## I. GENERAL INFORMATION

### A. File Number

NADA 140-999

### B. Sponsor

Orion Corporation
P. O. Box 425
SF - 20101
Turku, Finland

### C. Proprietary Name

Domitor®

### D. Established Name

medetomidine hydrochloride

### E. Dosage Form

Sterile injectable solution

### F. Dispensing Status

Rx

### G. Dosage Regimen

Domitor should be administered at the rate of 750 mcg IV or 1000 mcg IM per square meter of body surface. Use the table below to determine the correct dosage on the basis of body weight.

| **Body Weight (lbs) – IV Admin.** | **Injection Vol (mL)** | **Body Weight (lbs) – IM Admin.** |
|---|---|---|
| 3-4 | 0.1 | |
| 5-7 | 0.15 | 4-5 |
| 8-11 | 0.2 | 6-7 |
| 12-15 | 0.25 | 8-9 |
| 16-21 | 0.3 | 10-14 |
| 22-31 | 0.4 | 15-20 |
| 32-43 | 0.5 | 21-27 |
| 44-55 | 0.6 | 28-35 |
| 56-68 | 0.7 | 36-44 |
| 69-82 | 0.8 | 45-53 |
| 83-97 | 0.9 | 54-63 |
| 98-121 | 1.0 | 64-78 |
| 122-156 | 1.2 | 79-101 |
| 157-194 | 1.4 | 102-126 |
| 195+ | 1.6 | 127-165 |
| | 2.0 | 166+ |

Following injection of Domitor, the dog should be allowed to rest quietly for 15 minutes.

### H. Route of Administration

Intravenous or intramuscular injection

### I. Indication

DOMITOR is indicated for use as a sedative and analgesic in dogs over 12 weeks of age, to facilitate clinical examinations, clinical procedures, minor surgical procedures not requiring muscle relaxation, and minor dental procedures not requiring intubation. The IV route of administration is more efficacious for dental care.

## II. EFFECTIVENESS

Dose response studies were conducted with medetomidine hydrochloride to determine the optimal i.v. and i.m. dosages for producing sedation and analgesia in dogs. These dosages were then used in several clinical studies.

### A. First Pivotal Study:

Type of Study: Dose response study in dogs

Investigator: Robert L. Hamlin, D.V.M., Ph.D., Department of Physiology and Pharmacology, College of Veterinary Medicine, The Ohio State University, Columbus, OH 43210.

General Design of Investigations:

1. Purpose: The objective of the studies was to determine the optimal i.v. and i.m. doses of medetomidine hydrochloride for producing sedation and analgesia in dogs.

2. Test Animals: Forty-eight mature, random-source dogs of both sexes, weighing from five to 40 kg, were assigned to groups of four dogs each based on similar weight range.

3. Type of Control: Placebo consisted of the same formulation as the other treatments except devoid of active ingredient (vehicle).

4. Dosage Form: All treatments were sterile injectable solutions. The proposed market formulation contains 1.0 mg/mL medetomidine hydrochloride. However, in order to maintain blinded conditions, coded test concentrations were 0, 0.37, 1.0, and 1.625 mg/mL.

5. Routes of Administration: The studies were composed of two segments. Medetomidine hydrochloride was administered by the i.v. route in one segment and by the i.m. route in the other segment.

6. Dosages Used: Dosages for the i.v. segment were 0, 280, 750 and 1220 mcg medetomidine hydrochloride per square meter ($M^2$) of body surface, and were

0, 375, 1000 and 1625 µg/M² for the i.m. segment. Each dog remained in its respective dose group for both study segments.

7. Test Duration: Each animal was studied for six hours.

8. Parameters Measured: The following parameters were measured at times of 0, 1/4, 1/2, 1, 2, 3, 4, 5 and 6 hours following injection. Scores for each parameter are noted in parenthesis and represent the degree of deviation from normal, unless otherwise noted, with score of 0 being normal. Parameters a - e were considered measures of sedation; parameters f and g were considered measures of analgesia; parameters *h* - *j* were clinical measures.

    a. Spontaneous Posture (0 - 4)( 0-normal, 1-tired but standing, 2-lying, able to rise, 3-lying,able to rise with difficulty, 4-unable to rise).

    b. Placement on Side (0 - 4)( 0-resists strongly, 1-modest resistance, 2-slight resistance, 3-no resistance, 4-spontaneous)

    c. Mouth can be Opened (0 - 3)( 0-with difficulty, 1-modest resistance, 2-slight resistance, 3-no resistance)

    d. Response to Noise (0 - 4)( 0-jumps, 1-hears and moves, 2-hears and twitches ear, 3-barely perceives, 4-no perception)

    e. General Condition (0 - 4)( 0-excitable, 1-awake-normal, 2-tranquil, 3-stuporous, 4-anesthetized)

    f. Toe-pinch Withdrawal Response ( 1 - 20 lbs. pressure required to elicit withdrawal response; scored as lbs. of pressure required)

    g. Response to Current ( 1 - 7; corresponds to milliamperes required to elicit response)

    h. Heart Rate (0 - 3)( 0-above 130; 1-below 50; 2-110-130 or 50-60, 3-60 - 110)

    i. Spontaneous Twitching (0-4)(0-severe, 1-modest, 2-slight, 3-rare, 4-never)

    j. Body Temperature (degrees Fahrenheit)

9. Adverse Reactions: Vomiting, bradycardia, and twitching were considered by the investigator to be side effects of administration of medetomidine hydrochloride. Seventeen percent of dogs receiving the compound by either i.v. or i.m. route vomited occasionally. However, of dogs receiving 750 µg/M² i.v. and 1000 µg/M² i.m., only one (8%) vomited following the i.v. route and none following the i.m. route. No dog vomited repeatedly or retched. There appeared to be no relationship between the amount of elapsed time from administration of the drug and occurrence of vomiting. Bradycardia, defined as a heart rate below 50 beats per minute, occurred in 81% of all dogs receiving the agent i.v. and in 89% of all dogs receiving it i.m. The reductions in heart rate and attending pronounced respiratory sinus arrhythmia no doubt stem from the alpha2 agonistic stimulation of vagal centers in the brain and from

reflexes initiated by systemic arterial hypertension which occurs early on due to alpha2 activity on blood vessels. As would be expected in animals with high vagal tone, a number of dogs developed second degree AV block, but this was not dose dependent. Second degree AV block was probably due to the central alpha2 adrenergic stimulation and reflexly in response to direct peripheral vasoconstriction, also attributable to the stimulation of alpha2 adrenergic receptors. One i.v. control dog had rare ventricular premature depolarizations both before and after injection and one dog, receiving 1000 µg/M² i.m., developed paroxysmal atrial tachycardia during a period of sinus bradycardia. This might have resulted from a reentrant pathway incorporating the AV node or it might have resulted from either oscillatory after potentials or increased automaticity as a consequence of the drug. Nonetheless, this tachycardia occurred only once, for a short burst. Twitching (jactitations) is a well-known consequence of alpha2 agonists. It occurred in 47% of dogs receiving medetomidine i.v. and in 58% receiving it i.m. The twitching was considered mild in all dogs but one that received medetomidine at the 1000 µg/M² dose by the i.m. route. Premature ventricular contractions (PVC) were considered by the investigator to be adverse reactions, as well as dogs having the following syndrome: very sensitive to touch, breathed deeply, whined on expiration, snarled and snapped without being conscious. This syndrome of reactions was seen only in dogs that had received the highest doses i.v. or i.m. Two dogs receiving medetomidine by each route of administration developed signs of the syndrome described above, but only one when receiving the optimal dose(750 µg/M² i.v.,1000 µg/M² i.m.). One dog in the control group had PVC's each time he was monitored, before and after administration of placebo. One dog (1000 µg/M² i.m.), at the 15 minute reading, showed a sinus bradycardia with an occasional PVC and paroxysmal atrial tachycardia.

10. Statistical Analysis: The proportion of positive responses among dose groups for sedative and analgesic/anesthetic, and combined responses, were compared separately. From these data 4 x 2 contingency tables were constructed for each property and both routes of administration. To determine whether the proportion of positive responses is equal at each dose level, a Chi-square test for equality of proportions was done on each table. This involved calculation of the expected number of positive responses for each dose level. If any expected cell count is less than 5, the approximation to the Chi-square distribution is not valid. If significance ($p<0.05$) was found it was desired to see which proportions were not equal. Bonferroni 95% simultaneous confidence intervals were constructed for the differences in the proportions. If the confidence interval contains zero, the two proportions are not different. The optimal dose is defined as the minimal dose which produces a number of positive responses greater than the placebo or a lower dose, and not significantly different ($p>0.05$) from the next higher dose. For the sedative property, 750 µg/M² given i.v. and 1000 µg/M² given i.m. met the optimal dose definition. For the analgesic/anesthetic property, 750 µg/M² given i.v. met the definition. However, the 1000 µg/M² i.m. dose was clinically superior to the other doses but this could not be confirmed by the statistical treatment. Of the 12 dogs studied at each dose group for the i.m. administered drug, only 2 (16%) of the low dose (375 µg/$M^{2)}$ group responded favorably, whereas 6 (50%) of the optimal dose group (1000 µg/$M^{2)}$ responded favorably, but this could not be confirmed by the statistical analysis.

Figure 1

Overall Response to Sedative Parameters Following I.V. Administration of Medetomidine to Dogs
(All points represent the average of 12 animals)
Sum of Sedative
Parameters a-e

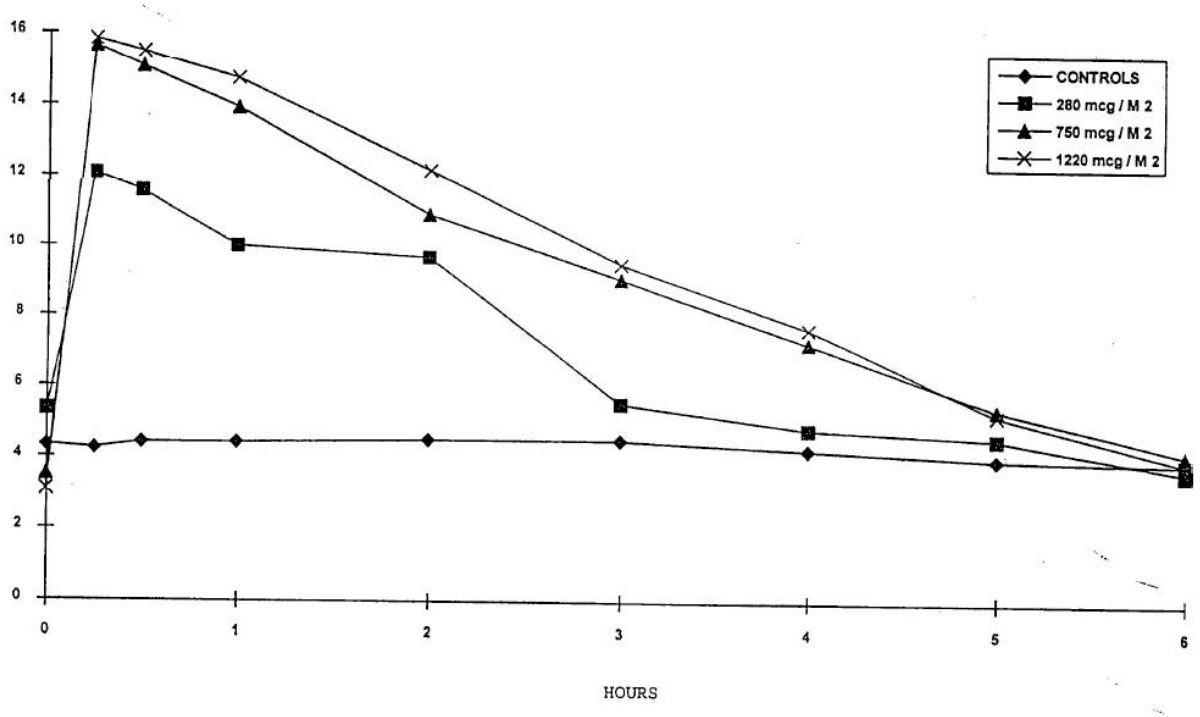


Figure 2

Overall Response to Analgesic Parameters Following I.V. Adminstration of Medetomidine to Dogs
(All points represent the average of 12 animals)

Sume of Analgesic
Parameters f, g

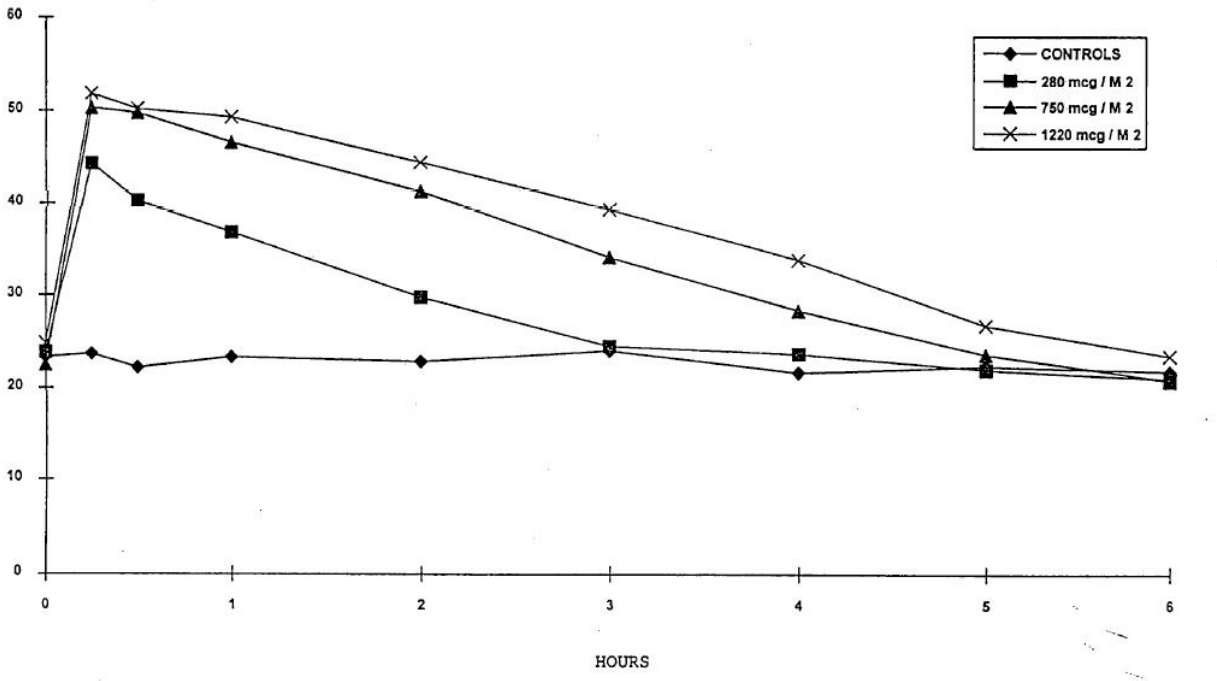


Figure 3

Overall Response to Sedative Parameters Following I.M. Administration of Medetomidine to Dogs
(All points represent the average of 12 animals)

