

Approval Date: FEB 10 2003

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 139-236

Cervizine 300
(xylazine hydrochloride)

Lloyd, Inc.
P.O. Box 130
604 West Thomas Avenue
Shenandoah, IA 51601-0130

NADA 139-236

FOIS-1

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FREEDOM OF INFORMATION SUMMARY

1. GENERAL INFORMATION

a. **File Number:** Supplemental New Animal Drug Application (S/NADA) 139-236

b. **Sponsor:** LLOYD, Inc.
604 W. Thomas Avenue
P.O. Box 130
Shenandoah, Iowa 51601-0130
Drug Labeler Code: 061690

c. **Established Name:** Xylazine hydrochloride

d. **Proprietary Name:** Cervizine 300 Injectable

e. **Dosage Form:** Injectable 300 mg/mL sterile solution

f. **How Supplied:** 20 mL multiple dose vials

g. **How Dispensed:** Prescription (Rx)

h. **Amount of Active Ingredients:** Xylazine hydrochloride 300 mg/mL solution

i. **Route of Administration:** Intramuscular

j. **Species/Class:** Fallow Deer, Mule Deer, Sika Deer, White-tailed Deer, and Elk/Cervidae

k. **Recommended Dosage:**

Fallow Deer (*Dama dama*) – 0.67 to 1.33 mL/100 lbs body weight (2.0 to 4.0 mg/lb or 4.4 to 8.8 mg/kg);

Mule (*Odocoileus hemionus*), Sika (*Cervus nippon*) & White-tailed (*Odocoileus virginianus*) Deer – 0.33 to 0.67 mL/100 lbs body weight (1.0 to 2.0 mg/lb or 2.2 to 4.4 mg/kg);

Elk (*Cervus canadensis*) – 0.08 to 0.17 mL/100 lbs Bodyweight (0.25 to 0.5 mg/lb or 0.55-1.1 mg/kg)

l. **Pharmacological Category:** Sedative/Analgesic

m. **Indications:** Xylazine should be used in Cervidae (Fallow Deer, Mule Deer, Sika Deer, White-tailed Deer and Elk) when it is desirable to produce a state of sedation accompanied by a shorter period of analgesia. Xylazine may be used for the following:

1. To calm and facilitate handling of fractious animals.
2. Diagnostic procedures.
3. Minor surgical procedures.
4. Therapeutic medication for sedation and relief of pain following injury or surgery.
5. As a preanesthetic to local anesthetic. Cervizine 300 at the recommended dosages can be used in conjunction with local anesthetics, such as procaine or lidocaine.

n. Effect of Supplement: This supplement provides for a 300 mg/mL xylazine concentration, in addition to the approved concentration of 100 mg/mL for Cervidae.

2. EFFECTIVENESS:

AnaSed (xylazine hydrochloride) 100 mg/mL and Cervizine 300 Injectable (xylazine hydrochloride) 300 mg/mL are injectable solutions that contain the same active and inactive ingredients and are buffered to the same pH. Xylazine hydrochloride is freely soluble in water at 100 mg/mL and 300 mg/mL. Based on the formulation characteristics of the proposed xylazine product, no additional effectiveness studies were required for approval of the xylazine 300 mg/mL product.

3. TARGET ANIMAL SAFETY:

AnaSed (xylazine hydrochloride) 100 mg/mL and Cervizine 300 Injectable (xylazine hydrochloride) 300 mg/mL are injectable solutions that contain the same active and inactive ingredients and are buffered to the same pH. Xylazine hydrochloride is freely soluble in water at 100 mg/mL and 300 mg/mL. Based on the formulation characteristics of the proposed xylazine product, no additional studies were required for approval of the xylazine 300 mg/mL product.

4. HUMAN SAFETY:

This drug is intended for use in Fallow, Mule, Sika, and White-Tailed deer and Elk, which are non-food animals. Because this new animal drug is not intended for use in food-producing animals, data on human safety pertaining to drug residues in food animals were not required for approval of this supplemental NADA.

Human Warnings are provided on the product label as follows: "Avoid accidental administration to humans. Should such exposure occur, notify a physician immediately. Artificial respiration may be indicated. Do not use in Cervidae less than 15 days before or during the hunting season."

5. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfies the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act (FFDCA), and Section 514 of the implementing regulations. The data demonstrate that Cervizine 300, when administered under labeled conditions of use, is safe and effective for use in Cervidae (Fallow Deer, Mule Deer, Sika Deer, White-tailed Deer and Elk) when it is desirable to produce a state of sedation accompanied by a shorter period of analgesia.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is judged to be critical for the assessment of conditions requiring its use as well as for proper use of the drug.

Under the Center's supplemental approval policy (21 CFR 514.106(b)(2)), this is a Category II change; therefore, this action did not require a reevaluation of the safety and effectiveness data in the parent application.

Cervizine 300 Injectable is under the following U.S. Patent Numbers:

<u>U.S. Patent Number</u>	<u>Date of Expiration</u>
4,614,798	September 30, 2003

6. ATTACHMENTS:

Facsimile labeling is attached as indicated below:

- a. Vial Label
- b. Individual Box Label
- c. Package Insert



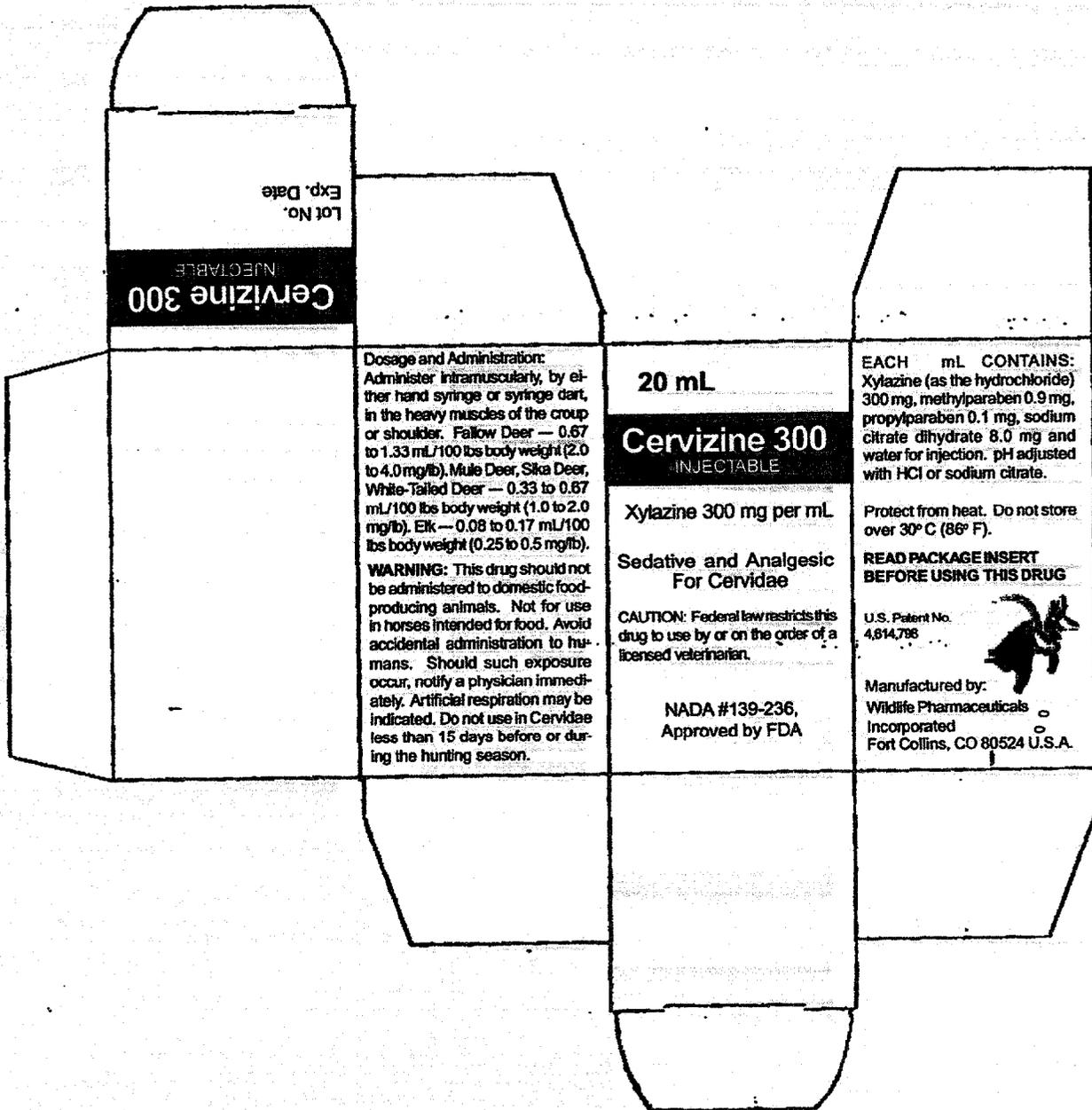
Dosage and Administration:
 Administer intravenously, by either hand syringe or catheter dart, in the heavy muscles of the crop or shoulder. Follow Dose — 0.57 to 1.50 mL/100 lbs body weight (2.0 to 4.6 mg/lb). Male Deer, Elk Deer, White-Tailed Deer — 0.33 to 0.67 mL/100 lbs body weight (1.0 to 2.0 mg/lb). Elk — 0.20 to 0.17 mL/100 lbs body weight (0.25 to 0.5 mg/lb).
WARNING: This drug should not be administered to domestic food-producing animals. Not for use in horses intended for food. Avoid accidental administration to humans. Should such exposure occur, notify a physician immediately. Artificial respiration may be indicated. Do not use in Cervizine less than 15 days before or during the hunting season.

