I. GENERAL INFORMATION

A. File Number

NADA 139-236

B. Sponsor

VET-A-MIX, Inc.
604 W. Thomas Ave.
PO Box A

C. Proprietary Name

AnaSed(TM), Injectable Solution

D. Established Name

xylazine injectable solution, 20 mg/ml

E. Dosage Form

20 ml multiple dose vials as a sterile solution containing 20 mg xylazine/ml.

F. Dispensing Status

Prescription

G. Dosage Regimen

Intravenous	0.5 mg/20 lb body weight (0.5 mg/lb, or 1.1 mg/kg)
intramuscular or subcutaneous	1.0 mg/20 lb body weight (1.0 mg/lb, or 2.2 mg/kg).
NOTES	In large dogs (over 50 lbs), a dosage of 0.5 mg/kg (1.1 mg/kg) administered intramuscularly may provide sufficient sedation and/or analgesia for most procedures.

H. Route of Administration

Intravenous, intramuscular or subcutaneous

I. Species/Class

Dogs

J. Indication

Xylazine should be used in dogs when it is desirable to produce a state of sedation accompanied by a shorter period of analgesia. Xylazine has been used successfully as follows:

a. Diagnostic procedures: Examination of mouth and ears, abdominal palpation, rectal palpation, vaginal examination, catheterization of the bladder and radiographic examinations of head and extremities.
b. Orthopedic procedures, such as application of casting materials and splints.
c. Dental procedures.
d. Minor surgical procedures of short duration such as debridement, removal of cutaneous neoplasms and suturing of lacerations.
e. To calm and facilitate restraint of fractious animals.
f. Major surgical procedures:
    1. When used as a preanesthetic to general anesthesia.
    2. When used in conjunction with local anesthetics.

K. Effect of Supplement

Supplement provides for use of the product in an additional species (dog).

II. EFFECTIVENESS

Two adequate and well controlled studies were conducted to establish the effectiveness of AnaSed. Additionally, a literature review was submitted which confirmed the proposed dosage of xylazine and provided information on the pharmacologic, physiologic, and clinical effects of xylazine at therapeutic and toxic dose levels.

Pivotal Studies:

A. Pivotal Studies

1. Controlled Laboratory Study

A combined study of dose titration (efficacy) and toxicity of the xylazine was conducted. The trials involved 30 adult dogs, randomly divided into 5 test groups of 3 males and 3 females, to test graded doses of xylazine with a geometric progression of 2. A summary of dosing by test groups follows, with the number of dogs tested per group:

Group	Subjects	Xylazine (I.V.)	Dose Titr.	Toxicology
1	6	0.0x (Placebo Control)	6	6
2	6	0.5x (0.25 mg/lb)	6	-
3	6	1.0x (0.50 mg/lb)	6	6
4	6	2.0x (1.00 mg/lb)	6	6
5	6	4.0x (2.00 mg/lb)	6	6

Tests were conducted in 3 replicates (Phases), each replicate containing dogs of both sexes and all groups. Xylazine (AnaSed(TM), Canine Injectable Xylazine HCl, Vet-A-Mix, Inc., containing 20 mg xylazine/ml) was administered by a single IV injection into a cephalic vein. The effect on sedation was assessed by recording the Recumbency Time (RT), Arousal Time (AT) and

Walk Time (WT) after injection of xylazine. The effect on analgesia was done by a toe pinch prior to injection, at five minutes, 15 minutes, and 35 minutes post injection of xylazine. Responses were graded where 0 = a violent reaction and 3 = no response.

The study directors were Gary D. Osweiler, DVM, PhD and Joseph W. Denhart, DVM, College of Veterinary Medicine, Iowa State Univ., Ames, Iowa 50011.

The 6 dogs in the control Group 1 had no RT, AT, or WT. This was expected, since those dogs received no drug. The ANOVA used to test sedation was therefore conducted on the 4 groups containing the 24 dogs which received xylazine (groups 2,3,4 & 5). The ANOVA was conducted on all 5 groups in testing analgesia (Toe Pinch).

a. Sedative Effects

Following are results of the study and statistical analysis. The table summarizes means of the results.