Sum of Sedative
Parameters a-e

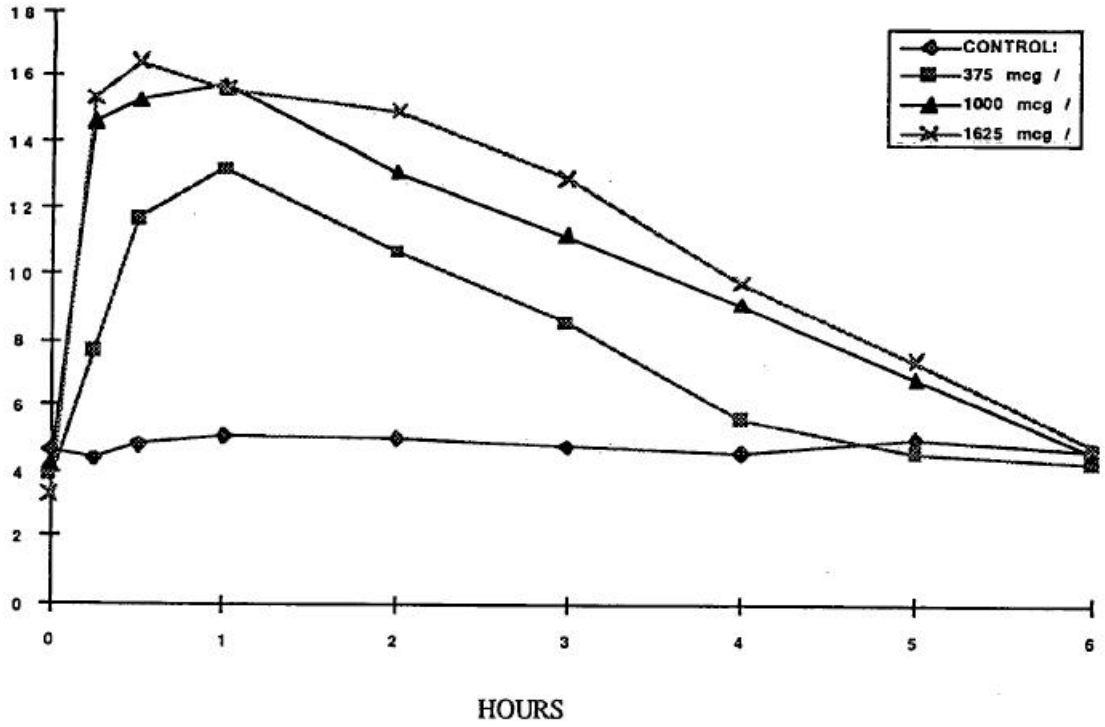


Figure 4

Overall Response to Analgesic Parameters Following I.M. Administration of Medetomidine to Dogs
(All points represent the average of 12 animals)

Sum of Analgesic
Parameters f, g

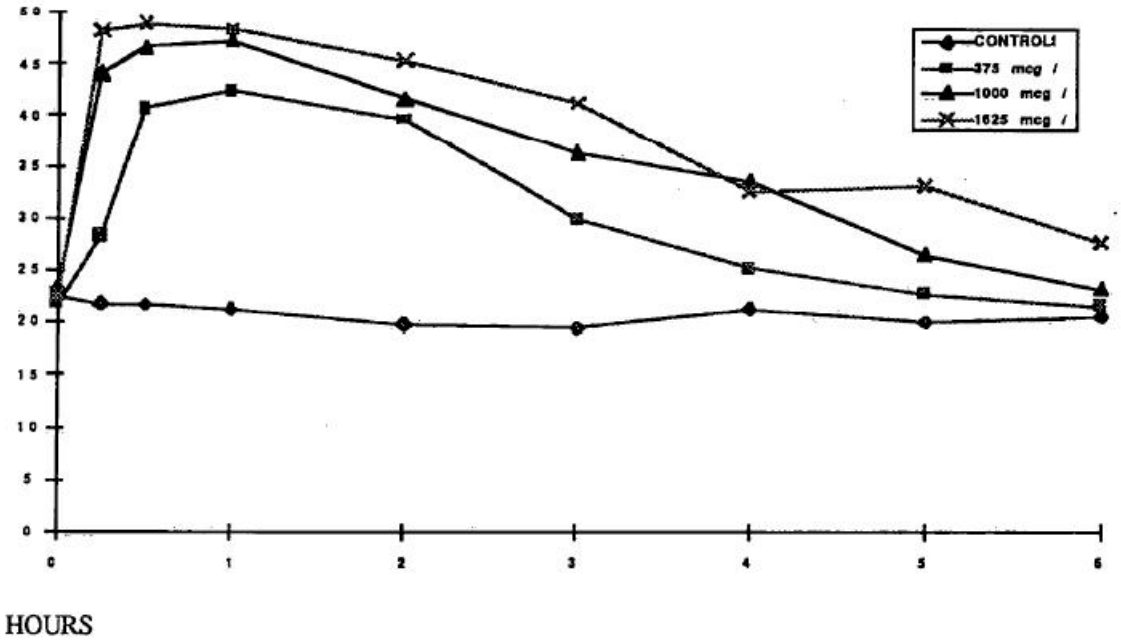
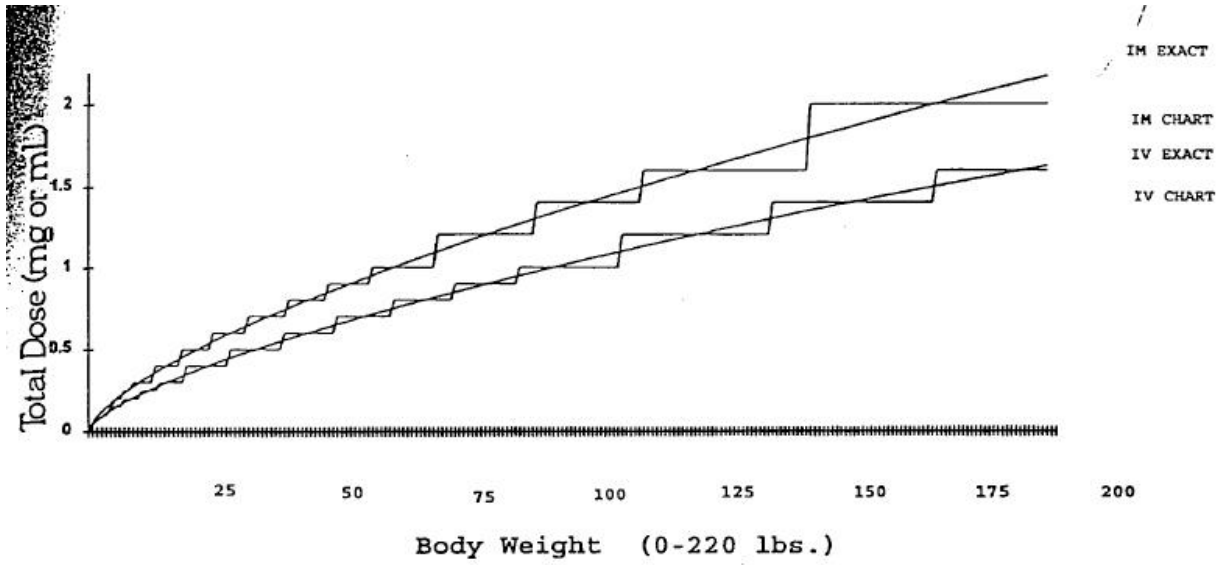


Figure 5




Medetomidine Dosing Chart

| **Body Weight (lbs) – IV Admin.** | **Injection Vol (mL)** | **Body Weight (lbs) – IM Admin.** |
|---|---|---|
| 3-4 | 0.1 | |
| 5-7 | 0.15 | 4-5 |
| 8-11 | 0.2 | 6-7 |
| 12-15 | 0.25 | 8-9 |
| 16-21 | 0.3 | 10-14 |
| 22-31 | 0.4 | 15-20 |
| 32-43 | 0.5 | 21-27 |
| 44-55 | 0.6 | 28-35 |
| 56-68 | 0.7 | 36-44 |
| 69-82 | 0.8 | 45-53 |
| 83-97 | 0.9 | 54-63 |
| 98-121 | 1.0 | 64-78 |
| 122-156 | 1.2 | 79-101 |
| 157-194 | 1.4 | 102-126 |
| 195+ | 1.6 | 127-165 |
| | 2.0 | 166+ |

11. Results: A summary of results for the i.v. segment is presented in Table 1 and shown graphically in Figures 1 and 2. Results for the i.m. segment are summarized in Table 2 and presented graphically in Figures 3 and 4.

    The 750 µg/M² i.v. and 1000 µg/M² i.m. doses of medetomidine hydrochloride tested in these studies were shown to be optimal for producing sedation and analgesia in the dog when administered on the basis of body surface area. For purposes of providing dosing information in labeling, however, the use of body surface area is problematic because, 1) a detailed and legible chart converting body surface area to i.v. and i.m. dosages for dogs weighing from one to 200 lbs. is too large for use in labeling and, 2) use of the body weight to body surface conversion formula requires the practitioner to perform unfamiliar calculations to determine precise dosages. A dosing chart has therefore been developed for labeling in which an easily measured dose volume has been provided for each of a number of narrowly defined body weight groupings. Figure 5 presents this dose chart as well as a graph depicting the relationship between the charted weight group dose and the exact dose calculated on the basis of body surface area.

12. Conclusions: This study shows that the optimal dose of medetomidine is 750 µg/M² i.v. and 1000 µg/M² i.m. for both sedative and analgesic effects. These doses produced the desired clinical effects 1/2 hour after both i.m. or i.v. administration, and by 3 hours after injection the dogs were as alert as dogs either serving as vehicle controls or receiving the lower dose.

**B. Second Pivotal Study:**

Type of Study: Clinical evaluation of effectiveness in comparison with Innovar (fentanyl plus droperidol).

Investigators: Dr. D. Dyson and Dr. Glen Pettifer, Department of Clinical Studies, Ontario Veterinary College, University of Guelph, Guelph, Ontario, Canada N1G 2W1.

General Design of Investigations:

1. Purpose: The objective of this study was to evaluate the sedative and analgesic effects of medetomidine in dogs in a clinical setting, and to compare these effects with those of the recommended dose of Innovar (Pitman Moore, Inc.)

2. Test Animals: Eighty mature dogs (49 beagles and 31 animals of other breeds; 35 females and 45 males) from the University of Guelph Laboratory Animal Facilities, were assigned at random to four treatment groups of similar composition regarding breed, sex and attitude.

3. Type of Control: Innovar (0.4 mg fentanyl and 20 mg droperidol) was used as a positive control at the recommended dose. Both drugs were administered by a third party and treatment was unknown to the evaluating clinical investigator. Both drugs were used by two routes of administration, i.v. and i.m. Treatments were assigned at random.

4. Dosage Form: All treatments were sterile injectable solutions. Medetomidine was used as the market formulation (1.0 mg/mL). Innovar was used in the commercial concentration (0.4 mg fentanyl and 20 mg droperidol per mL).

5. Routes of Administration: Both medetomidine and Innovar were used i.v. and i.m.

6. Dosages Used: The dose for medetomidine was 750 mcg per square meter ($M^2$) body surface i.v. and 1000 mcg per $M^2$ body surface i.m. The dose of Innovar was 1 mL per 10 kg body weight i.m. or 1 mL per 20 kg bodyweight i.v.

7. Duration of Study: Each animal was studied for 180 minutes.

8. Parameters Measured: The following parameters were measured just before treatment (0 time) and 15, 30, 60, 90, 120 and 180 minutes after administration of the test substance. Scores for each parameter are noted in parenthesis and represent the degree of deviation from normal, with score of 0 being normal. Parameters a to c were considered measures of sedation; parameters c and d (if procedure was painful) were considered measures of analgesia; and e to h were clinical measures selected to evaluate drug safety under clinical conditions:

    a. Spontaneous Posture (0 - 4)( 0-normal, 1-tired but standing, 2-lying, able to rise, 3-lying, able to rise with difficulty, 4-unable to rise)

    b. Response to Noise (0 - 4)( 0-hypersensitive, 1- normal, 2-weak, 3-no reaction)<</li>

    c. Procedure can be performed (0 - 4); assessment starting at 15 minutes after treatment:( 0-cannot be performed, 1-with difficulty, 2-moderate resistance, 3-slight resistance, 4-no resistance).

        (i) Shave abdomen

        (ii) Shave neck

        (iii) Shave ear

        (iv) Clean ears

        (v) Express anal glands

    d. Toe pinch withdrawal response (1 to 20 lbs pressure required to elicit withdrawal response; scored as lbs. of pressure required).

    e. Heart rate (ECG) and dysrhythmia (yes or no)

    f. Respiratory Rate and Body Temperature

    g. Packed cell volume (at 0 time only)

    h. Arterial blood gases (pCO2, p02, ABE), lactate and pH (at 0, 15, 60 and 180 minutes).

i. Attitude (normal to excitable; at 0 time only)

j. Time from injection to:

(i) Dog unable to stand

(ii) Dog again able to attain sternal recumbency

(iii) Dog again able to stand

k. Investigator assessment of overall drug effects regarding:

(i) Applicability for the intended purpose (poor to excellent)

(ii) Sedative effect (none to excellent)

(iii) Analgesic effect (none to excellent)

9. Adverse Effects (Side Effects): The overall level of all side effects did not differ between drugs and treatment groups, with 75% and 70% for medetomidine i.v. and i.m., respectively, and 70% and 60% for Innovar i.v. and i.m., respectively. Side effects consisted mostly of short episodes of twitching, jerking or paddling and were seen more often with medetomidine, although designated "strong" in three cases only. With Innovar, shivering throughout the study or in its late stages (from 60 minutes on) was the most frequently reported adverse effect. Vomiting occurred only with medetomidine, in 10% and 15% of the cases treated i.v. and i.m., respectively. The prevalence of bradycardia following treatment was significantly higher in medetomidine treated cases than in Innovar treated cases. Prevalence of four dysrhythmias ( sinus arrhythmia, respiratory arrhythmia, T wave changes, and AV block arrhythmia) were also noted during the study, but these arrhythmias did not vary significantly among the four treatment groups at baseline and at each of the six PTI sampling times except for respiratory sinus arrhythmia at 90 minutes PTI and AV block arrhythmia at 15 minutes PTI. None of the adverse effects was regarded as serious, and none required treatment.

10. Statistical Analysis: Data on quantitative variables were statistically analyzed by analysis of variance (ANOVA) among the four treatment groups. Data only collected once were analyzed by ANOVA followed by the least-significant-difference (LSD) method of comparison of the four treatment means. Treatment, intended use of the drug for sedation or analgesia, sex and age were included in the ANOVA as main effects. Data on quantitative variables collected at several times were analyzed by repeated-measure ANOVA followed by LSD with the appropriately pooled mean-square error (according to Cochran & Cox, Experimental Design, 2nd 3d., pp. 298-302). Data on qualitative variables were analyzed by standard chi-square tests for two-way contingency tables to evaluate differences among the four treatment groups. Data on prevalence of dysrhythmias were analyzed by multiple logistic regression (MLR) analysis.

11. Results: The four treatment groups were not found to be significantly different with respect to their distribution of breed, sex, and attitude, and with regard to their mean body temperature, mean packed cell volume, mean heart rate and mean respiratory rate. A summary of the results (i.m. and i.v.,

respectively) for posture and noise, analgesia for toe-pinch, heart rate and respiratory rates are also shown in Tables 3 and 4. Initiation and duration of sedative drug effects are shown in Table 5. Prevalence of dysrhythmias by treatment and over time is summarized in Tables 6a and 6b. Sedation related mean posture scores did not differ overall among the four treatment groups, but scores for both i.v. groups were higher than those for the two i.m. groups. Mean noise scores were significantly higher for medetomidine i.v. and i.m. over a two-hour period (Tables 3 and 4). Analgesia scores almost doubled with all treatments but were not significantly different between groups. Heart rates were significantly different overall and over time due to the typical bradycardia with medetomidine (Tables 3 and 4). The respiratory rates for both drug treatments were not significantly different overall, but were significantly lower for medetomidine during the first hour after treatment (Tables 3 and 4). In spite of bradycardia and lower respiratory rates, blood gases, ABE (acid-base excess) and pH did not vary significantly overall and over time between treatment groups. The prevalence (percent positive) of bradycardia arrhythmia among medetomidine-treated dogs was significantly higher than among Innovar-treated dogs (Tables 6a, 6b, $p<0.001$). However, the prevalence of sinus arrhythmia, T wave changes, and second degree AV block arrhythmia was not significantly different among the four treatment groups ($p=0.362$, $p=0.558$, $p=0.903$, respectively). Although the prevalence of respiratory sinus arrhythmia was significantly different among the four treatment groups, the prevalence during the 180 minute period following treatment initiation was very similar to that prior to treatment initiation, and was less in medetomidine-treated dogs than in Innovar-treated dogs. Mean scores for each of the five tested procedures increased rather uniformly from 0 to 15 minutes but did not vary between treatment groups. Time to being unable to stand, to return to sternal recumbency and to stand again were each significantly different between the four treatment groups: It took longest for medetomidine i.m. treated dogs to lay down and return to standing; both i.v. treatments uniformly delayed return to sternal recumbency (Table 5).

