, N.K. 1983. J Wild Manage 47:252-255). Studies in elk (*Cervus elaphus*) have documented recovery times in 13 elk sedated with xylazine at dose range of .10 to 3.03 mg/kg to have a mean recumbency time of 504 +/- 208 (SD) minutes (Fletcher, J. 1974. Vet Rec 94:85-86). Eight adult elk (4 males, 4 females) sedated with 1.19 +/- 0.23 mg/kg (males) and 0.68 +/- 0.02 mg/kg (females) xylazine and recumbency times of 232.6 +/- 55.1 and 270 +/- 18.2 minutes respectively (Renecker, L.A. and C.D. Olsen.

1986. J Wildl Dis 22(1):91-96). Ten elk (*Cervus elaphus*) sedated by 1.0 to 1.5 mg/kg xylazine had average times to standing of 104 minutes (MacKintosh, C.G. and G. Van Reenan. 1984. NZ Vet J 32(11):181-184). The data adequately and scientifically documents the prolonged sedation resulting from use of xylazine in the family *Cervidae* (deer).

2. The welfare and humane treatment of all the animals in these field investigations were considered a priority. The hazards of xylazine sedation and prolonged recumbency in *Cervidae* are considerable and put the animal at risk. Each cited study describes post sedation bloat, aspiration of rumen contents, and self-induced trauma due to incoordination during recovery as common complications. Based upon these previously referenced studies, it is inappropriate and inhumane to require untreated control groups in the field investigations and to unnecessarily subject additional animals to this risk. Furthermore, the animals in these investigations are, by law, subject to federal, state and municipal regulations regarding their handling, and cannot be put unnecessarily at risk.
3. Substantial evidence of drug efficacy was obtained in clinical field trials involving 240 members of the family *Cervidae* (225 deer, 25 elk). The total recovery time was 20.5 (deer) and 36.5 (elk) minutes when yohimbine was administered following xylazine versus an expected recovery time of 100 to 200 minutes for xylazine alone. The recumbency time after administration of yohimbine was +/- 5 minutes. The reduction in recumbency time attributable to yohimbine is clearly demonstrated. Therefore, the effectiveness of yohimbine hydrochloride as an antagonist to xylazine sedation in *Cervidae* is conclusively established by the alternative methodology used in the clinical field trials.

Additionally there is currently no other antagonist approved to reverse the agonist effects of xylazine in the family *Cervidae*. Based on the above criteria, the request is considered valid, and the waiver of adequate and well-controlled field investigations is granted.

Gerald B. Guest, DVM
Director
Center for Veterinary Medicine

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.