Group	Xylazine (I.V.)	RT (Min)	AT (Min)	WT (Min)
1	0.0x (Control)	N/A	N/A	N/A
2	0.5 x (0.25 mg/lb)	1.78	10.56	19.72
3	1.0x (0.50 mg/lb)	1.37	28.79	32.85
4	2.0x (1.00 mg/lb)	2.23	24.72	59.79
5	4.0x (2.00 mg/lb)	2.10	65.97	131.10

Generally some type of modeling is done in a dose titration study, but in this instance the data collected do not appear to warrant this type of analysis. Walk Time is the only sedation variable in which the treatment means were significantly different and this was probably largely due to the 2.0 mg/lb group which was included primarily for toxicology purposes. The standard deviations for Arousal Time and Recumbency Time are large indicating that the data is highly variable. However, the drug appears to cause sedation and .5 mg AnaSed appears to give the most favorable results when all three variables are considered -- shorter time to recumbency than either .25 mg, 1.0 mg or 2.0 mg, slightly longer arousal time than 1.0 mg but definitely shorter than 2.0 mg (arousal time for .25 mg appears too short) and much better walk time than either 1.0 or 2.0 mg.

b. Analgesic Effects

The following table summarizes the results of the toe pinch test:

An analysis of variance done at +5 minutes and +15 minutes post injection showed that the treatment means were significantly different ($p=.03$ and $p=.01$, respectively). Using pairwise comparisons tests for the +5 minute toe

pinch test all of the treatment means are significantly different from the control. In the +15 minute toe pinch test the treatment groups 1.0 mg and 2.0 mg are significantly different from the control at p<.05. The treatment group 0.5 mg is significantly different from the control at P=.08.

Group	Xylazine (I.V.)	-15 Min	+5 Min	+15 Min	+35 Min
1	0.0x (Control)	1.33	1.00	1.17	1.00
2	0.5x (0.25 mg/lb)	1.00	2.17	1.17	1.33
3	1.0x (0.50 mg/lb)	0.67	2.17	2.00	2.17
4	2.0x (1.00 mg/lb)	1.00	2.00	2.50	2.33
5	4.0x (2.00 mg/lb)	1.50	2.33	2.50	2.33

c. Conclusions

Sedation and analgesia were effected at all doses. However, it appeared that the minimum reliable dose was 0.50 mg/lb IV. This dose effected mean sedation times of approximately 30 minutes and analgesia for 5 to 35 minutes.

2. Controlled Clinical Field Trial

Clinical trials were conducted at Urbana, IL (Drs. John C. Thurmon, William Tranquilli, and G. John Benson); Nashville, TN (Drs. Robert F. Ingram and Jerry W. Perry); and Houston, TX (Drs. Frederick K. Soifer, S.A. Fronefield, and Marc T. Hays) Rompun® was used as active control. Rompun® and AnaSed(TM) were tested in a double blind study in 182 dogs of both sexes. Sedation was tested by observing recumbency time, arousal time, and walk time as in the laboratory study. Analgesia was tested by observing response to a needle prick. The xylazine products were administered by IV, IM or SC injection.

Procedures conducted in these clinical trials following the administration of xylazine included dentistry, nail trimming, grooming, suturing of wounds, radiography, and physical examinations of fractious animals. Following are results and statistical analyses. Responses to AnaSed(TM) were satisfactory.

Summary of clinical trials where AnaSed(TM) and Rompun® were compared at three locations using behavioral scores:

There were:

- 60 animals at Urbana, Illinois
- 60 animals at Nashville, Tennessee
- 62 animals at Houston, Texas

Animals were from both sexes and were given AnaSed(TM) or Rompun® either I.V., I.M. or S.C..