Applicability for intended procedure was equally rated for both drugs regardless of route. Analgesia was rated higher for medetomidine, with combined "excellent" and "good" ratings in 80% of cases for both i.v. and i.m., versus 65% for Innovar given i.v. and 50% when given i.m. (non-significant). Sedation was rated very similar for both medetomidine and Innovar, with combined "excellent" and "good" ratings for medetomidine being 70% for i.v. and 85% for i.m. treatment, versus 85% for Innovar given i.v. and 65% for i.m. treatment.

12. Conclusions: Medetomidine hydrochloride (Domitor®) was found to be as effective as fentanyl/droperidol (Innovar-Vet) for analgesia and sedation when used in a variety of breeds and sizes of dogs. The most obvious side effect produced by the administration of medetomidine by either route of administration was the profound sinus bradycardia, but the arterial pressures and arterial blood gases remain within clinically acceptable limits. Other side effects include vomiting following injection, and muscle twitching during the sedation period. None of the side effects required treatment.

    The peripheral vasoconstriction produced by [[alpha]]2 receptor activation following medetomidine administration did not appear to affect peripheral

perfusion or O2 delivery as no significant increases in lactate concentrations were observed.

Table 3: Scores[1] for Posture (POST), Noise, Toe Pinch (TOE), Heart Rate (HR) and Respiratory Rate (RR) by I.M. Treatment Group[2] and Time Post-Treatment-Initiation (PTI)

| Minutes PTI | Medetomidine POST | Medetomidine Noise | Medetomidine TOE | Medetomidine HR | Medetomidine RR | Innovar POST | Innovar Noise | Innovar TOE | Innovar HR | Innovar RR |
|---|---|---|---|---|---|---|---|---|---|---|
| 0X | 0.00$^{a}$±0.00 | 0.90$^{a}$±0.31 | 7.75$^{a}$±2.86 | 132.40$^{a}$±36.88 | 43.40$^{a}$±30.55 | 0.00$^{a}$±0.00 | 0.90$^{a}$±0.31 | 8.60$^{a}$±2.23 | 126.65$^{a}$±26.05 | 41.00$^{a}$±30.67 |
| 15X | 3.00$^{a}$±1.08 | 2.00$^{c}$±0.97 | 12.95$^{ab}$±3.49 | 53.65$^{b}$±14.89 | 20.85$^{c}$±9.85 | 3.00$^{a}$±0.97 | 1.10$^{a}$±1.07 | 11.85$^{a}$±5.13 | 94.80$^{a}$±26.63 | 36.95$^{a}$±33.91 |
| 30X | 3.40$^{a}$±0.94 | 2.10$^{b}$±0.85 | 14.75$^{a}$±3.65 | 47.30$^{b}$±11.84 | 15.45$^{b}$±7.77 | 3.20$^{a}$±0.95 | 1.20$^{a}$±0.77 | 12.55$^{a}$±5.54 | 92.60$^{a}$±19.62 | 37.45$^{a}$±33.69 |
| 60X | 3.65$^{c}$±0.67 | 2.20$^{b}$±0.70 | 12.45$^{a}$±4.32 | 42.30$^{b}$±11.97 | 14.45$^{b}$±5.75 | 3.05$^{a}$±0.83 | 1.45$^{a}$±0.94 | 10.95$^{a}$±3.94 | 101.00$^{a}$±30.44 | 29.90$^{a}$±20.71 |
| 90X | 3.20$^{b}$±0.77 | 1.90$^{b}$±0.64 | 11.60$^{a}$±4.63 | 45.50$^{c}$±15.07 | 14.35$^{b}$±5.26 | 2.35$^{ab}$±0.75 | 1.25$^{a}$±0.64 | 9.45$^{a}$±2.63 | 110.15$^{a}$±30.76 | 25.50$^{ab}$±22.84 |
| 120X | 2.80$^{b}$±0.95 | 1.75$^{b}$±0.72 | 11.15$^{b}$±4.08 | 47.75$^{c}$±19.90 | 14.10$^{a}$±6.14 | 2.10$^{a}$±0.55 | 1.20$^{a}$±0.52 | 9.50$^{ab}$±3.10 | 124.80$^{a}$±41.26 | 21.40$^{a}$±5.62 |
| 180X | 1.90$^{a}$±0.97 | 1.35$^{a}$±0.59 | 9.30$^{a}$±3.21 | 67.05$^{c}$±37.54 | 19.10$^{a}$±6.79 | 1.85$^{a}$±0.37 | 1.05$^{a}$±0.39 | 8.40$^{a}$±2.11 | 124.00$^{a}$±32.98 | 22.75$^{a}$±7.60 |

[1] See "Parameters Measured" for scoring procedure.

[2] Treatment group means per sampling time within scoring parameter are significantly different ($p<0.05$) if followed by different letters.

Table 4: Scores[1] for Posture (POST), Noise, Toe Pinch (TOE), Heart Rate (HR) and Respiratory Rate (RR) by I.V. Treatment Group[2] and Time Post-Treatment-Initiation (PTI)

| Minutes PTI | Medetomidine POST | Medetomidine Noise | Medetomidine TOE | Medetomidine HR | Medetomidine RR | Innovar POST | Innovar Noise | Innovar TOE | Innovar HR | Innovar RR |
|---|---|---|---|---|---|---|---|---|---|---|
| 0X | 0.00$^{a}$±0.00 | 1.00$^{a}$±0.32 | 8.30$^{a}$±2.89 | 124.15$^{a}$±26.80 | 35.60$^{a}$±24.16 | 0.00$^{a}$±0.00 | 0.95$^{a}$±0.22 | 8.90$^{a}$±3.04 | 122.50$^{a}$±26.91 | 33.40$^{a}$±23.25 |
| 15X | 3.75$^{b}$±0.72 | 2.55$^{d}$±0.83 | 14.70$^{b}$±3.59 | 48.70$^{b}$±12.24 | 15.10$^{c}$±11.27 | 3.50$^{b}$±0.69 | 0.55$^{a}$±0.83 | 15.00$^{b}$±3.46 | 82.25$^{a}$±16.36 | 68.25$^{b}$±49.23 |
| 30X | 3.65$^{a}$±0.59 | 2.65$^{c}$±0.49 | 14.10$^{a}$±3.11 | 49.90$^{b}$±10.61 | 14.05$^{b}$±4.29 | 3.20$^{a}$±0.77 | 1.05$^{a}$±1.05 | 13.55$^{a}$±4.62 | 96.15$^{a}$±21.12 | 40.70$^{a}$±40.56 |
| 60X | 3.15$^{a}$±0.67 | 2.20$^{b}$±0.62 | 13.10$^{a}$±3.40 | 49.55$^{b}$±13.38 | 14.85$^{b}$±4.56 | 2.55$^{b}$±0.60 | 1.40$^{a}$±0.68 | 12.65$^{a}$±4.27 | 110.50$^{a}$±26.63 | 27.25$^{a}$±16.10 |
| 90X | 2.55$^{c}$±1.00 | 1.70$^{b}$±0.80 | 11.25$^{a}$±4.30 | 52.15$^{c}$±14.35 | 17.55$^{b}$±7.49 | 1.95$^{a}$±0.51 | 1.20$^{a}$±0.52 | 10.05$^{a}$±3.79 | 131.45$^{b}$±33.55 | 28.15$^{a}$±17.97 |
| 120X | 2.15$^{a}$±0.93 | 1.40$^{ab}$±0.50 | 9.30$^{ab}$±2.98 | 62.20$^{c}$±24.97 | 17.85$^{a}$±6.67 | 1.85$^{a}$±0.37 | 1.05$^{a}$±0.22 | 7.95$^{a}$±2.16 | 141.85$^{b}$±37.05 | 23.85$^{a}$±5.29 |
| 180X | 1.25$^{b}$±0.79 | 1.00$^{a}$±0.32 | 9.20$^{a}$±2.12 | 72.25$^{c}$±28.01 | 21.50$^{a}$±7.05 | 1.60$^{ab}$±0.60 | 1.00$^{a}$±0.32 | 9.45$^{a}$±2.42 | 140.20$^{b}$±32.30 | 26.80$^{a}$±18.02 |

[1] See "Parameters Measured" for scoring procedure.

[2] Treatment group means per sampling time within scoring parameter are significantly different ($p<0.05$) if followed by different letters.

Table 5: Summary for the time (in minutes) from treatment until the dog was unable to stand (NOSTAND), until sternal recumbency was attained (STERNAL), and until the dog was able to stand (STAND).

| **Variable** | **Innovar I.M.** | **Innovar I.V.** | **Medetomidine I.M.** | **Medetomidine I.V.** |
|---|---|---|---|---|
| NOSTAND | 8.53[a]±10.33 (n=19) | 1.68[a]±1.73 (n=20) | 19.35[b]±22.34 (n=20) | 4.13[a]±2.96 (n=20) |
| STERNAL | 33.60[a]±40.05 (n=20) | 35.70[a]±59.72 (n=20) | 69.35[b]±28.14 (n=20) | 69.25[b]±42.31 (n=20) |
| STAND | 60.00[a]±59.21 (n=20) | 48.45[a]±45.98 (n=20) | 106.50[b]±58.06 (n=20) | 79.50[ab]±53.56 (n=20) |

Table 6a: Prevalence (percent positive) of Dysrhythmias, by Minutes Post-Treatment-Initiation (PTI), Following I.M. Treatment

| **Minutes PTI** | **Medetomidine SA[1]** | **Medetomidine RSA[2]** | **Medetomidine SBRAD[3]** | **Medetomidine TWAVE[4]** | **Medetomidine AVBLK[5]** | **Innovar SA** | **Innovar RSA** | **Innovar SBRAD** | **Innovar TWAVE** | **Innovar AVBLK** |
|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 10.0 | 70.0 | 0.0 | 0.0 | 5.0 | 10.0 | 80.0 | 0.0 | 0.0 | 0.0 |
| 15 | 20.0 | 70.0 | 80.0 | 0.0 | 0.0 | 10.0 | 85.0 | 0.0 | 0.0 | 0.0 |
| 30 | 15.0 | 60.0 | 85.0 | 5.0 | 0.0 | 10.0 | 90.0 | 0.0 | 0.0 | 0.0 |
| 60 | 20.0 | 55.0 | 95.0 | 5.0 | 0.0 | 10.0 | 90.0 | 0.0 | 0.0 | 0.0 |
| 90 | 15.0 | 55.0 | 90.0 | 5.0 | 0.0 | 10.0 | 90.0 | 0.0 | 0.0 | 0.0 |
| 120 | 15.0 | 65.0 | 95.0 | 5.0 | 10.0 | 10.0 | 85.0 | 0.0 | 0.0 | 0.0 |
| 180 | 20.0 | 75.0 | 75.0 | 0.0 | 0.0 | 5.0 | 85.0 | 0.0 | 0.0 | 0.0 |

[1] SA = Sinus Arythmia
[2] RSA = Respiratory Sinus Arythmia
[3] SBRAD = Bradycardia Arythmia
[4] TWAVE = T Wave Changes Arythmia
[5] AVBLK = Second Degree AV Block

Table 6b: Prevalence (percent positive) of Dysrhythmias, by Minutes Post-Treatment-Initiation (PTI), Following I.V. Treatment

| **Minutes PTI** | **Medetomidine SA[1]** | **Medetomidine RSA[2]** | **Medetomidine SBRAD[3]** | **Medetomidine TWAVE[4]** | **Medetomidine AVBLK[5]** | **Innovar SA** | **Innovar RSA** | **Innovar SBRAD** | **Innovar TWAVE** | **Innovar AVBLK** |
|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 15.0 | 85.0 | 0.0 | 0.0 | 0.0 | 5.0 | 75.0 | 0.0 | 0.0 | 0.0 |
| 15 | 15.0 | 85.0 | 90.0 | 10.0 | 15.0 | 10.0 | 65.0 | 5.0 | 0.0 | 0.0 |
| 30 | 15.0 | 85.0 | 85.0 | 0.0 | 5.0 | 15.0 | 75.0 | 0.0 | 0.0 | 0.0 |
| 60 | 10.0 | 80.0 | 100.0 | 0.0 | 5.0 | 15.0 | 75.0 | 0.0 | 0.0 | 0.0 |
| 90 | 10.0 | 90.0 | 85.0 | 10.0 | 0.0 | 15.0 | 70.0 | 0.0 | 0.0 | 0.0 |
| 120 | 20.0 | 65.0 | 60.0 | 5.0 | 0.0 | 20.0 | 65.0 | 0.0 | 0.0 | 0.0 |
| 180 | 15.0 | 85.0 | 40.0 | 10.0 | 0.0 | 15.0 | 65.0 | 0.0 | 0.0 | 0.0 |

[1] SA = Sinus Arythmia
[2] RSA = Respiratory Sinus Arythmia
[3] SBRAD = Bradycardia Arythmia
[4] TWAVE = T Wave Changes Arythmia
[5] AVBLK = Second Degree AV Block

## C. Third Pivotal Study

1. Type of Study: Clinical evaluation of effectiveness in comparison with xylazine.

2. Investigators:

   a. Dr. James S. Reid, Dr. Eric Chafetz, Vienna Animal Hospital, 531 Maple Avenue West, Vienna, VA 22180.

   b. Dr. Herbert A. Lederer, Dr. James F. Norton, Berwyn Veterinary Medical Group, 2845 South Harlem Avenue, Berwyn, IL 60402.

   c. Dr. C. L. Tyner and Dr. B. J. Woody, Veterinary Teaching Hospital, Dept. of Clinical Sciences, College of Veterinary Medicine, Mississippi State University, MS 39762.

3. General Design of Investigation:

   a. Purpose: To evaluate the sedative and analgesic effects of medetomidine in dogs in a clinical setting, and to compare these effects with those of the recommended dose of xylazine.

   b. Test Animals: Case reports for 162 dogs of both sexes, consisting of 41 breeds, weighing an average of 38 lbs (range: 3.0 to 111.0 lbs) and ranging in age from 2 weeks to 15.5 years (mean age: 2.9 years). Dogs were assigned at random to four treatment groups of similar mean weight, distribution of sexes and age.

   c. Type of Control: Xylazine was used as a positive control at the recommended dose. Both drugs were letter coded and two routes of administration (i.v. and i.m.) were assigned at random.

   d. Dosage Form: All treatments were sterile injectable solutions. Medetomidine was used as the proposed market formulation of 1.0 mg/mL, in 10 mL vials. Xylazine was used in the commercial concentration of 20 mg/mL; however, in order to blind the study, it was supplied in 10 mL vials.

   e. Routes of Administration: Both medetomidine and xylazine were used i.v. and i.m.

   f. Dosage Used: The dose for medetomidine was 750 mcg per square meter ($M^2$) body surface i.v. and 1000 mcg per $M^2$ i.m. The dose of xylazine, following manufacturer's recommendations, was 1.1 mg per kg body weight i.v. and 2.2 mg per kg i.m.

   g. Duration of the Study: Each animal was studied for 180 minutes.

   h. Parameters Measured: The following parameters were measured just before treatment (0 time) and 15, 30, 60, 90, 120 and 180 minutes after administration of the test substance. Scores for each parameter are noted in parenthesis and represent the degree of deviation from normal, with score of 0 being normal. Parameters a to c were considered measures of

sedation, parameters c and d (if procedure was painful) were considered measures of analgesia; and e was considered a clinical measure.

(i) Spontaneous Posture (0 - 4)

(ii) Response to Noise (0 - 4)

(iii) Procedure can be performed (0 - 4)

(iv) Toe-pinch withdrawal response (1 to 20 lbs. pressure required to elicit withdrawal response; scored as lbs. of pressure required).

(v) Heart rate

(vi) Times from injection to:

(a) Dog unable to stand

(b) Dog again able to attain sternal recumbency

(c) Dog again able to stand

(vii) Investigator assessment of overall drug effects regarding:

(a) Applicability for the intended purpose (poor to excellent)

(b) Sedative effect (none to excellent)

(c) Analgesic effect (none to excellent)

(viii) Prevalence of dysrhythmias

(ix) Side effects

4. Adverse Effects (Side Effects): Vomiting was the most noticeable side effect, occurring more often in dogs treated with medetomidine IV than IM, and less frequently in dogs treated with xylazine IV than IM The overall level of all side effects was low (jerking, retching, apneutic breathing, gastric distention, prolonged recovery, pale mucous membranes)(Table 10) and not significantly different between groups. None was lasting or required medication.