20 mL
Cervizine 300
 INJECTABLE
 Xylazine 300 mg per mL
 Sedative and Anesthetic
 For Cervidae

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.
 NADA #130-236, Approved by FDA

EACH mL CONTAINS: Xylazine (as the hydrochloride salt) 300 mg, meprobamate 0.9 mg, propylparaben 0.1 mg, sodium chloride 8.0 mg and water for injection, pH adjusted with HCl or sodium citrate.
 Protect from heat.
 Do not store over 30° C (86° F).
READ PACKAGE INSERT BEFORE USING THIS DRUG.
 U.S. Patent No. 4,814,788
 Manufactured by:
 Wildlife Pharmaceuticals
 Incorporated
 Fort Collins, CO 80524 U.S.A.

Lot No.
 Exp.



Lot No.
Exp. Date

Cervizine 300
INJECTABLE

Dosage and Administration:
Administer intramuscularly, by either hand syringe or syringe dart, in the heavy muscles of the crop or shoulder. Fallow Deer — 0.67 to 1.33 mL/100 lbs body weight (2.0 to 4.0 mg/lb). Mule Deer, Sika Deer, White-Tailed Deer — 0.33 to 0.67 mL/100 lbs body weight (1.0 to 2.0 mg/lb). Elk — 0.08 to 0.17 mL/100 lbs body weight (0.25 to 0.5 mg/lb).

WARNING: This drug should not be administered to domestic food-producing animals. Not for use in horses intended for food. Avoid accidental administration to humans. Should such exposure occur, notify a physician immediately. Artificial respiration may be indicated. Do not use in Cervidae less than 15 days before or during the hunting season.

20 mL

Cervizine 300
INJECTABLE

Xylazine 300 mg per mL

Sedative and Analgesic
For Cervidae

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

NADA #139-236,
Approved by FDA

EACH mL CONTAINS:
Xylazine (as the hydrochloride) 300 mg, methylparaben 0.9 mg, propylparaben 0.1 mg, sodium citrate dihydrate 8.0 mg and water for injection. pH adjusted with HCl or sodium citrate.

Protect from heat. Do not store over 30° C (86° F).

READ PACKAGE INSERT BEFORE USING THIS DRUG

U.S. Patent No.
4,814,798



Manufactured by:
Wildlife Pharmaceuticals
Incorporated
Fort Collins, CO 80524 U.S.A.

A sleeplike state, the depth of which is dose-dependent, is usually maintained for 1 to 2 hours, while analgesia lasts from 15 to 30 minutes. The centrally acting muscle-relaxant effect causes relaxation of the skeletal musculature complementing sedation and analgesia.