Measures of sedation were in minutes. The measure of analgesia was a ranked response to prick tests, administered twice before and three times after injection of xylazine. The two measures taken before the injection of the drug were averaged to serve as a baseline and then compared to measures after the injection of the drug. Analyses here are done on corrected post injection scores obtained by subtracting the baseline from the post injection score. For both analgesia and sedation measures there were no significant differences between the two drugs.

The means of measures of sedation by drug, administration, and location are given below:

RECUMBENCY TIME

	Location			
Drug	Illinois	Tennessee	Texas	Total
AnaSed, IV	7.44	2.05	3.55	4.22
Rompun, IV	6.44	2.10	1.80	3.34
AnaSed, IM	12.22	7.55	12.91	10.81
Rompun, IM	14.10	6.20	7.11	9.21
AnaSed, SC	16.56	13.56	14.78	14.96
Rompun, SC	14.70	11.50	12.67	12.97

AROUSAL TIME

	Location			
Drug	Illinois	Tennessee	Texas	Total
AnaSed, IV	10.78	16.90	24.55	17.87
Rompun, IV	13.22	19.00	19.20	17.28
AnaSed, IM	13.67	20.27	19.73	18.16
Rompun, IM	11.10	30.80	17.11	19.76
AnaSed, SC	9.33	25.78	34.44	23.19
Rompun, SC	15.20	29.60	13.88	19.76

WALK TIME

	Location			
Drug	Illinois	Tennessee	Texas	Total
AnaSed, IV	16.56	25.70	39.30	27.55
Rompun, IV	17.56	30.10	41.30	30.07
AnaSed, IM	16.00	38.55	49.27	35.81
Rompun, IM	15.90	42.30	44.33	33.83
AnaSed, SC	12.56	37.56	66.00	38.70
Rompun, SC	16.60	45.20	62.78	40.79

The means of measures of analgesia (needle prick response) by drug, administration, and location corrected by means of baseline responses are given below.

A3 (+5 Min)

	Location			
Drug	Illinois	Tennessee	Texas	Total
AnaSed, IV	1.20	1.80	0.91	1.29
Rompun, IV	1.15	2.10	0.60	1.28
AnaSed, IM	1.15	1.41	0.41	0.98
Rompun, IM	1.00	1.35	0.61	1.00
AnaSed, SC	0.65	0.55	0.35	0.52
Rompun, SC	0.60	0.45	0.23	0.42

A4 (+15 Min)

	Location			
Drug	Illinois	Tennessee	Texas	Total
AnaSed, IV	1.30	1.70	1.09	1.35
Rompun, IV	1.25	1.90	0.50	1.22
AnaSed, IM	1.15	1.86	0.86	1.30
Rompun, IM	1.10	1.75	0.94	1.27
AnaSed, SC	1.05	1.44	0.65	1.03
Rompun, SC	1.10	1.25	0.69	1.00

A5 (+35 Min)

	Location			
Drug	Illinois	Tennessee	Texas	Total
AnaSed, IV	1.00	0.90	1.00	0.97
Rompun, IV	1.05	1.20	0.40	0.88
AnaSed, IM	1.05	1.68	0.77	1.17
Rompun, IM	0.90	1.75	0.72	1.14
AnaSed, SC	0.65	1.78	0.55	0.97
Rompun, SC	1.20	1.35	0.68	1.06

b. Corroborative Studies - Abstracts of Literature Showing Effectiveness

1. Moye RJ, Pailet A, Smith MW Jr: Clinical use of xylazine in dogs and cats. *Veterinary Medicine/Small Animal Clinician* 236-241, March, 1973.

   Use of xylazine in 107 dogs and cats over 18 months demonstrated many clinical uses. IV, IM or SC routes were used. Alone, (59% of cases) effective analgesia and sedation occurred. As a preanesthetic, xylazine reduced the required amount of anesthetic by as much as 75%. The only major side effects noted were reduction in heart and respiratory rates and a transitory drop in blood pressure.

2. Oliver JE Jr., Young WO: Evaluation of pharmacologic agents for restraint in cystometry in the dog and cat. *Am. J. Vet. Res.* 34:665-668, 1973.