5. Statistical Analysis: Data on quantitative variables were statistically analyzed by analysis of variance (ANOVA), along with multiple comparisons of means to evaluate the differences, if any, among the four treatment groups. Data on each quantitative variable collected at only one time were statistically analyzed by ANOVA, followed by application of the least-significant-difference (LSD) method of comparison of the four treatment means. Treatment, intended use of the drug, sex of the dog, and age of the dog were included as main effects in the ANOVA procedure. All first-order interactions of the main effects were included in the ANOVA procedure, while all higher-order interactions were pooled with the error term. Data on any quantitative variable collected at several times were statistically analyzed by repeated measures ANOVA, followed by multiple comparisons among the four treatment group means at each measurement time based on the LSD procedure with the appropriately pooled mean-square error. Score variables were statistically analyzed as a

quantitative variable by repeated-measures ANOVA in order to take account of the repeated measurements on each dog over the PTI sampling times. Data on quantitative variables were statistically analyzed by standard chi-square tests for two-way contingency tables to evaluate the differences, if any, among the four treatment groups.

6. Results: The four treatment groups were not significantly different with respect to their distribution of intended use, sex, age, attitude, mucous membrane color, pulse quality, auscultation of lung and heart, and the prevalence of heartworm upon entry to the study. They did not differ in mean body weight, mean body temperature and heart rate at this time. Radiography, examinations and wound suturing were the most frequent indications for drug use. A summary of the results (i.m. and i.v., respectively) for sedation is presented in Tables 7 and 8 for posture score and noise response scores and for analgesia for toe-pinch and procedure score. The latter records sedation with non-painful procedures, and sedation and analgesia with painful procedures. Effects on heart rate are also shown in Tables 7 and 8. Initiation and duration of sedative drug effects are shown in Table 9, and results regarding drug applicability and the overall assessment of sedative and analgesic drug effects are presented in Table 10. Prevalence of dysrhythmia is shown in Table 11.

   The mean posture score (Tables 7, 8) was significantly different among the four treatment groups overall ($p<0.001$) and at each sampling time except for 0 and 30 minutes PTI with the medetomidine treatment group means being generally higher than the corresponding xylazine treatment group means at 60 through 180 minutes PTI.

   The differences among the four treatment groups with respect to the noise score (Tables 7,8) were statistically significant both overall ($p<0.001$) and at each PTI sampling time except for 0 minutes PTI. In particular, the mean noise score for both the IM and the IV medetomidine treatment groups were significantly higher than the corresponding IM and IV xylazine treatment group means at 60, 90, and 120 minutes PTI.

   The mean heart rate (Tables 7,8) was not significantly different among the four treatment groups overall ($p=0.300$) and at 0 and 30 minutes PTI. The mean heart rate for each of the two medetomidine treatment groups was significantly less than those of the two xylazine treatment groups at 120 minutes PTI.

   The mean toe pinch response (Tables 7,8) was significantly different overall among the four treatment groups ($p=0.002$) with statistically significant differences among the four treatment groups means at each of the sampling times from 15 through 180 minutes PTI except at 30 minutes PTI. The response after medetomidine was generally higher and lasted longer than the response with xylazine.

   The mean procedure score (Tables 7,8) varied significantly among the four treatment groups at 15 and 30 minutes PTI ($p=0.008$ and $p=0.010$, respectively) but not at 60 minutes PTI ($p=0.131$). At each of these three PTI sampling items, the mean procedure score for the medetomidine-IV treatment

group was significantly higher than those for both xylazine treatment groups. The difference in the mean procedure score between the medetomidine-IM and xylazine-IM treatment groups was not statistically significant at each of these three PTI sampling times. The mean times from treatment until the dog was unable to stand (NOSTAND), until sternal recumbency was attained (STERNAL), and until the dog was able to stand again (STAND) (Table 9) were each significantly different ($p<0.001$) among the four treatment groups. In particular, the mean STERNAL time and the mean STAND time were significantly higher in the medetomidine-IM treatment group than in each of the other three treatment groups. The medetomidine-IV and the xylazine-IM treatment groups were not significantly different but were each significantly higher than the xylazine-IV treatment group with respect to both the mean STERNAL time and the mean STAND time. The mean NOSTAND time for the medetomidine-IV treatment group was not significantly different than that for the xylazine-IV treatment group but was significantly less than that for the xylazine-IM treatment group.

The rating of the applicability of the drug (excellent, moderate, and poor, Table 10) was significantly different among the four treatment groups ($p<0.001$) with the greatest difference being between the two IV treatment groups. The evaluations of analgesia and of sedation (excellent, good, slight, and none) were both significantly different among the four treatment groups ($p<0.001$ for each) with both the analgesia and the sedation evaluations for the two medetomidine treatment groups being higher than those for the two xylazine treatment groups.

Prevalence of dysrhythmia (Table 11) varied significantly among the four treatment groups only at 15 minutes PTI ($p=0.010$). The prevalence of dysrhythmia at 15 minutes PTI was significantly lower ($p=0.002$) for the IM treatment groups combined than for the IV treatment groups combined (15.5% and 37.2%, respectively); the prevalence of dysrhythmia at 15 minutes for the medetomidine treatment groups combined was not significantly different from that for the xylazine treatment groups combined (26.6% and 25.3%, respectively).

7. Conclusions: Medetomidine was consistently rated as more efficient as a sedative and analgesic than xylazine for a wide variety of clinical uses. Medetomidine i.v. was rated highest, and xylazine i.v. rated lowest, with the ratings for medetomidine and xylazine i.m. being more similar.

   Bradycardia lasted longer after medetomidine treatment, but drops in heart rate were present with the use of both drugs Dysrhythmias were seen more frequently after i.v. use of both drugs, but lasted longer with medetomidine.

Table 7: Scores[1] for Posture (POST), Noise, Toe Pinch (TOE), Heart Rate (HR) and Procedure (PROC) by I.M. Treatment Group[2] and Time Post-Treatment-Initiation (PTI)

| Minutes PTI | Medetomidine POST (n=39) | Medetomidine Noise (n=39) | Medetomidine TOE (n=37) | Medetomidine HR (n=39) | Medetomidine PROC[3] | Xylazine POST (n=44) | Xylazine Noise (n=44) | Xylazine TOE (n=42) | Xylazine HR (n=44) | Xylazine PROC[3] |
|---|---|---|---|---|---|---|---|---|---|---|
| 0X | 0.05$^{a}$±0.32 | 0.97$^{a}$±0.28 | 11.03$^{a}$±3.89 | 130.28$^{a}$±29.26 | | 0.00$^{a}$±0.00 | 1.02$^{a}$±0.15 | 11.62$^{a}$±4.64 | 122.34$^{a}$±24.20 | |
| 15X | 3.03$^{a}$±1.46 | 2.41$^{a}$±0.75 | 17.57$^{a}$±4.36 | 63.79$^{a}$±26.16 | 2.89$^{a}$±1.55 (27) | 3.43$^{b}$±1.09 | 2.39$^{a}$±0.72 | 17.24$^{a}$±5.02 | 56.2$^{ab}$±26.83 | 2.94$^{a}$±1.29 (36) |
| 30X | 3.87$^{a}$±0.41 | 2.64$^{a}$±0.58 | 18.38$^{a}$±2.98 | 54.31$^{a}$±21.92 | 3.15$^{a}$±0.96 (39) | 3.70$^{a}$±0.79 | 2.66$^{a}$±0.48 | 18.40$^{a}$±3.32 | 51.41$^{a}$±21.32 | 3.00$^{a}$±1.20 (41) |
| 60X | 3.62$^{a}$±0.75 | 2.62$^{a}$±0.54 | 17.86$^{a}$±3.69 | 56.23$^{ab}$±20.59 | 3.21$^{ab}$±0.96 (28) | 3.43$^{a}$±0.93 | 2.32$^{b}$±0.71 | 17.24$^{ab}$±3.99 | 56.14$^{ab}$±20.63 | 3.00$^{b}$±1.24 (23) |
| 90X | 3.56$^{a}$±0.72 | 2.41$^{a}$±0.55 | 18.08$^{a}$±3.88 | 58.54$^{ab}$±23.43 | | 2.39$^{c}$±1.24 | 1.80$^{c}$±0.67 | 15.95$^{bc}$±4.68 | 62.66$^{ab}$±27.87 | |
| 120X | 2.87$^{a}$±1.03 | 2.08$^{a}$±0.58 | 16.54$^{a}$±4.44 | 60.31$^{a}$±25.43 | | 1.64$^{c}$±1.10 | 1.50$^{bc}$±0.59 | 14.67$^{b}$±5.05 | 76.45$^{b}$±38.20 | |
| 180X | 1.46$^{a}$±1.17 | 1.59$^{a}$±0.72 | 15.57$^{a}$±4.78 | 78.10$^{a}$±35.44 | | 0.10$^{bc}$±0.76 | 1.16$^{b}$±0.43 | 13.29$^{bc}$±5.32 | 88.64$^{ab}$±38.50 | |

[1]See "Parameters Measured" for scoring procedure.
[2] Treatment group means per sampling time within scoring parameter are significantly different ($p<0.05$) if followed by different letters.
[3] For PROC, number of dogs per PTI in parenthesis.

Table 8: Scores[1] for Posture (POST), Noise, Toe Pinch (TOE), Heart Rate (HR) and Procedure (PROC) by I.V. Treatment Group[2] and Time Post-Treatment-Initiation (PTI)

| Minutes PTI | Medetomidine POST (n=37) | Medetomidine Noise (n=37) | Medetomidine TOE (n=33) | Medetomidine HR (n=37) | Medetomidine PROC[3] | Xylazine POST (n=38) | Xylazine Noise (n=38) | Xylazine TOE (n=37) | Xylazine HR (n=38) | Xylazine PROC[3] |
|---|---|---|---|---|---|---|---|---|---|---|
| 0X | 0.00$^{a}$±0.00 | 0.92$^{a}$±0.28 | 11.79$^{a}$±3.93 | 124.24$^{a}$±22.08 | | 0.08$^{a}$±0.49 | 1.03$^{a}$±0.16 | 10.65$^{a}$±4.90 | 124.89$^{a}$±28.96 | |
| 15X | 3.81$^{c}$±0.62 | 2.84$^{b}$±0.44 | 19.64$^{b}$±1.08 | 50.73$^{b}$±20.62 | 3.68$^{b}$±0.65 (31) | 3.71$^{bc}$±0.77 | 2.45$^{a}$±0.50 | 17.57$^{a}$±3.49 | 60.97$^{ab}$±24.87 | 2.71$^{a}$±1.20 (35) |
| 30X | 3.95$^{a}$±0.33 | 2.89$^{b}$±0.31 | 19.33$^{a}$±2.16 | 51.43$^{a}$±1.65 | 3.70$^{b}$±0.53 (33) | 3.74$^{a}$±0.60 | 2.32$^{c}$±0.47 | 17.70$^{a}$±5.31 | 59.21$^{a}$±23.44 | 2.79$^{a}$±1.15 (34) |
| 60X | 3.62$^{a}$±0.72 | 2.57$^{a}$±0.50 | 18.42$^{a}$±3.24 | 51.30$^{a}$±18.44 | 3.79$^{a}$±0.43 (14) | 2.63$^{b}$±1.08 | 1.87$^{c}$±0.66 | 15.89$^{b}$±4.48 | 62.84$^{b}$±24.97 | 2.88$^{b}$±1.09 (16) |
| 90X | 2.92$^{b}$±0.89 | 2.05$^{b}$±0.52 | 17.36$^{ab}$±3.37 | 55.84$^{a}$±20.02 | | 1.37$^{d}$±1.00 | 1.47$^{d}$±0.56 | 1.47$^{d}$±0.56 | 14.43$^{c}$±5.44 | 68.55$^{b}$±24.92 |
| 120X | 2.08$^{b}$±1.06 | 1.70$^{b}$±0.66 | 15.39$^{ab}$±4.08 | 62.41$^{a}$±24.52 | | 0.84$^{d}$±0.86 | 1.29$^{c}$±0.46 | 13.76$^{b}$±5.06 | 81.26$^{b}$±35.04 | |
| 180X | 0.92$^{b}$±0.98 | 1.19$^{b}$±0.40 | 14.91$^{ab}$±4.15 | 79.05$^{a}$±29.60 | | 0.39$^{c}$±0.64 | 1.11$^{b}$±0.31 | 12.14$^{c}$±4.28 | 96.74$^{b}$±33.74 | |

[1] See "Parameters Measured" for scoring procedure.
[2] Treatment group means per sampling time within scoring parameter are significantly different ($p<0.05$) if followed by different letters.
[3] For PROC, number of dogs per PTI in parenthesis.

Table 9: Summary for the time (in minutes) from injection until the dog was unable to stand (NOSTAND), until sternal recumbency was attained (STERNAL), and until the dog was able to stand again (STAND) by treatment group(1)

| **Variable** | **Medetomidine I.M.** | **Medetomidine I.V.** | **Xylazine I.M.** | **Xylazine I.V.** |
|---|---|---|---|---|
| NOSTAND | 11.78[a]±12.63 (n=40) | 2.99[c]±4.51 (n=39) | 8.52[ab]±7.93 (n=44) | 5.41[bc]±7.27 (n=39) |
| STERNAL | 106.68[a]±67.30 (n=40) | 80.28[b]±39.78 (n=39) | 76.61[b]±25.75 (n=44) | 47.82[c]±23.17 (n=38) |
| STAND | 138.38[a]±75.53 (n=40) | 96.13[b]±40.26 (n=39) | 91.43[b]±27.36 (n=44) | 69.41[c]±33.72 (n=39) |

[1] Treatment group means are significantly different ($p<0.05$) if followed by different letters.

Table 10: Distribution[1] of the applicability of the drug, the subjective evaluations of both analgesia/anesthesia and sedation, and presence of side effects by treatment group.

| | **Medetomidine I.M.** | **Medetomidine I.V.** | **Xylazine I.M.** | **Xylazine I.V.** |
|---|---|---|---|---|
| Applicability – Excellent | 24 (60.00) | 37 (94.87) | 26 (60.47) | 19 (48.72) |
| Applicability – Moderate | 15 (37.50) | 2 (5.13) | 12 (27.91) | 15 (38.46) |
| Applicability – Poor | 1 (2.50) | 0 (0.00) | 5 (11.63) | 5 (12.82) |
| Analgesia – Excellent | 19 (47.50) | 29 (76.32) | 14 (31.82) | 7 (18.42) |
| Analgesia – Good | 14 (35.00) | 7 (18.42) | 19 (43.18) | 12 (31.58) |
| Analgesia – Slight | 7 (17.50) | 2 (5.66) | 11 (25.00) | 18 (47.37) |
| Analgesia – None | 0 (0.00) | 0 (0.00) | 0 (0.00) | 1 (2.63) |
| Sedation – Excellent | 32 (82.05) | 37 (97.37) | 30 (68.18) | 18 (46.15) |
| Sedation – Good | 3 (7.69) | 1 (2.63) | 11 (25.00) | 16 (41.03) |
| Sedation – Slight | 4 (10.26) | 0 (0.00) | 3 (6.82) | 5 (12.82) |
| Side Effects – Present | 9 (22.50) | 5 (12.82) | 6 (13.64) | 2 (5.13) |
| Side Effects - Absent | 31 (77.50) | 34 (87.18) | 38 (86.36) | 37 (97.87) |
| Number of Dogs | 40 | 39 | 44 | 39 |

[1] The percent of each response category, shown in parenthesis, was based on the total number of dogs per treatment group excluding any missing data.

