Approval Date: February 18, 1988

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 140-442

B. Sponsor

Med-Tech, Inc.
7410 NW Tiffany Springs Parkway, Suite 260
Kansas City, Missouri 64153

C. Proprietary Name

Xylazine HCl Injection

D. Established Name

xylaxine HCl

E. Dosage Form, Route of Administration and Recommended Dosage

For intravenous or intramuscular administration in horses.

The recommended dosage for intravenous administration is 0.5 ml/100 lbs body weight (0.5 mg/lb). The recommended dosage for intramuscular administration is 1.0 ml/100 lbs body weight (1.0 mg/lb).

Following administration of Xylazine HCl Injection, the animal should be allowed to rest quietly until the full effect has been reached. These dosages produce a state of sedation which is usually maintained for 1 to 2 hours.

PREANESTHETIC TO LOCAL ANESTHESIA - At the recommended dosage rates, Xylazine HCl Injection may be used in conjunction with local anesthetics, such as procaine and lidocaine.

PREANESTHETIC TO GENERAL ANESTHESIA - At the recommended dosage rates, Xylazine HCl Injection produces an additive effect to central nervous system depressants, such as sodium pentobarbital, sodium thiopental and sodium thiamylal. Accordingly, the dosage of such compounds should be reduced and administration to the desired effect. Generally, 1/3 to 1/2 of the calculated dosage of the barbiturates will be needed to produce a surgical plane of anesthesia. Postanesthetic or emergence excitement has not been observed in animals preanesthetized with Xylazine HCl Injection.

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

F. Indication

Xylazine HCl Injection should be used in horses when it is desirable to produce a state of sedation. It has been successfully used when conducting various diagnostic,

orthopedic and dental procedures and for minor surgical procedures of short duration. It may also be used as a preanesthetic to local or general anesthesia.

II. EFFECTIVENESS

Relative bioavailability and clinical studies were conducted by TechAmerica Research Center, formerly know as Elars Bioresearch Laboratories, 225 Commerce Drive, Ft. Collins, CO 80524, under Med-Tech's INAD #2969. Additionally, a literature review was submitted which adequately supported the proposed dosage of xylazine and provided information on the pharmacologic, physiologic and clinical effects of xylazine at therapeutic and toxic dose levels.

Relative Bioavailability Study

A study was conducted to compare the relative bioavailability of Med-Tech's Xylazine Hydrochloride Injection and Haver Lockhart's Rompun®, for which there is an approved NADA. Twenty healthy, mature horses (ten males and ten females) of various breeds, ages and weights were randomly assigned to one of two groups of five males and five females each. The horses in Group I received a single intramuscular injection of Med-Tech's product at the rate of 1.0 mg per pound of body weight and the horses in Group II received Rompun® in the same manner and at the same dosage level. Following a 14 day washout period, the procedure was repeated with Group I animals receiving Rompun® and Group II animals receiving the Med-Tech product. Plasma xylazine levels and clinical parameters (attitude, head/neck carriage, ptosis, penile relaxation, audio response, muscular resistance and analgesia) were monitored following treatment. The plasma xylazine profiles were very similar between the products. Mean areas under the curves were within 2%, mean maximum concentrations were within 19%, and mean times at maximum concentrations were within 10%. Standard deviations and coefficients of variation were comparable for each test material. Statistical analyses were conducted on the parameters used to define the blood level profiles, and no statistically significant differences were found between Haver Lockhart's Rompun® and Med-Tech's Xylazine HCl Injection. This study demonstrates the bioequivalency of the Med-Tech Xylazine HCl Injection and Haver Lockhart's Rompun® xylazine injectable solution in terms of blood level profiles and no statistically significant differences were found between Harver Lockhart's Rompun® xylazine injectable solution in terms of blood level profiles and clinical parameters.

Clinical Trials

Clinical studies were conducted to determine the clinical sedative effectiveness of Med-Tech's Xylazine Hydrochloride Injection in horses, and to compare the effectiveness of Med-Tech's xylazine with that of Rompun®(Harver Lockhart) in producing sedation in horses. The following licensed practicing veterinarians conducted the studies:

Charles Mizushima
2550 East County Road 62E
Wellington, Colorado 80459

William Grantham
799 Main St., Suite K
Half Moon Bay, California 94019

J.K. Hahn
4747 SW 60th Avenue
Ocala, Florida 32674
Clay Lilley 251 N. Taylor Laramie, Wyoming 82072

Art Ortenburger
University of Missouri
Equine Center at Middlebush Farm Hwy. 63 South
Columbia, Missouri 65201

Forty two horses received Med-Tech's Xylazine HCl Injection (21 intravenously and 21 intramuscularly) and 41 received Rompun® (20 intravenously and 21 intramuscularly). Each horse received a single treatment of xylazine at the recommended level of 0.5 mg/pound for intravenous administration or 1.0 mg/pound for intramuscular administration. The extent of sedation in each animal was scored prior to treatment and at 10 minutes (IV) or 15 minutes (IM) post treatment. Following the performance of a clinical procedure, the overall sedation was evaluated by the investigator. Quantitatively, the two drugs scored similarly with respect to post treatment sedation; however, the intravenous mode of administration scored higher than the intramuscular mode for both drugs.