   A variety of central nervous system (CNS) depressants and a skeletal muscle paralyzing agent were evaluated for restraining dogs and cats

during air cystometry. General anesthetics frequently blocked the micturition reflex. Tranquilizers and other agents blocked the reflex, allowed the animal to inhibit the reflex or provided inadequate restraint. Xylazine was the only drug which provided adequate restraint without blocking the micturition reflex.

3. Oliver JE, Young WO: Air cystometry in dogs under xylazine induced restraint. *Am. J. Vet. Res.* 34:1433-1435, 1973.

   Continuation of research in previous paper. Xylazine induces adequate restraint for cystometograms.

4. Winstanley EW: The use of xylazine as a central nervous system depressant in the dog. *Irish Veterinary Journal* 71-73, April, 1974.

   Both experimental (6 dogs) and clinical trials (12 dogs) were carried out to assess the action of xylazine (0.15 mg of a 2% solution/kg body weight) in the dog. It was concluded that xylazine may be used as a hypnotic, as a mild sedative and as a pre-anesthetic sedative in recently fed dogs.

5. Lacuata AQ, Flores RP: A preliminary study on the anesthetic value of "xylazine" in dogs. *Philippine J. Vet. Med* . 11:122-133, 1972.

   Induction was smooth and brief and without excitement. Heart rate was reduced 50% with a 36% decrease in respiratory rate. Xylazine induced deep sleep or hypnosis. Strong analgesia resulted, as did excellent muscular relaxation. Recovery averaged 60 to 120 minutes. No untoward results occurred, but a dose of 34X and a dose of 90X was fatal to two dogs receiving these.

6. Lacuata AQ, Subang PM: A preliminary study on the preanesthetic value of "xylazine" given intravenously in dogs prior to pentobarbital anesthesia. *Philippine J. Vet. Med* . 12:143-152, 1973.

   At 0.02 ml/kg IV induced hypnosis and facilitated handling and induction of general anesthesia, also providing efficient analgesia and muscle relaxation. Xylazine significantly reduced the amount of pentobarbital for surgical anesthesia by 42% as calculated. Pulse rate was reduced 42% and respiratory rate 60%. Recovery took an average of 155 minutes, varying from smooth to violent. No untoward reactions were encountered.

7. Richter KP, Ling GV: Effects of xylazine on the urethral pressure profile of healthy dogs. *Am. J. Vet. Res* . 46:1881-1886, 1985.

   Thirteen healthy male dogs and 11 healthy female dogs were subjected to urodynamic assessment, using a simultaneous urethral pressure profile and urethral sphincter electromyogram (EMG). The study was done on the dogs in the nonsedated state and after xylazine sedation. Results showed a significant decrease in maximal urethral closure pressures in dogs of both sexes after they were given xylazine (from 79.79 cm of H2O to 23.00 cm

of H2O in female dogs, and from 99.77 cm H2O to 41.77 cm of H2O in male dogs). There was a significant reduction in EMG activities in dogs of both sexes after they were given xylazine. There was also little variability in measurements made on the same dog on consecutive days. Simultaneous intravesicular pressure and urethral pressure monitoring indicated that the effect of bladder distention on the urethral pressure profile was minimal and there was no spontaneous detrusor contractions. This study indicates that xylazine produced a significant artifact in the simultaneous urethral pressure profile/EMG.

8. Benson GJ, Thurmon JC, Neff Davis CA, Corbin JE, Davis LE, Wilkinson B, Tranquilli WJ: Effect of xylazine hydrochloride upon plasma glucose and serum insulin concentrations in adult pointer dogs. *J. Am. An. Hosp. Assoc.* 20:791-794, 1984.

   A clinical dose of xylazine to 12 pointer dogs caused serum insulin to decrease from control values at minute twenty through one hundred twenty. Thereafter, serum insulin rose, reaching control values at one hundred eighty minutes. Plasma glucose concentration was increased at 60 through 240 minutes. By 360 minutes, both glucose and insulin concentration were near normal.