Table 11 Prevalence (percent positive) of dysrhythmia by treatment group and time post-treatment-initiation (PTI)

| **Minutes PTI** | **Medetomidine I.M.** | **Medetomidine I.V.** | **Xylazine I.M.** | **Xylazine I.V.** |
|---|---|---|---|---|
| 0 | 0.0 | 0.0 | 0.0 | 2.56 |
| 15 | 20.00 | 33.33 | 11.36 | 41.03 |
| 30 | 12.50 | 28.21 | 23.73 | 35.90 |
| 60 | 10.00 | 23.68 | 13.64 | 17.95 |
| 90 | 7.50 | 18.42 | 6.82 | 12.82 |
| 120 | 5.13 | 12.82 | 6.98 | 7.69 |
| 180 | 0.00 | 5.13 | 2.33 | 2.63 |

**D. Fourth Pivotal Study**

1. Type of Study: Controlled clinical evaluation of effectiveness compared to xylazine.

2. Investigator:

   a. Dr. C.F. Short and Dr. J.E. Saidla, NYSCVM, Cornell University, Ithaca, NY 14853.

   b. Dr. J. W. Whitefield, Hudson Highland Vet. Med. Group, P. O. Box 1320, Hopewell Junction, NY 12533.

3. General Design of Investigations:

   a. Purpose: To evaluate the sedative and analgesic effects of medetomidine when used in a clinical setting, and to compare these effects with those of the recommended dose of xylazine.

   b. Test Animals: Sixty five dogs of both sexes, representing 22 breeds, weighing an average of 39.5 lbs. (ranging from 7-85 lbs.) with a mean age of just over four years (ranging from 2 mo. to 12 years) were randomly assigned to four treatment groups of similar mean weight, age, and distribution of sexes.

   c. Type of Control: Xylazine at the recommended dose was used as a positive control. Both drugs were letter coded and two routes of administration (i.v. and i.m.) were assigned at random.

   d. Dosage Form: All treatments were sterile injectable solutions. Medetomidine was used as the proposed market formulation of 1.0 mg/mL, in 10 mL vials. Xylazine was used in the commercial concentration of 20 mg/mL; however, in order to blind the study, it was supplied in 10 mL vials.

   e. Routes of Administration: Both medetomidine and xylazine were used i.v. and i.m.

   f. Dosage Used: The dose for medetomidine was 750 mcg per square meter ($M^2$) body surface i.v. and 1000 mcg per $M^2$ i.m. The dose of xylazine,

following manufacturer's recommendations, was 1.1 mg per kg body weight i.v. and 2.2 mg per kg i.m.

g. Duration of the Study: The study lasted approximately nine months.

h. Parameters Measured: The following parameters were measured just before treatment (0 time) and 15, 30, 60, 90, 120 and 180 minutes after administration of the test substance. Scores for each parameter are noted in parenthesis and represent the degree of deviation from normal, with score of 0 being normal. Parameters a to c were considered measures of sedation, parameters c and d (if procedure was painful) were considered measures of analgesia; and e was considered a clinical measure.

(i) Spontaneous Posture (0 - 4)( 0-normal, 1-tired but standing, 2-lying, able to rise,3-lying, able to rise with difficulty, 4-unable to rise)

(ii) Response to Noise (0 - 4)( 0-hypersensitive, 1- normal, 2-weak, 3-no reaction)

(iii) Procedure can be performed (0 - 4)( 0-cannot be performed, 1-with difficulty, 2-moderate resistance, 3-slight resistance, 4-no resistance)

(iv) Pedal Reflex (0-3)( 0-normal, 1-slightly impaired, 2-clearly weak, 3-absent).

(v) Maximum scores achieved for a), b), d) during 180 minute test period

(vi) Heart rate

(vii) Times from injection to:

i. Dog unable to stand

j. Dog again able to attain sternal recumbency

k. Dog again able to stand

(i) Investigator assessment of overall drug effects regarding:

l. Applicability for the intended purpose (poor to excellent)

m. Sedative effect (none to excellent)

n. Analgesic effect (none to excellent)

(i) Prevalence of dysrhythmias

(ii) Side Effects

4. Adverse Effects (Side Effects): Vomiting was the most noticeable side effect, occurring least often in dogs treated with medetomidine i.v. and most often with medetomidine i.m. Dogs treated with xylazine i.v. showed an incidence similar to medetomidine i.v., while xylazine i.m. was intermediate. Dysrhythmias were seen more frequently after IV use of both drugs and lasted

longer with medetomidine IM. The overall level of all side effects was low (Table 15) and not significantly different between groups. None was lasting or required medication.

5. Statistical Analysis: Data on quantitative variables were statistically analyzed by analysis of variance (ANOVA) among the four treatment groups. Data collected only once were analyzed by ANOVA followed by the least-significant-difference (LSD) method of comparison of the four treatment means. Treatment, intended use of the drug for sedation or analgesia, sex and age were included in the ANOVA as main effects. Data on quantitative variables collected at several times were analyzed by repeated-measure ANOVA, followed by LSD with the appropriately pooled mean-square error (according to Cochran & Cox, Experimental Design, 2nd ed., pp. 298-302). Data on qualitative variables were analyzed by standard chi-square tests for two-way contingency tables to evaluate differences among the four treatment groups.

6. Results: For 24 of the 65 dogs in this study, time 0 was taken to be the time at which sedative effects were first observed rather than the time immediately prior to injection. Consequently, data on response variables taken over time (i.e. over the 180 minute observation period for posture score, pedal reflex score, response to noise, heart rate and procedure scores) were not included in the statistical analysis. The following results are based on data from the remaining 41 dogs. A summary of the results (i.m. and i.v., respectively) for sedation is presented in Tables 12 and 13 for posture score and noise response scores and for analgesia for pedal reflex and procedure score. The latter records sedation with non-painful procedures, and sedation and analgesia with painful procedures. Effects on heart rate are also shown in Tables 12 and 13. Initiation and duration of sedative drug effects are shown in Table 14, and results regarding drug applicability and the overall assessment of sedative and analgesic drug effects, and side effects are presented in Table 15. Prevalence of dysrhythmias is shown in Table 16.

   The four treatment groups were not significantly different with respect to their distribution of intended use, sex, age, attitude, general health and the prevalence of heartworm upon entry to the study, and they did not differ in mean body weight, mean body temperature and heart rate at time 0.

   The mean posture score (Tables 12,13) was not significantly different among the four treatment groups overall ($p=0.467$), but statistically significant differences among the four treatment groups were found at 15 through 120 minutes PTI with the medetomidine treatment group means being generally higher than the corresponding xylazine treatment group means at each of these five PTI times.

   The differences among the four treatment groups with respect to the noise score (Tables 12,13) were statistically significant both overall ($p=0.021$) and at each PTI sampling time except for 0 and 180 minutes PTI; in particular, the mean noise score for each medetomidine treatment group was significantly higher than that of the corresponding xylazine treatment group at 120 minutes PTI.

   The mean heart rate (Tables 12, 13) was significantly different among the four treatment groups both overall ($p=0.004$) and at each sampling time except for

0 minutes PTI. The mean heart rate for each of the two medetomidine treatment groups was significantly less than those of the two xylazine treatment groups at 120 minutes PTI.

The mean pedal reflex score (Tables 12, 13) was not significantly different overall among the four treatment groups (p=0.201) although there were statistically significant differences among the four treatment group means at 15 through 120 minutes PTI. In particular, the mean pedal reflex score of the medetomidine-IV treatment group was significantly higher than that of the xylazine-IV treatment group at 15, 30, and 90 minutes PTI.

The mean procedure score (Tables 12, 13) did not vary significantly among the four treatment groups at 15, 30, or 60 minutes PTI (p=0.871, p=0.733, and p=0.322, respectively), although the mean procedure score for the medetomidine-IV treatment group was considerably higher than that for the xylazine-IV treatment group at each of these three PTI sampling times.

The mean sedation-related times (Table 14) from injection until the dog was unable to stand (NOSTAND) was significantly different among the four treatment groups (p=0.010) with each of the two IM treatment groups being significantly higher than the two IV treatment groups with respect to the mean NOSTAND time.

The mean times from injection until the dog attained sternal recumbency (STERNAL) and until the dog was able to stand again (STAND) were each not significantly different among the four treatment groups (p=0.403 and p=0.275, respectively). However, the medetomidine-IM treatment group was significantly higher than both xylazine treatment groups with respect to the mean STAND time.

Both the rating of the applicability of the drug (excellent, moderate, and poor) and the evaluation of analgesia (excellent, good, slight, and none) (Table 15) were significantly different among the four treatment groups (p=0.019 and p=0.017, respectively) with both the applicability evaluation and the analgesia evaluation for the two medetomidine treatment groups being higher than those for the two xylazine treatment groups.

The evaluations of sedation (excellent, good, and slight), although higher in the medetomidine treatment groups than in the xylazine treatment groups, were not significantly different among the four treatment groups (p=0.100). The four treatment groups were not significantly different with respect to the occurrence of side effects (p=0.954). Prevalence of dysrhythmia (Table 16) did not vary significantly among the four treatment groups at any of the sampling times 0 through 180 minutes PTI.

Regardless of age, breed, body weight or health status of dogs at admission, both medetomidine and xylazine were found to be safe and effective for the procedures for which they were used. Medetomidine, however, was consistently rated more efficient as a sedative and analgesic than xylazine, with medetomidine i.v. rated highest, and xylazine i.m. rated lowest.

7. Conclusions: Irrespective of age, breed, or body weight, both medetomidine and xylazine were found to be effective and safe. Overall, medetomidine i.v. ranked highest and xylazine i.m. lowest.

Table 12: Scores[1] for Posture (POST), Noise, Pedal Reflex (PR), Heart Rate (HR) and Procedure (PROC) by I.M. Treatment Group[2] and Time Post-Treatment-Initiation (PTI)

| Minutes PTI | Medetomidine POST | Medetomidine Noise | Medetomidine PR | Medetomidine HR | Medetomidine PROC[3] | Xylazine POST | Xylazine Noise | Xylazine PR | Xylazine HR | Xylazine PROC[3] |
|---|---|---|---|---|---|---|---|---|---|---|
| 0X | 0.00$^{a}$±0.00 | 1.00$^{a}$±0.00 | 0.38$^{a}$±1.06 | 109.50$^{a}$±21.05 | | 0.00$^{a}$±0.00 | 0.92$^{a}$±0.29 | 0.00$^{a}$±0.00 | 104.17$^{a}$±29.26 | |
| 15X | 3.25$^{ab}$±1.16 | 2.13$^{a}$±0.83 | 1.88$^{ab}$±0.99 | 45.38$^{a}$±9.46 | 2.88$^{a}$±1.55 (8) | 3.08$^{a}$±1.08 | 2.50$^{ab}$±0.67 | 1.92$^{ab}$±0.90 | 53.33$^{ab}$±22.08 | 2.58$^{a}$±1.56 (12) |
| 30X | 3.63$^{a}$±0.74 | 2.50$^{a}$±0.53 | 2.25$^{a}$±0.89 | 43.00$^{a}$±11.20 | 3.14$^{a}$±0.90 (7) | 3.17$^{a}$±0.83 | 2.58$^{a}$±0.51 | 1.92$^{ab}$±0.64 | 54.08$^{ab}$±16.42 | 2.92$^{A}$±1.00 (12) |
| 60X | 3.00$^{a}$±1.07 | 2.00$^{a}$±0.76 | 1.75$^{a}$±1.04 | 44.38$^{a}$±10.47 | 2.20$^{a}$±1.79 (5) | 2.67$^{ab}$±0.89 | 2.17$^{a}$±0.58 | 1.50$^{ab}$±0.52 | 61.25$^{bc}$±30.28 | 2.38$^{a}$±1.41 (8) |
| 90X | 2.63$^{a}$±1.30 | 1.88$^{a}$±0.64 | 1.38$^{a}$±0.92 | 51.38$^{a}$±18.09 | | 2.33$^{a}$±1.23 | 1.92$^{a}$±0.51 | 0.75$^{ab}$±0.62 | 59.25$^{ab}$±12.64 | |
| 120X | 2.13$^{a}$±1.36 | 1.88$^{a}$±0.64 | 1.13$^{a}$±0.64 | 50.50$^{a}$±11.83 | | 1.50$^{ab}$±1.00 | 1.42$^{bc}$±0.51 | 0.50$^{ab}$±0.67 | 68.50$^{b}$±31.65 | |
| 180X | 0.25$^{a}$±0.46 | 1.00$^{a}$±0.00 | 0.13$^{a}$±0.35 | 62.75$^{a}$±12.56 | | 0.50$^{a}$±0.90 | 1.08$^{a}$±0.29 | 0.17$^{a}$±0.39 | 72.00$^{ab}$±24.14 | |

[1] See "Parameters Measured" for scoring procedure.
[2] Treatment group means per sampling time within scoring parameter are significantly different ($p<0.05$) if followed by different letters.
[3] For all parameters except PROC, medetomidine group contained 8 dogs and xylazine group contained 12 dogs. For PROC, number of dogs per PTI in parenthesis.

Table 13: Scores(1) for Posture (POST), Noise, Pedal Reflex (PR), Heart Rate (HR) and Procedure (PROC) by I.V. Treatment Group(2) and Time Post-Treatment-Initiation (PTI)

| Minutes PTI | Medetomidine POST | Medetomidine Noise | Medetomidine PR | Medetomidine HR | Medetomidine PROC[3] | Xylazine POST | Xylazine Noise | Xylazine PR | Xylazine HR | Xylazine PROC[3] |
|---|---|---|---|---|---|---|---|---|---|---|
| 0X | 0.00$^{a}$±0.00 | 0.90$^{a}$±0.32 | 0.00$^{a}$±0.00 | 115.00$^{a}$±19.85 | | 0.00$^{a}$±0.00 | 0.90$^{a}$±0.32 | 0.30$^{a}$±0.95 | 109.40$^{a}$±25.14 | |
| 15X | 4.00$^{b}$±0.00 | 2.80$^{b}$±0.42 | 2.50$^{b}$±0.71 | 47.30$^{a}$±13.20 | 3.64$^{a}$±0.92 (11) | 3.80$^{ab}$±0.42 | 2.20$^{a}$±1.03 | 1.50$^{a}$±0.85 | 60.50$^{a}$±0.85 | 2.80$^{a}$±1.03 (10) |
| 30X | 3.90$^{a}$±0.32 | 2.60$^{a}$±0.52 | 2.50$^{a}$±0.85 | 56.50$^{b}$±16.49 | 3.44$^{a}$±1.33 (9) | 3.10$^{a}$±0.99 | 2.00$^{b}$±0.82 | 1.50$^{b}$±0.97 | 56.10$^{b}$±17.99 | 2.00$^{a}$±1.41 (8) |
| 60X | 3.30$^{a}$±1.06 | 2.00$^{a}$±0.82 | 1.60$^{ab}$±1.07 | 53.20$^{ab}$±7.38 | 3.14$^{a}$±1.57 (7) | 2.10$^{b}$±0.99 | 1.50$^{b}$±0.85 | 1.00$^{b}$±0.94 | 65.10$^{c}$±17.98 | 0.80$^{a}$±1.30 (5) |
| 90X | 3.20$^{b}$±1.03 | 1.70$^{a}$±0.67 | 1.30$^{a}$±1.06 | 56.80$^{a}$±12.34 | | 1.20$^{c}$±0.79 | 1.10$^{b}$±0.57 | 0.75$^{ab}$±0.62 | 59.25$^{ab}$±12.64 | |
| 120X | 2.10$^{a}$±1.20 | 1.50$^{ab}$±0.53 | 0.90$^{ab}$±1.29 | 57.20$^{a}$±9.38 | | 1.50$^{ab}$±1.00 | 1.42$^{bc}$±0.51 | 0.50$^{ab}$±0.67 | 68.50$^{b}$±31.65 | |
| 180X | 0.40$^{a}$±0.70 | 1.10$^{a}$±0.32 | 0.10$^{a}$±0.32 | 82.60$^{bc}$±16.84 | | 0.50$^{a}$±0.90 | 1.08$^{a}$±0.29 | 0.17$^{a}$±0.39 | 72.00$^{ab}$±24.14 | |

[1] See "Parameters Measured" for scoring procedure.
[2] Treatment group means per sampling time within scoring parameter are significantly different ($p<0.05$) if followed by different letters.
[3] For all parameters except PROC, medetomidine group contained 10 dogs and xylazine contained 10 dogs. For PROC, number of dogs per PTI in parenthesis.