The overall evaluations were statistically analyzed using multiway tables and a log linear model. A Chi-square analysis using a model of marginal association revealed no statistically significant ($P<0.05$) interactions between treatments, modes of administration or investigators. The data support the effectiveness of Med-Tech's Xylazine HCl Injection and the therapeutic equivalency of Med-Tech's product and Rompun® as a sedative.

III. TARGET ANIMAL SAFETY

To determine whether there were any toxic effects due to Med-Tech's Xylazine HCl Injection when administered intravenously to horses, a target animal safety study was also conducted by the TechAmerica Research Center. Twelve healthy horses were randomly assigned to one of three groups with an equal number of males and females within each group. The horses in Group I received only physiological saline solution at 0.015 ml per pound one time. The animals in Groups II and III were treated once intravenously with Med-Tech's Xylazine HCl Injection (100 mg xylazine base/ml) at one and three times, respectively, the recommended rate of 0.5 mg/pd. Body weights were determined on days -7, 0, (prior to treatment) and 7. Clinical observations for signs of toxicity were conducted on days -7, and -1, prior to treatment on day 0, at 0.5, 1.0, 1.5, 2.0, 2.5 and 3.0 hours post treatment, and twice daily on days 1 through 7. In addition to the standard observations, scored evaluation of neck and head carriage, ptosis, lower lip relaxation and attitude were performed prior to treatment and at 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0 and 5.0 hours following treatment. Physical examinations were conducted on days -7, -1, 1, 3 and 7. Samples for hematology and serum chemistry evaluation were collected simultaneously with the physical examinations and also on day 0 (prior to treatment). Rectal temperature, heart rate and respiration rate were monitored in each animal twice daily on days -7 through 7 and feed and water consumption were measured daily for each animal on days -7 through 7.

Electrocardiograms were conducted prior to treatment and at 1, 2, 3, 4, 5, 10, 20, 30, 45, 60 and 90 minutes post treatment. No pathologic examinations were necessary as there were no deaths in any of the groups. Results revealed no significant treatment effects for body weight, temperature, respiratory rate or feed and water consumption. As expected, animals receiving 1.5mg xylazine per pound of body weight exhibited a

greater degree of sedation and more pronounced clinical responses (i.e., depression, inactivity, incoordination, drop in head and neck carriage, ptosis and lower lip relaxation) than those animals receiving 0.5 mg xylazine per pound. Animals receiving saline exhibited no sedation or clinical responses. Conventional one-way analyses of variance revealed statistically significant ($P<0.05$) differences between Groups I and II for protime (prothrombin time) on day 3 and for alkaline phosphatase on days 1, 3 and 7 and between Groups I and III for direct bilirubin on day 7. In all cases, however, values remained within normal limits and the differences were not treatment related. The only adverse effects related to treatment were transient cardiac dysrhythmia, primarily decreased heart rate and second degree atrioventricular blocks, observed in both treatment groups. Two animals receiving the proposed product at three times the recommended dose went down approximately one minute after treatment but were standing again within three minutes. A two-sample t-test was performed on the changes in the electrocardiograph values from their pre-treatment levels. Several statistically significant ($P<.05$) differences were noted at many of the time points between the control group and one or both treatment groups. The interferences with cardiac conductivity are widely recognized as transient effects of xylazine treatment and are of questionable clinical significance.

IV. HUMAN FOOD SAFETY

Human Food Safety: As labeled, the drug poses no hazard to human safety pertaining to drug residues, because it is labeled for use in animals not intended for food (horses).

Human Safety Relative to Possession, Handling and Administration: The labeling contains adequate caution/warning statements.

V. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of Section 512 of the Act and Section 514.111 of the implementing regulations. The data demonstrate that Xylazine HCl Injection, when used under its labeled conditions of use, is safe and effective.

Xylazine HCl Injection is used in the horse when conducting various diagnostic, orthopedic, and dental procedures, for minor surgical procedures of short duration, and as a preanesthetic to local or general anesthesia, all of which are procedures which should be performed by a licensed veterinarian only. Accordingly, Xylazine HCl Injection is a prescription new animal drug.

VI. ATTACHMENTS

Xylazine HCl package insert

Xylazine HCl master shipper product label

Copies of these labels may be obtained by writing to the: Freedom of Information Office
Center for Veterinary Medicine, FDA
7500 Standish Place
Rockville, MD 20855

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.