

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 140-866

B. Sponsor

VET-A-MIX, Inc.
604 West Thomas Avenue, P.O. Box A
Shenandoah, Iowa 51601 U.S.A.

C. Proprietary Name

Yobine™Injectable Solution

D. Established Name

yohimbine hydrochloride injectable solution

E. Dosage Form

20 mL multiple dose vials as a sterile solution containing 2.0 mg/mL

F. Route of Administration

Intravenous

G. Species / Class

Dogs

H. Indication

Xylazine Reversing Agent and Antidote For Use in Dogs Only

II. EFFECTIVENESS

A. Pivotal Studies. 1

1. Clinical (field) study
2. Names and addresses of investigators:

Dr. John C. Thurmon
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University of Illinois
Urbana, IL 61801

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2864 Hollywood Boulevard
Hollywood, FL 33020

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Dr. C. Lee Tyner
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Texas A&M University
Nashville, TN 37207

Dr. Jerry W. Perry
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Nashville, TN 37207

3. General design of the investigation

- a. Purpose of study. The purpose of the study was to test the safety and effectiveness of yohimbine as a reversing agent and antidote for xylazine in dogs.
- b. Test animals: > or =180 dogs of random age, sex, weight, and breed.
- c. Type of controls used. Two types of controls were used: (1) each animal was tested for behavioral/pharmacologic effects before and after injection of the Yobine(TM); and (2) half of the test animals were administered a placebo instead of the test drug.
- d. Diagnosis: Testing was done on animals which were given xylazine for procedures indicated for its use.
- e. Dosage form: sterile aqueous solution. The product tested was identical to the product to be marketed.
- f. Route of administration: I.V.
- g. Dosage used: Dose in study was 0.5 mL yohimbine per 20 pound body weight (0.05 mg/lb or 0.11 mg/kg).
- h. Test duration: Testing at sites started after October 10, 1986 and was terminated on June 1, 1987. Each animal was observed for > or =35 minutes.
- i. Pertinent parameters measured: Sedation times (Recumbency, Arousal, Walk) Analgesia (Prick response) Clinical Signs, Heart Rate, Respiration Rate

4. Results

Veterinarians conducting the clinical trials were instructed to administer xylazine (Rompun®, Bay Vet), using a random table, by one of the following routes and doses in mg/lb: (1) I.V. = 0.5; (2) I.M. = 1.0 for dogs < 50 lb, 0.5 for dogs > or = 50 lb; S.C. = 1.0.

Seventy one out of 258 cases were not usable, mainly due to the fact that animals frequently did not become adequately sedated in dogs given the xylazine I.M. at 0.5 mg/lb, and to other aberrations, such as drugs being combined in the

tests. Therefore, 187 cases were used in the trials. The following observations were recorded

Table I Least Square Means For Certain Variables Measuring Effects of a Yohimbine vs. Placebo Injection After Use of Xylazine Yohimbine Given by IV

Variable	Method of Xylazine Injection - IV - Yohimbine	Method of Xylazine Injection - IV - Placebo	Method of Xylazine Injection - IM - Yohimbine	Method of Xylazine Injection - IM - Placebo	Method of Xylazine Injection - SC - Yohimbine	Method of Xylazine Injection - SC - Placebo
Arousal time	12.25	21.55	17.59	21.75	14.81	26.27
Difference in heart rate prior to and post injection	15.90	61.45	13.17	58.83	18.28	60.03
Difference in respiratory rate prior to and post injection	31.31	39.65	20.96	51.20	32.26	46.73
Prick test score time 2	1.90	2.76	1.88	2.67	1.91	2.88
Prick test time 3	1.71	2.69	1.76	2.46	1.74	2.66
Walk time	14.55	32.25	19.39	44.85	17.19	35.52

Note: Yohimbine was injected 15 minutes (min) after xylazine I.V. and 25 minutes after xylazine I.M. and S.C.

5. Conclusions drawn from the study. Yohimbine significantly shortened the arousal time, increased the heart and respiratory rates, and decreased analgesia in xylazine-treated dogs.
6. No adverse effects were reported.