Table 14: Summary for the time (in minutes) from injection until the dog was unable to stand (NOSTAND), until sternal recumbency was attained (STERNAL), and until the dog was able to stand again (STAND) by treatment group[1].

| **Variable** | **Medetomidine I.M.** | **Medetomidine I.V.** | **Xylazine I.M.** | **Xylazine I.V.** |
|---|---|---|---|---|
| NOSTAND | 11.93[a]±10.53 (n=14) | 2.81[b]±3.11 (n=18) | 8.81[a]±7.37 (n=16) | 2.80[b]±2.21 (n=15) |
| STERNAL | 72.86[a]±28.90 (n=14) | 56.19a[b]±19.57 (n=16) | 54.47[ab]±32.10 (n=15) | 40.07[b]±27.09 (n=15) |
| STAND | 111.21[a]±45.61 (n=14) | 99.06[ab]±36.60 (n=17) | 77.06[ab]±41.55 (n=18) | 69.20[b]±29.16 (n=15) |

[1] Treatment group means are significantly different ($p<0.05$) if followed by different letters.

Table 15: Distribution[1] of the applicability of the drug, the subjective evaluations of both analgesia/anesthesia and sedation, and presence of side effects by treatment group.

| | **Medetomidine I.M.** | **Medetomidine I.V.** | **Xylazine I.M.** | **Xylazine I.V.** |
|---|---|---|---|---|
| Applicability – Excellent | 8 (57.1) | 14 (77.8) | 3 (16.7) | 6 (40.0) |
| Applicability – Moderate | 5 (35.7) | 2 (11.1) | 11 (61.1) | 7 (46.7) |
| Applicability – Poor | 1 (7.1) | 2 (11.1) | 4 (22.2) | 2 (13.3) |
| Analgesia – Excellent | 6 (42.9) | 12 (66.7) | 2 (11.1) | 5 (33.3) |
| Analgesia – Good | 6 (42.9) | 2 (11.1) | 6 (33.3) | 6 (40.0) |
| Analgesia – Slight | 2 (14.3) | 4 (22.2) | 10 (55.6) | 3 (20.0) |
| Analgesia – None | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (6.7) |
| Sedation – Excellent | 6 (42.9) | 12 (66.7) | 4 (22.2) | 5 (33.3) |
| Sedation – Good | 5 (35.7) | 4 (22.2) | 6 (33.3) | 3 (20.0) |
| Sedation – Slight | 3 (21.4) | 2 (11.1) | 8 (44.4) | 7 (46.7) |
| Side Effects – Present | 4 (28.6) | 4 (22.2) | 4 (22.2) | 3 (20.0) |
| Side Effects - Absent | 10 (71.4) | 14 (77.8) | 14 (77.8) | 12 (80.0) |
| Number of Dogs | 14 | 18 | 18 | 15 |

[1] The percent of each response category, shown in parenthesis, was based on the total number of dogs per treatment group excluding any missing data.

Table 16: Prevalence[1] of dysrhythmia by treatment group and time post-treatment-initiation (PTI)

| **Minutes PTI** | **Medetomidine I.M.** | **Medetomidine I.V.** | **Xylazine I.M.** | **Xylazine I.V.** | **Chi-Square Statistics[2]** |
|---|---|---|---|---|---|
| 0 | 0.0 | 0.0 | 0.0 | 10.0 | 3.38* (0.377) |
| 15 | 33.3 | 36.4 | 15.4 | 40.0 | 2.05* (0.563) |
| 30 | 33.3 | 45.5 | 23.1 | 10.0 | 1.46* (0.691) |
| 60 | 33.3 | 36.4 | 15.4 | 10.0 | 3.01* (0.391) |
| 90 | 33.3 | 18.2 | 15.4 | 10.0 | 1.87* (0.600) |
| 120 | 22.2 | 0.0 | 7.7 | 10.0 | 2.96* (0.399) |
| 180 | 22.2 | 0.0 | 7.7 | 10.0 | 2.96* (0.399) |
| Number of Dogs[3] | 9 | 11 | 13 | 10 | |

[1] Prevalence (i.e. percent positive) was based on the number of dogs[3] per treatment group with complete data on dysrhythmia.
[2] The significance level of the chi-square test statistic is shown in parenthesis; for any chi-square statistice followed by an asterisk, more than 20% of the expected frequencies were less than 5.

## E. Fifth Pivotal Study

1. Type of Study: Clinical evaluation of effectiveness compared to xylazine for dental care in dogs.

2. Investigator: Dr. C.F. Short and Dr. J.E. Saidla, NYSCVM, Cornell University, Ithaca, NY 14853.

3. General Design of Investigations:

   a. Purpose: The objective of this study was to evaluate the sedative and analgesic effects of medetomidine when used for dental care, and to compare these effects with those of the recommended dose of xylazine. This study was part of a larger multicenter study, in that of the 65 dogs that were included in the Fourth Pivotal Study, 54 of them also received a dental examination/procedure in addition to other examination/treatment. These dental cases have been analyzed separately.

   b. Test Animals: Fifty four dogs of both sexes, representing 16 breeds, weighing an average of 37.46 lbs. (ranging from 11-85 lbs.) with a mean age of four years and four months were randomly assigned to four treatment groups of similar mean weight, age, and distribution of sexes.

   c. Type of Control: Xylazine at the recommended dose was used as a positive control. Both drugs were letter coded and two routes of administration (i.v. and i.m.) were assigned at random.

   d. Dosage Form: All treatments were sterile injectable solutions. Medetomidine was used as the proposed market formulation of 1.0 mg/mL, in 10 mL vials. Xylazine was used in the commercial concentration of 20 mg/mL. However, in order to blind the study, it was supplied in 10 mL vials.

   e. Routes of Administration: Both medetomidine and xylazine were used i.v. and i.m.

   f. Dosage Used: The dose for medetomidine was 750 mcg per square meter ($M^2$) body surface i.v. and 1000 mcg per $M^2$ i.m. The dose of xylazine, following sponsor's recommendations, was 1.1 mg per kg body weight i.v. and 2.2 mg per kg i.m.

   g. Duration of the Study: The study lasted approximately nine months.

   h. Parameters Measured: The following parameters were measured just before treatment (0 time) and 15, 30, 60, 90, 120 and 180 minutes after administration of the test substance. Scores for each parameter are noted in parenthesis and represent the degree of deviation from normal, with score of 0 being normal. Parameters a to c were considered measures of sedation, parameters c and d (if procedure was painful) were considered measures of analgesia; and e was considered a clinical measure.

      (i) Spontaneous Posture (0 - 4)(0-normal, 1- tired but standing, 2- lying,able to rise,3- lying,able to rise with difficulty,4-unable to rise)

(ii) Response to Noise (0 - 4)(0-hypersensitive,1- normal,2-weak,3-no reaction)

(iii) Procedure can be performed (0 - 4)(0-cannot be performed, 1-with difficulty,2-moderate resistance,3-slight resistance,4-no resistance).

(iv) Pedal Reflex (0-3)(0-normal,1-slightly impaired,2-clearly weak,3-absent).

(v) Maximum scores for a), c), d) achieved during the 180 minute test period

(vi) Heart rate

(vii) Times from injection to:

(a) Dog unable to stand

(b) Dog again able to attain sternal recumbency

(c) Dog again able to stand

(viii) Investigator assessment of overall drug effects regarding:

(a) Applicability for the intended purpose (poor to excellent)

(b) Sedative effect (none to excellent)

(c) Analgesic effect (none to excellent)

4. Adverse Effects (Side Effects): Vomiting was the most noticeable side effect, occurring in 7.1% and 25% of all dogs treated with medetomidine i.v. and i.m., and 7.6% and 20.0% of all dogs treated with xylazine i.v. and i.m, respectively. The frequency of dysrhythmias did not vary between groups, and it was more pronounced after i.m. treatment with both drugs. Profound bradycardia was also a common side effect, however, the overall level of all side effects was low and not significantly different between groups. None was lasting or required medication.

5. Statistical Analysis: Data on quantitative variables were statistically analyzed by analysis of variance (ANOVA) among the four treatment groups. Data collected only once were analyzed by ANOVA followed by the least-significant-difference (LSD) method of comparison of the four treatment means. Treatment, intended use of the drug for sedation or analgesia, sex and age were included in the ANOVA as main effects. Data on quantitative variables collected at several times were analyzed by repeated-measure ANOVA, followed by LSD with the appropriately pooled mean-square error (according to Cochran & Cox, Experimental Design, 2nd ed., pp. 298-302). Data on qualitative variables were analyzed by standard chi-square tests for two-way contingency tables to evaluate differences among the four treatment groups.

6. Results: The four treatment groups were not significantly different with respect to their distribution of intended use, sex, age, attitude, mucous

membrane color, pulse quality, auscultation of lung and heart, and the prevalence of heartworm upon entry to the study. They did not differ in mean body weight, mean body temperature and heart rate at this time. For 24 of the 54 remaining dogs in this study, time 0 was taken to be the time at which sedative effects were first observed rather than the time immediately prior to injection. Consequently, data on response variables taken over time (i.e. over the 180 minute observation period for posture score, pedal reflex score, response to noise, heart rate and procedure scores) were not included in the statistical analysis. The following results are based on data from the remaining 30 dogs. A summary of the results (i.m. and i.v., respectively) for sedation is presented in Tables 17 and 18 for posture score and noise response scores and for analgesia for pedal reflex and procedure score. The latter records sedation with non-painful procedures, and sedation and analgesia with painful procedures. Effects on heart rate are also shown in Tables 17 and 18. Initiation and duration of sedative drug effects are shown in Table 19, and results regarding drug applicability and the overall assessment of sedative and analgesic drug effects are presented in Table 20.

Sedation-related mean posture and mean noise scores were not significantly different overall, but the effect of medetomidine lasted longer when compared with xylazine.

Analgesia scores were higher for medetomidine: for pedal reflex response at 30 and 90 minutes after i.v. and i.m. administration, respectively, and for procedure from 15 to 60 minutes after i.v. treatment, in comparison with xylazine i.v. In order to use the data from all 54 dogs to compare the four treatment groups with respect to the analgesia and sedation responses observed at several times following injection, the maximum posture score (MPOSTURE), the maximum pedal reflex score (MPEDAL), and the maximum procedure score (MPROCEDURE) during the 180 minute test period was obtained for all 54 dogs in this study. Although the four groups did not vary significantly overall in these three parameters, the medetomidine i.m. and i.v. group means for each of these three parameters were higher than the corresponding xylazine i.m. and i.v. group means. The mean MPOSTURE of the xylazine i.m. group, and the mean MPROCEDURE of the medetomidine i.m. group was significantly higher ($p<0.05$) than that of the xylazine i.v. group.

Bradycardia lasted longer after medetomidine treatment. Dysrhythmias were seen more frequently after i.v. use of both drugs ($p<0.05$), and lasted longer with medetomidine.

Time to lying down (NO STAND) was longest with medetomidine i.m. and shortest with both drugs i.v., but the time to sternal recumbency was also the longest with medetomidine i.m. In general, xylazine's effects were significantly shorter.

Applicability received "excellent" ratings for medetomidine with an overall value of 65.4% versus 32.1% for xylazine. Combined "excellent" and "moderate" ratings were 92.9% and 91.7% for medetomidine i.v. and i.m., respectively, versus 84.7% and 73.3% for xylazine i.v. and i.m., respectively. Sedation was rated higher for medetomidine, with "excellent" ratings for medetomidine i.v. and i.m. of 78.6% and 50.0%, respectively, versus xylazine i.v. and i.m. of 38.5% and 26.7%, respectively. Combined "excellent" and

"good" ratings were 85.7% and 83.3% for medetomidine i.v. and i.m., respectively, versus 53.8% and 60.0% for xylazine i.v. and i.m., respectively (n.s.).

Analgesia was rated higher for medetomidine with "excellent" ratings for medetomidine i.v. and i.m. of 78.6% and 50.0% respectively, versus xylazine i.v. and i.m. at 38.5% and 13.3.%, respectively. Combined ratings of "excellent" and "good" for medetomidine i.v. and i.m. were 91.7% and 85.7% respectively and for xylazine i.v. and i.m. of 76.9% and 46.7%, respectively.

Medetomidine was consistently rated more efficient as a sedative and analgesic than xylazine, with medetomidine i.v. rated highest, and xylazine i.v. rated lowest. Ratings for medetomidine i.m. and xylazine i.m. were more similar. Suitability for dental care procedures was rated higher for medetomidine.

7. Conclusions: Medetomidine used with i.v. and i.m. dosing regimens was shown to be an effective and safe sedative and analgesic drug for dental care in dogs. Its effectiveness was consistently scored and rated higher than that of xylazine for diagnostic and therapeutic dental procedures.

Table 17: Scores[1] for Posture (POST), Noise, Pedal Reflex (PR), Heart Rate (HR) and Procedure (PROC) by I.M. Treatment Group[2] and Time Post-Treatment-Initiation (PTI)

| Minutes PTI | Medetomidine POST | Medetomidine Noise | Medetomidine PR | Medetomidine HR | Medetomidine PROC[3] | Xylazine POST | Xylazine Noise | Xylazine PR | Xylazine HR | Xylazine PROC[3] |
|---|---|---|---|---|---|---|---|---|---|---|
| 0X | 0.00$^{a}$±0.00 | 1.00$^{a}$±0.00 | 0.50$^{a}$±1.22 | 103.33$^{ab}$±19.50 | | 0.00$^{a}$±0.00 | 1.00$^{a}$±0.00 | 0.00$^{a}$±0.00 | 101.89$^{ab}$±24.56 | |
| 15X | 3.50$^{a}$±1.22 | 2.33$^{a}$±0.82 | 2.17$^{a}$±0.98 | 42.83$^{a}$±9.52 | 3.67±0.52 (6) | 3.56$^{a}$±0.73 | 2.67$^{ab}$±0.50 | 2.22$^{a}$±0.83 | 48.22$^{a}$±7.51 | 3.11±1.17 (9) |
| 30X | 3.50$^{a}$±0.84 | 2.50$^{a}$±0.55 | 2.17$^{ab}$±0.98 | 40.67$^{a}$±10.46 | 3.00±1.00 (5) | 3.33$^{a}$±0.87 | 2.56$^{a}$±0.53 | 2.00$^{a}$±0.71 | 53.44$^{a}$±8.29 | 3.00±1.12 (9) |
| 60X | 3.00$^{a}$±1.26 | 2.17$^{a}$±0.75 | 1.83$^{a}$±1.05 | 41.17$^{a}$±9.47 | 2.20±1.79 (5) | 2.78$^{a}$±0.97 | 2.22$^{a}$±0.67 | 1.56$^{a}$±0.53 | 54.56$^{ab}$±10.67 | 2.67±1.51 (6) |
| 90X | 2.83$^{a}$±1.47 | 2.00$^{a}$±0.63 | 1.50$^{a}$±1.05 | 47.50$^{a}$±16.44 | | 2.44$^{a}$±1.33 | 2.00$^{a}$±0.50 | 0.67$^{b}$±0.50 | 56.78$^{ab}$±7.93 | |
| 120X | 2.50$^{a}$±1.38 | 2.00$^{a}$±0.63 | 1.17$^{a}$±0.75 | 48.50$^{a}$±13.29 | | 1.44$^{b}$±1.01 | 1.44$^{b}$±0.53 | 0.33$^{b}$±0.50 | 62.00$^{bc}$±13.38 | |
| 180X | 0.17$^{a}$±0.41 | 1.00$^{a}$±0.00 | 0.17$^{a}$±0.41 | 60.00$^{a}$±13.21 | | 0.22±0.44 | 1.00$^{a}$±0.00 | 0.11$^{a}$±0.33 | 70.22$^{ab}$±11.72 | |

[1] See "Parameters Measured" for scoring procedure.
[2] Treatment group means per sampling time within scoring parameter are significantly different ($p<0.05$) if followed by different letters.
[3] For all parameters except PROC, medetomidine group contained 6 dogs and xylazine group contained 9 dogs. For PROC, number of dogs per PTI in parenthesis.