9. Bargai U: The effect of xylazine hydrochloride on the radiographic appearance of the stomach and intestine in the dog. *Vet. Radiol.* 23:60-63, 1982.

   Radiographs taken prior to and 30 to 90 minutes after each of 12 dogs was given 2% xylazine HCl at 2.0 to 3.0 mg/kg IV or IM indicated 0 to 200% increase in gastric length (avg 95%) and -40 to 611% increase in width (avg 125%). Intestinal diameter increased 15 to 275% (avg 124%). Since radiographic changes were consistent with gastric dilation and paralytic ileus, xylazine should not be used as a sedative for abdominal radiography.

10. Yates WD: Clinical use of xylazine, a new drug for old problems. *VM/SAC* 483-486, May 1973.

    Xylazine was used as a sedative analgesic in 93 dogs and 22 cats and as a preanesthetic in 130 dogs and 49 cats. Handling of patients was easy, induction was smooth and a quiet, peaceful recovery ensued. Five typical clinical canine case histories were presented. The versatility of xylazine, combined with its predictable effectiveness makes it an invaluable asset in small animal practices.

III. TARGET ANIMAL SAFETY

a. Pivotal Studies

1. Acute Toxicity

2. Names of Investigators:

The toxicology study was conducted at the College of Veterinary Medicine, Iowa State University, Ames, IA. The study director was Dr. Gary D. Osweiler; the Assistant Study Director was Dr. Joseph W. Denhart. Clinical Pathology was directed by Dr. Arlo E. Ledet. Patricia Varilek, Quality Assurance Monitor at Vet-A-Mix, Inc., was the Quality Assurance Unit Manager.

3. General Design of the Investigation:

a. Purpose of the study: The study was designed to test the safety of AnaSed(TM), Xylazine Injection, 20 mg/ml in dogs treated at 0 (control), 1x, 2x and 4x the normal dose.

b. Test animals: 12 female and 12 male healthy adult mixed breed dogs, which were randomly assigned to four test groups.

c. Dosage form: Sterile aqueous solution. The product tested was identical to the product to be marketed.

d. Doses used:

Group	Subjects	Xylazine (I.V.)
1	6	0.0x (Placebo Control)
3	6	1.0x (0.50 mg/lb)
4	6	2.0x (1.00 mg/lb)
5	6	4.0x (2.00 mg/lb)

The groups and subjects were the same as Groups 1, 3, 4 and 5 used in the dose titration study in Part 4.

e. Route of administration: IV

f. Test Duration: Each dog was observed for > or = 4 weeks.

g. Experimental Parameters Measured:

(1) Serum biochemistry at -(3 to 7), 0, +2, +7 days.
(2) Hematology at -(3 to 7), 0, +2, +7 days.
(3) Necropsy and histopathology on 1 female and1 male each from groups 1 and 5 of the first 2 replications.

4. Results
Following is a tabulation of the results using the Dunnett test for differences between control and treatment groups, with a P<.05 difference indicated by an asterisk.