B. Pivotal Studies. 2

1. Dose Titration Study.

2. Names and addresses of investigators who did the study:

Gary D. Osweiler, D.V.M., M.S., Ph.D.
Veterinary Diagnostic Laboratory
College of Veterinary Medicine
Iowa State University

Ames, Iowa 50011
Dean H. Riedesel, D.V.M., Ph.D.
Department of Veterinary Clinical Science
College of Veterinary Medicine
Iowa State University
Ames, Iowa 50011

3. General design of the investigation:

- a. Purpose of the study: The study was designed to test the efficacy and safety of graded doses of yohimbine on dogs treated with xylazine at 1x or 5x the normal dose.
- b. Test animals: 15 female and 15 male young healthy adult dogs of mixed breed, which were randomly assigned to five test groups
- c. Type of control group used: Two types of controls were used: (1) each dog was tested for various parameters two times before administering the treatments, and (2) one group received a placebo solution.
- d. Diagnosis: NA, since healthy dogs were used.
- e. Dosage form: Sterile aqueous solution. The product tested was identical to the product to be marketed.
- f. Route of Administration: I.V.
- g. Dosages used:

Group	Xylazine (IV)	Yohimbine (IV)
1	1x (0.5 mg/lb)	0x (Vehicle Cont.)
2	1x (0.5 mg/lb)	0.2x (0.01 mg/lb)
3	1x (0.5 mg/lb)	1x (0.05 mg/lb)
4	1x (0.5 mg/lb)	5x (0.25 mg/lb)
5	5x (2.5 mg/lb)	1x (0.05 mg/lb)

Xylazine (Rompun®) was administered by a single I.V. injection into a saphenous or cephalic vein; yohimbine was administered by a single I.V. injection into the opposite vein 5 minutes later.

- h. Test duration: Each dog was observed for $>$ or $=$ 28 days. Concentrated tests were conducted 24 hr after treatment.
- i. Pertinent parameters measured:
 - Clinical signs
 - Hematology
 - Blood serum chemistries
 - Urinalysis
 - Sedation
 - Analgesia
 - Electrocardiogram (ECG)

4. Results

Using Dunnett test for differences between control and treatment groups, there were no significant differences in hematology, serum chemistries, urinalysis, and analgesia. The heart rate returned to normal faster as the level of the yohimbine dose given increased through 0.05 mg/lb. One dog was excluded from the test due to a mistake in dosing.

For the variables MAT (mean arousal time) and MWT (mean walk time), a model fitting procedure using Anderson and Nelson's Linear Plateau models and polynomial regression models was done on the least squares means of the response times to help determine the recommended dose level.

For both MAT and MWT the Linear Plateau Model III, (1) fit very well. This model is a straight line between 0 (placebo) and 0.01 mg/lb dose and a plateau from 0.01 mg/lb to 0.25 mg/lb.

5. Conclusions Drawn From the Study:

Yobine(TM) was safe when dosed I.V. at 0.01 to 0.25 mg/lb after treatment with xylazine and was effective at doses of 0.05 to 0.25 mg/lb in reversing the pharmacologic and toxicologic effects of xylazine.

- 6. No adverse effects were reported, except increase CNS activity (brief seizures and muscle tumors) in two dogs in group four.

C. Corroborative Studies - Abstracts of Literature Showing Effectiveness:

Hatch RC, Kitzman JV, Zahner JM, Clark JD: Antagonism of xylazine sedation with yohimbine, 4-aminopyridine, and doxapram in dogs. *Am J Vet Res* 46:371-375, 1985. Groups of atropinized dogs (six dogs/group) were sedated with xylazine IM, 2 mg/kg. When recumbent dogs were given IV saline, yohimbine (0.05, 0.1 and 0.2 mg/kg) 4-aminopyridine (0.3, 0.6 and 0.9 mg/kg), doxapram (0.5, 1.0, 2.0 and 4.0 mg/kg) or the smallest doses of these antagonists as dual or triple combinations.