Table 18: Scores[1] for Posture (POST), Noise, Pedal Reflex (PR), Heart Rate (HR) and Procedure (PROC) by I.V. Treatment Group[2] and Time Post-Treatment-Initiation (PTI)

| Minutes PTI | Medetomidine POST | Medetomidine Noise | Medetomidine PR | Medetomidine HR | Medetomidine PROC[3] | Xylazine POST | Xylazine Noise | Xylazine PR | Xylazine HR | Xylazine PROC[3] |
|---|---|---|---|---|---|---|---|---|---|---|
| 0X | 0.00$^{a}$±0.00 | 1.00$^{a}$±0.00 | 0.00$^{a}$±0.00 | 113.71$^{a}$±24.10 | | 0.00$^{a}$±0.00 | 0.88$^{a}$±0.35 | 0.38$^{a}$±1.06 | 100.25$^{ab}$±18.00 | |
| 15X | 4.00$^{a}$±0.00 | 2.86$^{b}$±0.38 | 2.43$^{a}$±0.79 | 40.71$^{a}$±9.53 | 3.43±1.13 (7) | 4.00$^{a}$±0.00 | 2.50$^{ab}$±0.76 | 1.75$^{a}$±0.71 | 60.63$^{b}$±21.63 | 2.88±1.13 (8) |
| 30X | 3.86$^{a}$±0.38 | 2.57$^{a}$±0.53 | 2.89$^{b}$±0.95 | 50.29$^{a}$±11.70 | 3.43±1.51 (7) | 3.00$^{a}$±1.07 | 2.25$^{a}$±0.46 | 1.63$^{a}$±0.92 | 51.63$^{a}$±12.78 | 1.86±1.46 (7) |
| 60X | 3.57$^{a}$±0.79 | 2.29$^{a}$±0.49 | 1.43$^{a}$±0.79 | 51.43$^{a}$±8.22 | 3.11±1.67 (6) | 2.00$^{b}$±1.07 | 1.63$^{b}$±0.74 | 1.13$^{a}$±0.99 | 64.88$^{b}$±18.95 | 0.75±1.50 (4) |
| 90X | 3.14$^{a}$±1.21 | 1.71$^{ab}$±0.76 | 0.86$^{ab}$±0.69 | 57.71$^{ab}$±13.44 | | 1.13$^{b}$±0.83 | 1.25$^{b}$±0.46 | 0.63$^{b}$±0.92 | 68.88$^{b}$±23.05 | |
| 120X | 1.86$^{a}$±1.35 | 1.43$^{b}$±0.53 | 0.29$^{b}$±0.76 | 56.00$^{ab}$±10.25 | | 0.75$^{b}$±0.71 | 1.13$^{b}$±0.35 | 0.38$^{ab}$±0.74 | 74.38$^{c}$±20.47 | |
| 180X | 0.14$^{a}$±0.38 | 1.00$^{a}$±0.00 | 0.00$^{a}$±0.00 | 76.29$^{bc}$±11.86 | | 0.50$^{a}$±0.93 | 1.13$^{a}$±0.35 | 0.00$^{a}$±0.00 | 89.25$^{c}$±24.11 | |

[1] See "Parameters Measured" for scoring procedure.
[2] Treatment group means per sampling time within scoring parameter are significantly different ($p<0.05$) if followed by different letters.
[3] For all parameters except PROC, medetomidine group contained 7 dogs and xylazine group contained 8 dogs. For PROC, number of dogs per PTI in parenthesis.

Table 19: Summary for the time (in minutes) from injection until the dog was unable to stand (NOSTAND), until sternal recumbency was attained (STERNAL), and until the dog was able to stand again (STAND) by treatment group[1].

| **Variable** | **Medetomidine I.M.** | **Medetomidine I.V.** | **Xylazine I.M.** | **Xylazine I.V.** |
|---|---|---|---|---|
| NOSTAND | $10.25^{a}$±9.89 (n=12) | $1.96^{c}$±1.91 (n=14) | $6.15^{b}$±2.88 (n=13) | $2.38^{c}$±0.96 (n=13) |
| STERNAL | $77.75^{a}$±27.47 (n=12) | $54.54^{ab}$±18.90 (n=13) | $56.83^{ab}$±35.79 (n=12) | $37.92^{b}$±24.55 (n=13) |
| STAND | $112.25^{a}$±49.09 (n=12) | $94.57^{ab}$±28.27 (n=14) | $72.80^{b}$±35.56 (n=15) | $70.08^{b}$±29.47 (n=13) |

[1] Treatment group means are significantly different ($p<0.05$) if followed by different letters.

Table 20: Distribution[1] of the applicability of the drug, the subjective evaluations of both analgesia/anesthesia and sedation, and presence of side effects by treatment group.

| | **Medetomidine I.M.** | **Medetomidine I.V.** | **Xylazine I.M.** | **Xylazine I.V.** |
|---|---|---|---|---|
| Applicability – Excellent | 6 (50.0) | 11 (78.6) | 3 (20.0) | 6 (46.2) |
| Applicability – Moderate | 5 (41.7) | 2 (14.3) | 8 (53.3) | 5 (38.5) |
| Applicability – Poor | 1 (8.3) | 1 (7.1) | 4 (26.7) | 2 (15.4) |
| Analgesia – Excellent | 6 (50.0) | 11 (78.6) | 2 (13.3) | 5 (38.5) |
| Analgesia – Good | 5 (41.7) | 1 (7.1) | 5 (33.3) | 5 (38.5) |
| Analgesia – Slight | 1 (8.3) | 2 (14.3) | 8 (53.3) | 3 (23.1) |
| Sedation – Excellent | 6 (50.0) | 11 (78.6) | 4 (26.7) | 5 (38.5) |
| Sedation – Good | 4 (33.3) | 1 (7.1) | 5 (33.3) | 2 (15.4) |
| Sedation – Slight | 2 (16.7) | 2 (14.3) | 6 (40.0) | 6 (46.2) |
| Side Effects – Present | 3 (25.0) | 2 (14.3) | 3 (20.0) | 2 (15.4) |
| Side Effects - Absent | 9 (7.50) | 12 (85.7) | 12 (80.0) | 11 (84.6) |
| Number of Dogs | 12 | 14 | 15 | 13 |

[1] The percent of each response category, shown in parenthesis, was based on the total number of dogs per treatment group excluding any missing data.

## III. TARGET ANIMAL SAFETY

Studies were conducted in dogs to evaluate the safety of medetomidine hydrochloride to the target species when administered by the intramuscular route and by the intravenous route.

**Pivotal Studies:**

### A. First Pivotal Study:

1. Type of Study: Target animal safety study in dogs.

2. Investigator: Lauri Nieminen, Ph.D., Orion Corporation FARMOS, Turku, Finland.

3. General Design of the Study:

   a. Purpose: To assess the toxicity of medetomidine hydrochloride when administered by daily intramuscular injection for 28 days.

   b. Test Animals: Twenty-four young adult beagle dogs, weighing 9 - 15 kg at study initiation, were randomly divided into four groups containing three males and three females per group.

   c. Dosage Form: All test treatments were sterile injectable solutions. The formulation used in this study differed from the proposed market formulation only by the absence of propylparaben. The agency has determined that the test formulation is sufficiently similar to the proposed market formulation that the results of this study are adequate for predicting the toxicity of medetomidine hydrochloride when administered to dogs by the i.m. route.

   d. Dosages Used: Medetomidine hydrochloride was administered at dosages of 0 µg/kg (test formulation vehicle containing no active), 80 µg/kg, 240 µg/kg and 400 µg/kg. These doses are approximately equivalent to 0, 2X, 6X and 10X the optimal intramuscular dose.

   e. Route of Administration: All doses were administered by the i.m. route. Injection sites were the gluteal and femoral muscles.

   f. Test Duration: The dosing phase of the study lasted for 28 consecutive days.

   g. Pertinent Parameters Measured:

      (i) Mortality

      (ii) Body Weights

      (iii) Food Consumption

      (iv) Clinical Signs

      (v) Fecal Exams

(vi) Electrocardiograms

(vii) Ophthalmoscopy

(viii) Laboratory Parameters

(a) Urinalysis

(b) Hematology

(c) Clinical Chemistry

(ix) Necropsy, pathology/histopathology

4. Statistical Analysis: Two-way analysis of variance (ANOVA) was the primary analytical method used. Brown-Forsythe adjusted F-statistics and p-values were used, if variances could not be assumed to be equal (Levene's test). If the (sex by dose) interaction was statistically significant, the analysis was continued by comparing each dose group against the others separately for male and female dogs (altogether 2 X 6 = 12 comparisons) with Bonferroni corrected ($p<0.10/12 = 0.008$) Fisher LSD tests. If the interaction was insignificant, but the dose effect was significant, the comparisons were made on dose marginal means, respectively (6 comparisons, $p<0.10/6=0.017$). Repeated measures analysis of (co)variance (AN(C)OVA) with two grouping factors (sex and dose) and one within factor (time) was applied for those outcome variables that had repeated measurements over time. The before treatment value was used as a covariate if it was available. If the pooled orthogonal components showed nonsphericity, Greenhouse-Geisser adjusted F-statistics and p-values were used. Bonferroni corrected contrasts were applied in pairwise dose comparisons if AN(C)OVA indicated significant differences. For outcome variables with one before and one after study measurement, the change between the two values was analyzed. As the power of the statistical tests is very low due to the small number of animals per treatment group, the working level of significance was changed from 0.05 to 0.10. This applies also to the Bonferroni corrected pairwise dose comparisons.

5. Results:

   a. Mortalities: No mortalities were observed in any dose group.

   b. Body Weights: No significant differences between any treatment group and controls.

   c. Food Consumption: No significant differences between any treatment group and controls.

   d. Clinical Signs: The control group animals behaved normally after dosage of the placebo solution. Vomiting was found only once. In the low dose group (80 µg/kg), the dogs were sedated after dosage. However, at the last observation in the evening about seven hours after dosing, the dogs were normal. Five of the six dogs vomited during the study period. Two dogs vomited six times, one dog three times and two dogs once. Altogether 17 vomiting cases were found. The dogs in the middle dose group (240 µg/kg), were sedated after dosage, and at the last observation about

seven hours after dosage the dogs were slightly sedated but could walk normally. Vomiting cases were found 27 times. One dog vomited 18 times, two dogs vomited four times and one dog only once. Two dogs did not vomit at all. Dogs in the high dose group (400 µg/kg), were sedated after dosage and sedation was evident during the last observation about five or six hours after dosing. At the last observation the dogs staggered or were lying down. However, the next morning the dogs were always normal. Vomiting was found eight times. One dog vomited three times, two dogs vomited twice, one dog once. Two dogs did not vomit at all.

e. Fecal Exams: The consistency of the feces in the control group was normal or occasionally soft, and no other abnormalities were observed. Soft feces was found occasionally and diarrhea was found once in the low dose group. No apparent abnormalities were noted in this group. The medium dose group dogs exhibited normal or occasionally soft feces, and three dogs had diarrhea. No apparent abnormalities were noted in this group. The dogs in the high dose group exhibited diarrhea on three instances, but there were no other apparent abnormalities.

f. Electrocardiograms: One control dog showed sinus arrest in the prestudy ECG which was absent on the ECG taken on final study day. All other dogs showed normal observations on both ECGs. Statistically significant differences could not be shown for treated dogs compared to controls with regard to heart rate.

g. Ophthalmoscopy: No drug related findings were observed in males. One female at the medium dose had minimal horizontal opacity at the central area of both corneas. Similar findings were observed in all females at the high dose level. In one female opacity was seen in both corneas, in the second female in the left cornea and in the third female in the right cornea. No other drug-related findings were observed in females.

h. Laboratory Parameters:

(i) Urinalysis: Urine examination was done at the end of the study to the animals of the control and high dose groups. There were no significant differences between these groups in urine volume, pH or microscopy of urine sediment. Osmolarity was decreased significantly in the high dose group males. Urine volume was also increased in this dose group but the increase was not significant. All control males and one control female had protein in the urine. No protein was found in urine of the high dose group of males or females. One male in the high dose group had hemopigments in urine.

(ii) Hematology: Before dosing there was a decrease in blood hemoglobin values, numbers of red blood cells and packed cell volume in males of the medium dose group and a decrease in the number of red blood cells in males of the high dose group, as compared to the control group. These differences were slight and were not discernible at the end of dosing period. In the number or in the differential count of reticulocytes, white blood cells and platelets, there were no statistically significant differences in any

dose group before or after the dosing period. There was a tendency for decreased thrombin time in males of the medium dose group at the end of the dosing period. No other statistically significant differences were found. There were no statistically significant changes in quick time measurements in any dose group at the end of the study. In red blood cell indices, the only statistically significant difference found was an increase in mean corpuscular hemoglobin of males in the high dose group before dosing. This increase was not found at the end of the dosing period and it was probably due to a lower value in the control male group.

(iii) Clinical Chemistry: There were no statistically significant differences in serum sodium, potassium, chloride, inorganic phosphate, albumin, urate, cholesterol, triglycerides, total bilirubin or conjugated bilirubin values in any dose group before or after dosing. Serum calcium before dosing showed a tendency to be lower in the medium and high dose groups of females compared in the control group. These differences were not seen after dosing. There was a tendency for serum protein values in the medium dose group to be lower than in the control group before dosing. Serum creatinine values were decreased after dosing compared to controls in the low and high dose groups of males and in the medium and high dose group of females. These changes were statistically significant. Serum iron values tended to be increased after dosing in the low dose group of males when compared to controls. No other increases were found. This increase was due to the low values of the controls and was not toxicologically significant. There were no significant differences in serum enzyme values compared to controls at any dose level. Blood glucose levels were lower before dosing in the medium dose group and significantly lower in the high dose group of males. Also in the high dose group of females, blood glucose values were lower before dosing. After dosing, blood glucose values were lower in the low dose female group than in controls ($p<0.05$), significantly lower in the medium dose groups of males and females, highly significantly lower in the high dose groups of males and significantly lower in females.

i. Necropsy, pathology/histopathology:

(i) Organ Weights: There were no statistically significant differences in any dose group compared to controls regarding the heart, lungs, liver, kidneys, adrenals, spleen, thyroids, pancreas, pituitary, testes/ovaries, prostate/uterus or brain. The observed differences in weights were slight and have no toxicological significance. There were no statistically significant differences in relative organ weights in any dose group compared to controls.

(ii) Bone Marrow Exams: There were no statistically significant differences in any of the dose groups compared to controls in percentage of lymphocytes, monocytes, megacaryocytes, plasma cells, blast

cells, promyelocytes, myelocytes, metamyelocytes, band cells, segmented neutrophils, eosinophils or basophils. In addition, there were no statistically significant differences in the ratio of myelopoietic and erythropoietic cells compared to controls.

(iii) Gross Pathology: No abnormalities were seen that could be related to administration of the test compound.

(iv) Histopathology: The only drug related changes were seen in the eyes of females of the high dose group. In two animals small cysts were observed in the corneal epithelium of one eye. In all females of the high dose level and in one female of the medium dose level minimal horizontal opacity at the central area of the cornea was observed in the ophthalmological studies. The histological changes that were observed in the cornea were possibly due to the drying of eyes caused by long-lasting repeated sedation. The horizontal position of the opacity that was observed in ophthalmology is strongly indicative of this. The muscle from the injection site was also examined in the histopathological studies. Some minor degenerative changes were observed. Similar changes were also observed in the control dogs so these changes were evidently due to the injection procedure. The tissue irritation potential of medetomidine hydrochloride seems to be very minimal.

6. Conclusions: Medetomidine hydrochloride is well tolerated by dogs when administered by the i.m. route at doses up to 400 µg/kg for 28 days. Drug-related effects under these conditions are considered to be of minor toxicological or clinical importance and are primarily a consequence of long-lasting repeated sedation.