In Cervidae under the influence of xylazine, the respiratory rate is reduced as in natural sleep. Following treatment with xylazine, the heart rate is decreased and a transient change in the conductivity of the cardiac muscle may occur, as evidenced by a partial atrioventricular block. This resembles the atrioventricular block often observed in normal horses.^{1,2,3,4} Although a partial A-V block may occasionally occur following intramuscular injection of xylazine, the incidence is less than when it is administered intravenously. Intravenous administration of xylazine causes a transient rise in blood pressure, followed by a slight decrease.

Xylazine has no effect on blood clotting time or other hematologic parameters.

REFERENCES:

1. Detweiler, D. K.: The Diagnosis and Significance of Cardiac Arrhythmias in Progress in Equine Practice. Edited by E. J. Catcott and J. F. Smithcors. American Veterinary Publications, Inc., Santa Barbara, CA and Wheaton, IL, (1966), 280-281.
2. Glazier, D. B.: Atrioventricular Heart Block. Irish Vet. J., Vol. 12 (1958), 194-198.
3. Holmes, J. R., Alps, B. J.: Observations on Partial Atrioventricular Heart Block in the Horse. Can. Vet. J., Vol. 7, No. 12, (1966), 280-290.
4. Smetzer, D. L., Smith, C. R., Senta, T.: Second Degree Atrioventricular Block in the Horse. Am. J. Vet. Res., Vol. 30, No. 6, (1969), 933-946.

STORAGE INFORMATION:

Protect from heat. Do not store over 30° C (86° F).

HOW SUPPLIED: Cervizine 300 is supplied in 20 mL multiple-dose vials as a sterile solution.

NADA #139-236, Approved by FDA



Manufactured by
Wildlife Pharmaceuticals, Incorporated
Fort Collins, CO 80524 U.S.A

July 2001

Cervizine 300 INJECTABLE (Xylazine) 300 mg/mL Injectable

Sedative and Analgesic for Use in
Cervidae (Fallow Deer, Mule Deer, Sika
Deer, White-Tailed Deer and Elk)

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: Xylazine (as the hydrochloride) 300 mg, methylparaben 0.9 mg, propylparaben 0.1 mg, sodium citrate dihydrate 8.0 mg and water for injection. pH adjusted with HCl or sodium citrate.

INDICATIONS: Xylazine should be used in Cervidae (Fallow Deer, Mule Deer, Sika Deer, White-Tailed Deer and Elk) when it is desirable to produce a state of sedation accompanied by a shorter period of analgesia.

Xylazine may be used for the following:

1. To calm and facilitate handling of fractious animals.
2. Diagnostic procedures.
3. Minor surgical procedures.
4. Therapeutic medication for sedation and relief of pain following injury or surgery.
5. As a preanesthetic to local anesthesia. Cervizine 300 at the recommended dosages can be used in conjunction with local anesthetics, such as procaine or lidocaine.

DOSAGE AND ADMINISTRATION:

1. Dosage

Administer intramuscularly, by either hand syringe or syringe dart, in the heavy muscles of the croup or shoulder.

Fallow Deer (*Dama dama*) — 0.67 to 1.33 mL/100 lbs body weight (2.0 to 4.0 mg/lb or 4.4 to 8.8 mg/kg).

Mule Deer (*Odocoileus hemionus*) — 0.33 to 0.67 mL/100 lbs body weight (1.0 to 2.0 mg/lb or 2.2 to 4.4 mg/kg).

Sika Deer (*Cervus nippon*) — 0.33 to 0.67 mL/100 lbs body weight (1.0 to 2.0 mg/lb or 2.2 to 4.4 mg/kg).

White-Tailed Deer (*Odocoileus virginianus*) — 0.33 to 0.67 mL/100 lbs body weight (1.0 to 2.0 mg/lb or 2.2 to 4.4 mg/kg).

Elk (*Cervus canadensis*) — 0.08 to 0.17 mL/100 lbs body weight (0.25 to 0.5 mg/lb or 0.55 to 1.1 mg/kg).

Following injection of xylazine, the animal should be allowed to rest quietly until the full effect has been reached.

These dosages produce sedation which is usually maintained for 1 to 2 hours, and analgesia which lasts for 15 to 30 minutes.

2. Preanesthetic to Local Anesthesia

Xylazine at the recommended dosages can be used in conjunction with local anesthetics, such as procaine or lidocaine.