Control MAT and MWT were 15.5 and 24.8 minutes respectively. The antagonists reduced these values to yield equipotent doses(mg/kg) of yohimbine, 0.2, 4-AP, 0.6 and doxapram 0.5.

Two additional groups were given an overdose of xylazine of 11 mg/kg, IM. One group was given saline, the other yohimbine, 0.4mg/kg. Control MAT-MWT were

41.5 and 144.5 minutes, respectively. Yohimbine decreased these values to 2.2 and 2.5 minutes, respectively.

Yohimbine was the most effective of the three agents stated. Combinations of yohimbine, 4-AP and doxapram did not offer a real advantage over yohimbine alone.

Hsu WH: Effect of yohimbine on xylazine-induced central nervous system depression in dogs. JAVMA 182:698-699, 1983. Intravenous injection of xylazine (1 to 10 mg/kg) introduced a dose dependent CNS depression that was prevented by a low dosage of yohimbine (0.1 mg/kg, IV). Xylazine at a dosage of 10 mg/kg induced convulsions in three of five dogs. In addition, the CNS depressant effect of xylazine (1 to 10 mg/kg) was reversed by yohimbine at dosages ranging from 0.01 to 1.0 mg/kg. The author concluded that yohimbine at a dosage of 0.1 mg/kg IV is suitable as an antagonist to control the duration and depth of xylazine induced CNS depression.

Hsu WH, McNeel SV: Effect of yohimbine of xylazine included prolongation of gastrointestinal transit in dogs. JAVMA 183:297-300, 1983. The normal mean time for barium sulfate to move from the stomach to the duodenojejunal junction was 4.8 ± 1.2 minutes. An IV injection of xylazine (1 mg/kg) prolonged the mean time to 157 ± 37.8 minutes. Yohimbine 0.1 mg/kg IV did not affect gastrointestinal mobility. It did, however, prevent both the gastrointestinal and sedative effects of xylazine.

Hsu WH, Lu ZX, Hembrough FB: Effect of xylazine on heart rate and arterial blood pressure in conscious dogs, as influenced by atropine, 4-aminopyridine, doxapram, and yohimbine. JAVMA 186:153-156, 1985. The effect of xylazine on heart rate (HR) and mean arterial blood pressure (ABP) was studied in 5 male dogs. IV injection (1 mg/kg) caused a decrease in HR accompanied by sinus arrhythmia plus an initial increase in ABP followed by a decrease.

Atropine sulfate (0.045 mg/kg, IM) increased ABP and HR but prevented xylazine induced bradycardia in only 3 of 5 dogs. Yohimbine given IV (0.1 mg/kg) antagonized hypertension, hypotension and bradycardia induced by xylazine. Doxapram and 4-aminopyridine were not found to be beneficial.

McNeel SV, Hsu WH: Xylazine induced prolongation of gastrointestinal transit in dogs: Reversal by yohimbine and potentiation by doxapram. JAVMA 185:878-881, 1984. The effects of yohimbine and doxapram on xylazine induced prolongation of gastroduodenal transit of barium sulfate were studied in 5 dogs. Base line time from stomach to duodenojejunal junction was 5.6 ± 4.0 minutes. Xylazine (IV 1 mg/kg) prolonged time to 95 ± 14.6 minutes.

Yohimbine (IV 0.1 mg/kg) reversed gastrointestinal and sedative effects of xylazine (time dropped to 22 ± 5.7 minutes).

Doxapram alone prolonged time to 43.0 ± 22.8 minutes while when given in combination with xylazine, transit time increased to 148.0 ± 32.7 minutes.

It was concluded that yohimbine is effective as an antidote to reverse the xylazine induced prolongation of gastrointestinal transit, whereas doxapram has no value.