TABLE 1. CANINE XYLAZINE TOXICOLOGY TEST--MEANS OF VALUES/GROUP

Dependent Variable	Mean Group 1 Control	Mean Group 3 0.5 mg/lb	Mean Group 4 10. mg/lb	Mean Group 5 2.0 mg/lb
SERUM BIOCHEMISTRY				
Blood Urea Nitrogen, mg/dl	13.472	12.694	11.500*	11.917
Creatinine, mg/dl	0.994	0.939	0.939	0.872*
Glucose, mg/dl	86.778	86.917	89.167	86.944
Total Bilirubin, mg/dl	0.128	0.114	0.139	0.144
Direct Bilirubin, mg/dl	0.019	0.008	0.017	0.028
Indirect Bilirubin, mg/dl	0.100	0.095	0.107	0.104
Alanine Amino Transferase, IU/L	45.889	30.361*	42.389	42.806
Alkaline Phosphatase, IU/L	47.028	43.611	53.222	46.694
Sodium, mEq/L	151.222	150.528	150.278	149.556*
Potassium, mEq/L	4.892	4.678	4.708	4.747
Chloride, mEq/L	117.694	117.417	117.861	117.444
Calcium, mg/dl	10.703	10.667	10.428	10.339
Phosphorus, mg/dl	5.164	5.117	4.350*	4.975
Magnesium, mg/dl	1.581	1.581	1.610	1.635
Total Protein, g/dl	6.017	5.928	6.156	5.864
Albumin, g/dl	3.903	3.947	3.842	3.764
Globulin, g/dl	2.117	1.969	2.317	2.094
HEMATOLOGY				
Hemoglobin, g/dl	15.783	15.789	16.033	15.017
Packed Cell Volume, %	46.667	46.778	47.972	44.361*
White Bld. Cells/mm3	12,130.556	14,647.222*	11,825.000	11,152.778
Red Bld. Cells, 106/mm3	6.668	6.740	6.753	6.237*
Banded Neutrophils/mm3	238.944	359.167	193.944	170.611
Segmented Neutrophils/mm3	7,953.667	9,072.778	7,372.944	7,117.778
Lmyphocytes/mm3	2,736.389	3,432.722*	3,097.833	2,788.833
Monocytes/mm3	453.667	504.722	344.333	507.722
Eosinophil/mm3	748.167	1,240.500	816.167	573.167
Basophils/mm3	.000	34.722*	.000	.000
Activated Clot. Time, Minutes	1.622	1.634	1.523	1.580

* Different from Control @ p <.05 Significance

Please refer to Table 1.

None of the Serum Biochemistry and Hematology parameters were significant by ANOVA by Group*Time interactions. All Serum Biochemistry values were within normal limits. The values which were significant by the Dunnett tests did not appear to be indicative of any toxicological trends.

After injections minor muscle twitching or tremors were observed, increasing with doses. Vomiting was common, not generally correlated with dosage rate.

Post mortem examination revealed the presence of heartworms in 2 dogs and whipworms in 1 dog. There were no gross pathological changes noted. Histopathology of organs of the 8 dogs failed to reveal any pathological changes related to the injections of xylazine.

5. Conclusions drawn from the study.

AnaSed(TM) was safe when dogs of both sexes were dosed IV at 0.5, 1.0 and 2.0 mg/lb (1.1, 2.2 and 4.4 mg/kg) body weight.

b. Corroborative Studies - Abstracts of Literature Showing Safety

1. Muir WW III, Werner LL, Hamlin RL: Effects of xylazine and acetylpromazine upon induced ventricular fibrillation in dogs anesthetized with thiamylal and halothane. *Am. J. Vet. Res* . 36:1299-1303, 1975.

Ventricular arrhythmias including ventricular fibrillation were produced with epinephrine in dogs induced to an anesthetic state with thiamylal and maintained with halothane. In dogs given (premedicated) xylazine 20 minutes prior to anesthesia, ventricular arrhythmias, including ventricular fibrillation, were induced with much smaller doses of epinephrine than in nonpremedicated dogs. Dogs premedicated with acetylpromazine 20 minutes prior to anesthesia with thiamylal and halothane displayed protection from epinephrine induced arrhythmias. Caution is advised from using xylazine in the presence of halothane if epinephrine is to be administered.

2. Muir WW III, Piper FS: Effect of xylazine on indices of myocardial contractility in the dog. *Am. J. Vet. Res.* 38:931-934, 1977.

Changes in cardiac contractility were assessed by two indices of myocardial contractile performance (dP/dt/Kp max, V max). Both indices demonstrated an initial positive inotropic response to intravenous administration of xylazine (1.1 mg/kg). This positive inotropic effect was followed by a return to or significant decrease from base line recordings in these times following xylazine administration. In addition, an increase in heart rate in control dogs was accompanied by a rise in both dP/dt/Kp max and V max, confirming earlier evidence of the Bowditch staircase effect in the intact dog ventricle.

3. Hubbell JAE, Muir WW: Effect of xylazine hydrochloride on canine splenic weight: an index of vascular capacity. *Am. J. Vet. Res.* 43:2188-2192, 1982.