3. Preanesthetic to General Anesthesia

Xylazine at the recommended dosage rates produces an additive effect to central nervous system depressants such as pentobarbital sodium, thiopental sodium and thiamylal sodium. Therefore, the dosage of such compounds should be reduced and administered to the desired effect. In general, only 1/3 to 1/2 of the calculated dosage of the barbiturates will be needed to produce a surgical plane of anesthesia. Post-anesthetic or emergence excitement has not been observed in animals preanesthetized with xylazine.

Xylazine has been used successfully as a preanesthetic agent for pentobarbital sodium, thiopental sodium, thiamylal sodium, nitrous oxide, ether, halothane, glyceryl guaicolate and methoxyflurane anesthesia.

WARNING: This drug should not be administered to domestic food-producing animals.

Do not use in Cervidae less than 15 days before or during the hunting season.

In Cervidae, occasional capture-associated deaths occur. Clinical trials reveal a mortality rate of approximately 3.5% attendant with the administration of xylazine.

Do not use xylazine in conjunction with tranquilizers.

Avoid accidental administration to humans. Should such exposure occur, notify a physician immediately. Artificial respiration may be indicated.

PRECAUTIONS: Careful consideration should be given before administering to Cervidae with significantly depressed respiration, severe pathologic heart disease, advanced liver or kidney disease, severe endotoxic or traumatic shock and stress conditions such as extreme heat, cold, high altitude or fatigue.

Analgesic effect is variable, and depth should be carefully assayed prior to surgical/clinical procedures. Variability of analgesia occurs most frequently at the distal extremities of Cervidae. **In spite of sedation, the practitioner and handlers should proceed with caution since defense reactions may not be diminished.**

It is preferable to administer Cervizine 300 to fasted Cervidae. As in all ruminants a safeguard against aspiration of food material into the lungs and/or bloat during deep sedation is necessary.

Care should be taken to administer Cervizine 300 in the heavy muscles of the croup or shoulder. Injections given subcutaneously, intraperitoneally or into fat deposits will give unpredictable results.

Cervidae should not be disturbed during induction or until the full effect of the drug has been reached which is usually 10 to 15 minutes following injection.

The usual time to initial effect of the drug is 2 to 5 minutes. The administrator of the drug should be fully cognizant of this interval prior to administration of drug to free-ranging deer or elk, especially at night or in heavily wooded areas.

If the animal has been underdosed (faulty injection or miscalculation on weight) it is advisable to wait one hour before administering a second dose.

Adequate ventilation -- especially in cages or crates is mandatory; keep head and neck in position to insure patent air passage and to prevent aspiration of stomach contents.

During sedation Cervidae should be prevented from assuming lateral recumbency. A sternal recumbent position is desirable.

While under the effects of xylazine, the animal should be protected from an extremely hot or cold environment.

Efforts should be made to prevent patient from rising until almost complete recovery is attained.

The transportation of Cervidae given Cervizine 300 should be carefully monitored to prevent excessive struggling, injury or death.

Hyperthermic reactions may occur, especially if the subject is in a highly excited psychic state when the drug is administered. Hosing the head and entire body with cold water has usually proven to be an effective deterrent.

The safe use of Cervizine 300 in Cervidae used for breeding purposes, during pregnancy or during lactation has not been evaluated.

Cervidae should be observed closely until all of the sedative effects of Cervizine 300 are gone.

ADVERSE REACTIONS: Xylazine in Cervidae used at recommended dosage levels may occasionally cause slight muscle tremors, bradycardia with partial A-V heart block and a reduced respiratory rate. Movement in response to sharp auditory stimuli may be observed. In Cervidae, salivation, various vocalizations (bellowing, bleating, groaning, grunting, snoring) on expiration, audible grinding of molar teeth, protruding tongue and elevated temperatures have also been noted in some cases.

PHARMACOLOGY: Xylazine, a non-narcotic compound, is a sedative and analgesic as well as a muscle relaxant. Its sedative and analgesic activity is related to central nervous system depression. Its muscle-relaxant effect is based on inhibition of the intraneural transmission of impulses in the central nervous system. The principal pharmacological activities develop within 10 to 15 minutes after intramuscular injection in Cervidae.