Hatch RC: Experiments on antagonism of barbiturate anesthesia with adrenergic, serotonergic, and cholinergic stimulants given alone and in combination. Am J Vet Res 34:1321-1331, 1973. Dogs (6 controls, 8 principals) were anesthetized to stage

III-2 with thiopental once a week. Immediately after IV injection, the dogs were given an IV injection of an amphetamine isomer, physostigmine, oxotremorine, or yohimbine, 0.5 mg/kg. Amphetamines and yohimbine shortened duration of anesthesia. A combination of yohimbine and d-amphetamine reversed thiopental anesthesia. Further emphasis of this research was on dose titration with the combinations.

Hatch RC, Booth NH, Clark JD, Crawford LM, Kitzman JV, Wallner B: Antagonism of xylazine sedation in dogs by 4-aminopyridine and yohimbine. Am J Vet Res 43:1009-1014, 1982. Groups of fasted atropinized dogs were given xylazine 2.2 mg/kg IM. When fully sedated, the dogs were given IV 4-aminopyridine (4-AP) (0.3 mg/kg), yohimbine (0.125 mg/kg) or a combination of 4-AP + yohimbine in weekly trials. Control groups were given saline solution. Two additional groups were given a 5x dose of xylazine (11 mg/kg) IM. One group was given 4-AP + yohimbine IV, the other was given saline.

Four AP decreased MWT to six min from 14.1 and 17.8 minutes. Mean total recovery time (TRT) was not affected. Yohimbine decreased MWT to 2.2 minutes and reduced TRT to 0.4 hours (from 0.8 and 2.7 hours). In the 5x groups, the combination reduced MWT to 1.4 and 1.9 minutes and the TRT to 0.5 hours.

Schmitt H, Le Douared J-C, Petillot N: Antagonism of the antinociceptive action of xylazine, and alpha-sympathomimetic agent, by adrenoceptor and cholinceptor blocking agents. Neuropharmacology 13:295-303, 1974. The potency of adrenoceptor and cholinceptor agent to antagonize the antinociceptive action of xylazine, an alpha-sympathomimetic agent, was studied.

Yohimbine (1-2 mg/kg) and piperoxan (2.5-10 mg/kg) given intraperitoneal, antagonized "very effectively" the antinociceptive effects of xylazine in two tests, electrical stimulation of the rat's tail and the hot plate test in mice.

III. TARGET ANIMAL SAFETY

A. Pivotal Studies.

1. Acute toxicity
2. Names and addresses of investigators: The investigators were Dr. Gary D. Osweiler and Dr. Dean H. Riedesel, listed in "Dose titration study " above.
 - a. General Design of the Investigation:
 - b. Purpose of the Study: The study was designed to test the safety of yohimbine in dogs treated at 0, 1x, 3x, and 5x the intended dose.
 - c. Test Animals: 12 female and 12 male young healthy adult dogs of mixed breed, which were randomly assigned to 4 test groups.
 - d. Dosage Form: Sterile aqueous solution. The product tested was identical to the product to be marketed.

e. Dosages Used:

Group	Treatment
1 (6 dogs)	0X Diluent control (vol. = 5X dose of yohimbine)
2 (6 dogs)	1X 0.05 mg of yohimbine/lb body weight
3 (6 dogs)	3X 0.15 mg of yohimbine/lb body weight
4 (6 dogs)	5X 0.25 mg of yohimbine/lb body weight

Each dog was administered the prescribed dose I.V. in a cephalic or saphenous vein 3 times at 6 hr intervals (0 time, 6 hr, and 12 hr).

f. Route of Administration: I.V.

g. Test Duration: Each dog was observed for > or = 28 days. Intensive testing was conducted for 24 hr. after treatment.

h. Experimental Parameters Measured:

- Clinical signs
- Hematology
- Serum biochemistry
- Urinalysis
- Electrocardiogram
- Necropsy
- Histopathology

3. Results Using Dunnett test for difference between control and treatment groups, there were no significant differences in hematology, serum chemistry, and urinalysis.

A routine necropsy and a histopathology failed to detect any treatment related changes.

4. Conclusions Drawn From the Study: Yobine(TM) was safe when each dog was dosed I.V. at 0.05, 0.15 and 0.25 mg/lb body weight 3 times at 6 hour intervals.