Splenic weight, an index of changes in vascular capacity, was used to assess the effects of xylazine hydrochloride in anesthetized dogs. Intravenous xylazine (0.01, 0.1 and 1 mg/kg) produced dose dependent decreases in vascular capacity as assessed by decreases in splenic weight which were significant ($P<.05$) at the 1 mg/kg dose. Phenoxybenzamine, an alpha-adrenergic receptor blocking drug, prevented the splenic contractile response to xylazine. Propranolol, a beta-adrenergic

receptor blocking drug, did not alter the splenic contractile response to xylazine. Intravenous xylazine (0.1 and 1 mg/kg) produced significant (P<.05) decreases in heart rate, splenic arterial flow, and systolic, mean, and diastolic blood pressures. Central venous pressure increased significantly (P<.05) in dogs given the 1 mg/kg dose.

4. Haskins SC, Patz JD, Farver TB: Xylazine and xylazine ketamine in dogs. *Am. J. Vet. Res.* 47:636-641, 1986.

   The cardiopulmonary consequences of IV administered xylazine (1.0 mg/kg) followed by ketamine (10 mg/kg) were evaluated in 12 dogs. Xylazine caused significant decreases in heart rate, cardiac output, left ventricular work, breathing rate, minute ventilation, physiologic dead space, oxygen transport, mixed venous partial pressure of oxygen, and oxygen utilization ratio.

   The subsequent administration of ketamine was associated with significant increases in heart rate (transient increase), cardiac output, the alveolar arterial PO2 gradient and venous admixture (transient increase), and arterial PCO2 (transient increase). It caused significant decreases in stroke volume (transient decrease), left ventricular stroke work (transient decrease), effective alveolar ventilation, arterial PO2 and oxygen content (transient decrease).

5. Klide AM, Calderwood HW, Soma LR: Cardiopulmonary effects of xylazine in dogs. *Am. J. Vet. Res.* 36:931-935, 1975.

   Neither IV or IM administration of xylazine changed significantly the arterial pH, arterial oxygen or carbon dioxide tension, but did significantly decrease heart rate, aortic flow, and increased peripheral resistance and blood pressure, though the latter decreased rapidly thereafter. Atropine did not significantly change any of these effects of xylazine.

IV. HUMAN FOOD SAFETY

1. Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this supplemental NADA. The drug is to be labeled for use in dogs, which are non-food animals.
2. Human safety relative to possession, handling and administration: Labeling bears adequate warning statement. Labeling states, "Warning: Not for Human Use."

V. AGENCY CONCLUSIONS

The data submitted in support of this supplemental NADA comply with the requirements of Section 512 of the Act and demonstrate that AnaSed (xylazine) Injectable Solution is safe and effective when it is desirable to produce a state of sedation accompanied by a shorter period of analgesia.

According to the Center's supplemental approval policy (42 FR 64367), this is a Category II change. The supplemental provided for the additional claim for use in dogs and, therefore, required complete new safety and effectiveness data for use of the new animal drug in dogs. This approval did not require a reevaluation of the safety and effectiveness data in the parent application.

Under section 512 (c) (2) (F) (iii) of the Generic Animal Drug and Patent Term Restoration Act of 1988, this supplement does not qualify for an exclusivity period because the reports supporting the supplemental approval do not qualify as "new clinical or field investigations" under that section because there is an earlier approval under section 512 (b)(1) of the Federal Food, Drug, and Cosmetic Act for xylazine in dogs based on similar investigations.

AnaSed(TM) is used in the dog 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, AnaSed is a prescription new animal drug.

VI. LABELING (Attached)

1. AnaSed(TM) package insert
2. AnaSed(TM) product label

Copies of these labels may be obtained by writing to the:

Food and Drug Administration
Freedom of Information Staff (HFI-35)
5600 Fishers Lane
Rockville, MD 20857

Or requests may be sent via fax to: (301) 443-1726. If there are problems sending a fax, call (301) 443-2414.

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