B. Corroborative Studies - Abstracts of Literature Showing Safety

Hatch RC et al.: Antagonism of xylazine sedation with yohimbine, 4-aminopyridine and doxapram in dogs. *Am J Vet Res* 46:371-375, 1985. This literature reference has also been cited as a corroborative study for effectiveness. The authors used a 1x, 2x and 4x dose of yohimbine in their investigations and noted that, "There was no residual sedation/ataxia 5 to 10 minutes after the largest dose of yohimbine. Signs of excitement or anxiety were not observed".

Luckens MM, Malone MH: Cardiovascular effect of reserpine, yohimbine, and reserpine-yohimbine mixtures on intact anesthetized dog. *J Pharm Sci* 62:1286-1290, 1973. Thirty-two mongrel dogs, both sexes, 9.5-40 kg weight were randomly divided into 8 groups. The dogs were given single IV treatments of 0.9% saline, reserpine, yohimbine or reserpine-yohimbine mixtures. Each animal was anesthetized to the point of blockage of the corneal reflex by slow IV titration of a

30% solution of urethan. Direct femoral arterial blood pressure, heart rate and respiratory rate were recorded kymographically. A standard dose of epinephrine was determined, IV, for each animal. After 2 control injections of the standard dose of epinephrine, 1 of the 8 treatments was administered, femoral vein, at zero time. Recording of blood pressure and other physiological parameters was continued throughout the 300 minute observation period. Yohimbine doses were 0.1 mg and 1.0 mg/kg body weight respectively. The 0.1 mg/kg dose did not change epinephrine depressor response, heart rate (HR), blood pressure or epinephrine pressor response. However, a 1.0 mg/kg dose produced marked changes in blood pressure, epinephrine pressor response and epinephrine depressor response. None of the animals in the yohimbine groups died.

Hsu WH: Effect of yohimbine on xylazine induced central nervous system depression in dogs. JAVMA 182:698-699, 1983. This article has also been cited as corroborative evidence for effectiveness. Yohimbine was studied as a reversal agent for the CNS effects of xylazine in 5 dogs, both sexes, at doses from 0.01 to 1.0 mg/kg. At doses of 0.01 to 0.1 mg/kg yohimbine did not alter behavior of the dogs. "At 0.33 mg/kg, yohimbine alone appeared to cause apprehension in all 5 dogs for 20 to 40 minutes." "Yohimbine alone at 1.0 mg/kg induced apprehension in all 5 dogs for at least 1 hour."

Hatch RC, Wilson RC, Jernigan AD, Clark JD, Brown J: Reversal of thiopental induced anesthesia by 4-aminopyridine, yohimbine, and doxapram in dogs pretreated with xylazine or acepromazine. Am J Vet Res 46:1473-1478, 1985. This article reports on a study of the reversal of thiopental anesthesia by various antagonists including yohimbine alone at 0.4 mg/kg. The authors also report that yohimbine is the most effective antagonist of thiopental anesthesia in xylazine treated dogs. They go on to state "and did not induce obvious undesirable side effects. Post arousal residual sedation and ataxia disappeared in 30 to 60 minutes and relapses did not occur."

Hsu WH: Xylazine-pentobarbital anesthesia in dogs and its antagonism by yohimbine. Am J Vet Res 46:852-855, 1985. This article reports on the study of the reversal of xylazine pentobarbital anesthesia in the dog and its reversal by yohimbine. The author states that "the primary disadvantages of xylazine are bradycardia with heart block and respiratory depression. These side effects are antagonized by yohimbine, thereby the case for its use as a safety factor. In the present study, after administration of yohimbine, respiratory rate and air flow were significantly increased."

IV. HUMAN FOOD SAFETY

A. 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 for use in dogs only, which are non-food animals.

B. 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 512 of the Act and Section 514.111 of the implementing regulations. The data demonstrated that Yobine Injectable Solution when used under the labeled conditions of use is safe and effective.

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.

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.