**B. Second Pivotal Study**

1. Type of Study: Target animal safety study in dogs.

2. Investigator: Dr. Edward Schwartz, White Eagle Toxicology Laboratories, 2003 Lower State Road, Doylestown, PA 18901.

3. General Design of Study:

   a. Purpose: To assess the toxicity of medetomidine hydrochloride when administered by intravenous injection for three days.

   b. Test Animals: Fourteen beagle dogs (7 M, 7 F), 9-12 months old and weighing 7-11 kg, and 20 mongrel dogs (11M, 9F) of the same age and weighing 8 - 20 kg, were stratified by age and sex and randomly assigned to one of four groups of seven animals each or one group of six animals.

   c. Dosage Form: All treatments were sterile injectable solutions.

   d. Dosage Used: Medetomidine hydrochloride was administered on the basis of square meters of body surface area ($M^2$) at dosages of 0 µg/$M^2$ (vehicle control), 750 µg/$M^2$, 2250 µg/$M^2$, 3750 µg/$M^2$ and 7500 µg/$M^2$. These dosages correspond to 0, 1X, 3X, 5X, and 10X the established clinical dose

for intravenous administration. Doses were administered daily for three days except the 10X dose (six dogs), which was given one time.

e. Route of Administration: All doses were administered intravenously.

f. Test Duration: The dosing phase of the study lasted for three days.

g. Pertinent Parameters Measured:

(i) Antemortem:

(a) Clinical Observations

(i) General Condition: 0-Awake/Normal to 4-Dead

(ii) Spontaneous Twitch: 0-None to 2-Convulsions

(iii) Mucous Membrane Color: 0-Normal to 2-Cyanotic

(iv) Respiration: 0-Normal or 1-Abnormal

(v) Femoral Pulse: 0-Normal or 1-Weak

(vi) Heart Rate/Rhythm (from electrocardiogram): 0-Normal or 1-Abnormal

(vii) Ophthalmoscopy: 0-Normal to 1-Abnormal

(viii) Body Temperature: Recorded in deg.F.

(b) Body Weight

(c) Heart Rate and Electrocardiography

(d) Clinical Pathology

(e) Hematology

(f) Blood Chemistry

(ii) Postmortem:

(a) Gross Pathology (3 dogs each from 1X, 3X, 5X; 4 dogs 10X)

(b) Tissue Collection (All necropsied animals)

(c) Histopathology (3 dogs 5X; 4 dogs 10X)

4. Statistical Analysis: Data on each quantitative variable (e.g., body weight and blood glucose) were analyzed by analysis of variance (ANOVA), with multiple comparisons of means when appropriate. In particular, data on each quantitative variable collected at several times (either days or both days and hours within each day) following treatment initiation (e.g., body weight and heart rate, respectively) were evaluated via an analysis of variance procedure appropriate for repeated-measurements. In the event of statistically significant differences among the five dose groups, the five treatment group means were

compared via the least-significant-difference (LSD) procedure; in the event of a statistically significant interaction between "Dose" and "Day" or "Hour", the five treatment group means were compared at each measurement time via application of the least-significant-difference (LSD) procedure with the appropriately pooled mean-square error. Data on clinical observation variables (e.g., mucous membrane color and respiration) were analyzed by standard chi-square tests for two-way contingency tables. The potential effect of medetomidine on such variables was further investigated via multiple logistic regression (MLR) analysis.

5. Results:

   a. Antemortem:

      (i) General Condition, Spontaneous Twitch: Anesthesia (profound sedation/marked analgesia) was produced by medetomidine by 15 minutes after injection in virtually all cases and persisted for 45 minutes to three hours. The duration of anesthesia was dose related with the shorter times being at the lowest dose and the longer durations at doses > 2250 µg/M². This anesthetic condition was followed by a stuporous state in doses > 2250 µg/M², continuing until 1.5 to 4 hours after dosing. This stupor was, in turn, followed by a brief period of tranquilization. Spontaneous twitching was observed sporadically at all dose levels, primarily during the anesthetic stages.

      (ii) Mucous Membrane Color: Pale mucous membranes were observed in all beagles sporadically from 15 minutes to two hours after dosing. In addition, cyanotic mucosa was observed one dog (3750 µg/M²) on days 1-3 from 15 minutes to one hour after dosing. The mucosa of mongrels at each of the dose levels, except at the highest dose, appeared pale at varying times up to four hours after dosing. No effect on mucous membrane color was observed in one dog given 7500 µg/M².

      (iii) Respiration: A short interval of apnea lasting up to approximately 1 minute was seen in all dogs during the period of anesthesia or stupor, followed by several rapid short breaths after which time transient apnea again ensued.

      (iv) Heart Rate: A dose related bradycardia was observed in beagles which lasted in most dogs for 4 hours after dosing. This decrease in heart rate was marked, decreasing to 40 beats/minute in some cases. In all instances the rate had returned to normal levels by 24 hours after dosing. A decrease in heart rate was noted in all mongrels beginning 15 minutes after dosing and persisting until 2-4 hours after dosing, except for one dog (7500 µg/M²) in which the decreases continued until 8 hours after dosing.

      (v) Pupil Size: Pupils were constricted from 15 minutes to approximately 4 hours after dosing. In two beagles (one each at 2250 µg/M² and 3750 µg/M²) the constriction was followed by a slow response to light on day 1 lasting for 24 hours.

(vi) Body Temperature: Slight to moderate decreases in body temperature were seen at all dose levels beginning at 1.5-2 hours after dosing and ending at 4 hours after dosing except in the case of two beagles at the highest dose in which the decrease was seen at 8 hours after dosing.

(vii) Body Weight: No effects on body weights were observed as a result of dosing.

(viii) Electrocardiography: All animals had a marked bradycardia. The following effects were seen in the indicated number of dogs in addition to the bradycardia:

| | Dose Level – 750 µg/M² | Dose Level – 2250 µg/M² | Dose Level – 3750 µg/M² | Dose Level – 7500 µg/M² |
|---|---|---|---|---|
| Incr. QRS interval | | 2 | 1 | 1 |
| Incr. QT interval | 3 | 3 | 2 | 2 |
| 1° and 2° AV block | | | 1 | |
| 2° AV block | 1 | 1 | | |
| QRS vector changes | | 1 | | |
| ST segment deviation | | | 1 | |

(ix) Hematology: No effect seen on any of the parameters measured.

(x) Clinical Chemistry: One beagle (750 µg/M²) showed increases in SGOT, LDH and CPK levels on day 3, and in SGOT, SGPT, LDH and CPK levels on days 3 and 4. One mongrel in each of the 2250 and 3750 µg/M² groups showed slightly elevated SGPT levels on days 2-4. No other departures from normal were seen in the clinical chemistry parameters measured.

b. Postmortem:

(i) Gross Pathology: Two dogs in each of the 750, 2250 and 3750 µg/M² groups, and three dogs in the 7500 µg/M² group, showed hearts which were contracted as if in systole and the ventricular walls appeared thickened.

(ii) Microscopic Pathology: No compound related changes were noted in any of the tissues examined.

6. Conclusions: Doses of medetomidine were given intravenously for three days at 0X, 1X, 3X, or 5X, (corresponding to 0, 750, 2250, or 3750 µg/m²) or one day at 10X (7500 µg/m²). This study found that medetomidine appears to be safe when administered up to 10X the recommended i.v. dosage in that no mortalities were reported.

**C. Third Pivotal Study:**

1. Type of Study: Safety study in heartworm-compromised vs. heartworm-free dogs.

2. Investigators: C. S. Venugopalan, Ph.D. and P. Crawford, D.V.M., Ph.D., Dept. of Veterinary Physiology, Pharmacology and Toxicology, Louisiana State University, Baton Rouge, LA 70803.

3. General Design of Study:

   a. Purpose: To evaluate and compare the sedative/analgesic and cardiopulmonary effects of medetomidine hydrochloride when administered by the intravenous and intramuscular routes in clinically normal, heartworm-infected and heartworm-free dogs.

   b. Test Animals: Ten naturally heartworm infected dogs (6M, 4F) comprised group 1, and 10 heartworm-free dogs (5M, 5F) comprised group 2. Each group was randomly subdivided into two groups of five dogs each.

   c. Dosage Form: All treatments were sterile injectable solutions.

   d. Dosages Used: Medetomidine hydrochloride was administered by the intravenous route at a dosage of 750 µg/M² body surface area, and by the intramuscular route at a dosage of 1000 µg/M².

   e. Route of Administration: In this two stage study, one subgroup of each overall group received the dosage by the intravenous route and the remaining two subgroups were dosed by the intra muscular route. One week later the routes of administration were reversed for the respective subgroups.

   f. Test Duration: Data collection on each dog lasted for 180 minutes post-injection. A one-week washout period was observed, followed by another 180 minute data collection period.

   g. Parameters Measured: The following parameters were measured and scored at 0, 15, 30, 60, 90, 120, and 180 minutes post injection:

      (i) Posture (0 = normal to 4 = unable to rise)

      (ii) Response to Noise (0 = hypersensitive to 3 = no reaction)

      (iii) Mock Radiographic Procedure (0 = cannot be performed to 4 = no resistance)

      (iv) Cardiopulmonary Assessment: heart rate, respiratory rate, ECG tracings, pulse quality, arterial blood gases, central venous and arterial blood pressures

      (v) Toe Pinch Pedal Reflex (0 = normal to 3 = absent)

      (vi) Times from injection until dog is unable to stand, is able to attain sternal recumbency, is able to stand

(vii) Miscellaneous observations (e.g., vomiting, dyspnea)

4. Statistical Analysis: Data on each variable were statistically analyzed by analysis of variance (ANOVA), along with multiple comparisons of means to evaluate the differences both between the routes of administration and between the heartworm-infected and heartworm-negative dogs. Data on each variable collected at several times following treatment initiation were statistically evaluated via the analysis of variance procedure appropriate for repeated-measurements within the context of a two-period crossover design. The mean difference between heartworm-positive and heartworm-negative dogs, both overall and for each route of administration, and the mean difference between IV and IM routes of medetomidine administration within both heartworm-infected and heartworm-negative dogs were evaluated at each measurement time via application of the least-significant-difference (LSD) procedure. Data on each variable collected at only one time within each administration were also statistically analyzed by an ANOVA procedure appropriate for a two-period crossover design with a "single measurement" rather than repeated measurements over time.

5. Results: Data collected on two dogs were excluded from statistical analyses since data on only one route of administration were available. In addition, data on the IV route of administration for one dog at 120 and 180 minutes and for two dogs at 180 minutes were not complete; consequently, all data on those three dogs at those specific times only were excluded from statistical analysis.

   Mean arterial blood pressure was not significantly different between IV and IM administration of medetomidine nor between heartworm-infected and heartworm-negative dogs ($p=0.500$ and $p=0.089$, respectively). Further, the lack of difference between IV and IM administration was similar for heartworm-infected and heartworm-negative dogs ($p=0.088$). The variation in arterial blood pressure over time was highly significant ($p<0.001$) and was significantly different between IV and IM administration ($p<0.009$). However, based on the LSD procedure, the mean difference in arterial blood pressure between IV and IM administration was statistically significant at only 0 and 180 minutes post-treatment-initiation (PTI) for only the heartworm-negative dogs; the mean difference at 180 minutes PTI, after adjustment for the difference at baseline, did not exceed the LSD critical value. Although mean arterial blood pressure of heartworm-infected dogs was higher than that of heartworm-negative dogs at each PTI time, only the difference at 120 minutes PTI was statistically significant. However, after adjustment for the mean difference at 0 minutes, the mean difference at 120 minutes PTI did not exceed the LSD value. Mean central venous pressure was significantly higher for heartworm-infected dogs than for heartworm-negative dogs ($p=0.002$). The mean central venous pressure of heartworm-positive dogs was significantly higher than that of heartworm-negative dogs at each of the seven PTI sampling times. Whereas the same result held for IM administration (except for 120 minutes PTI), the mean difference in central venous pressure for IV administration was not statistically significant at any of the seven PTI sampling times. However, after adjustment for the mean difference at baseline neither the overall mean differences nor the mean differences for IM administration exceeded the respective LSD values. The mean difference in central venous pressure between IV and IM administration was not statistically

significant overall nor between heartworm-infected and heartworm-negative dogs ($p=0.643$ and $p=0.297$, respectively). Both heart rate and respiratory rate were found to vary significantly ($p<0.001$) over the 180 minute observation period but differed significantly neither between the two heartworm cohorts (i.e., heartworm-infected dogs and heartworm-negative dogs; $p=0.332$ and $p=0.090$, respectively) nor between the two routes of administration ($p=0.226$ and $p=0.936$, respectively). The mean heart rate under IM administration was significantly lower than that under IV administration at 180 minutes PTI for both heartworm cohorts and at 90 minutes PTI for heartworm-negative dogs. No mean difference in mean respiratory rate was statistically significant at any of the six measurement times following treatment initiation. No significant difference in any of the four ECG variables was found between the two heartworm cohorts nor between IV and IM administration (except for a significantly higher P-R interval mean at 30 minutes PTI for heartworm-negative dogs under IM administration). Similarly, blood $pCO_2$, $pO_2$, and pH did not differ significantly overall between IV and IM administration; only the mean differences in blood pH at 90 and 120 minutes PTI for heartworm-negative dogs were found to be statistically significant. Whereas the two heartworm cohorts were not significantly different overall and at each PTI sampling time with respect to mean blood $pCO_2$, the heartworm-positive dogs were significantly ($p<0.01$) higher overall in both mean blood $pO_2$ and mean blood pH than the heartworm-negative dogs. Whereas both mean blood $pO_2$ and mean blood pH of heartworm-infected dogs were significantly higher than those of heartworm-negative dogs at each of the six sampling times following treatment initiation, the mean differences in blood pH at 15 through 90 minutes PTI did not exceed the LSD value after adjustment for the respective mean differences at time zero.

Whereas the noise-response score, the pedal reflex score, and the procedure score were not significantly different overall between IV and IM administration of medetomidine, the mean posture score was significantly higher ($p=0.005$) for IM administration than for IV administration. However, statistically significant differences between IV and IM administration were found in each of these scores at one or more PTI times for at least one of the two heartworm cohorts: the IV mean was higher than the IM mean at 30 minutes in both the noise score and the pedal reflex for heartworm-infected dogs; and the IM mean was higher than the IV mean at 60, 90, and 180 minutes PTI in the noise score for heartworm-negative dogs, at 90 and 120 minutes PTI and at 90 and 180 minutes PTI in the posture score for the heartworm-infected and the heartworm-negative cohorts, respectively, and at 120 minutes PTI in the procedure score for the heartworm-positive dogs. Although the two heartworm cohorts differed significantly in the mean score for posture and procedure, the difference between the two heartworm cohorts in any of these scores was not significantly different between the two routes of administration. The mean times from injection until the dog was unable to stand, until sternal recumbency, and until the dog was able to stand were all higher under IM administration than under IV administration. The mean difference between the two routes of administration was statistically significant for the first two time durations ($p<0.001$ and $p=0.032$, respectively), but was not statistically significant for the third time duration ($p=0.198$). The two heartworm co-horts were not significantly different in the mean times from injection until the dog was unable to stand ($p=0.423$) and able to stand ($p=0.145$), but the mean

time until sternal recumbency was significantly less for heartworm-infected dogs than for heartworm-negative dogs (p=0.021). The mean difference between IV and IM administration in each of these three time durations following injection was found to be similar for heartworm-infected and heartworm-negative dogs.

In this study, the effects of medetomidine were found to be significantly different overall between heartworm-infected and heartworm-negative dogs in only the central venous pressure, blood pO2 and pH, the posture score, and the time until sternal recumbency was attained. Whereas the route of administration of medetomidine was found to be significantly different overall with respect to only the posture score and the times from injection until the dog was unable to stand and until sternal recumbency was attained, the mean difference between IV and IM administration with respect to each of the 18 variables reported in this study was not significantly different between heartworm-positive and heartworm-negative dogs.In this study, the effects of medetomidine were found to be significantly different overall between heartworm-infected and heartworm-negative dogs in only the central venous pressure, blood pO2 and pH, the posture score, and the time until sternal recumbency was attained. Whereas the route of administration of medetomidine was found to be significantly different overall with respect to only the posture score and the times from injection until the dog was unable to stand and until sternal recumbency was attained, the mean difference between IV and IM administration with respect to each of the 18 variables reported in this study was not significantly different between heartworm-positive and heartworm-negative dogs.

6. Conclusions: In this study, there were no differences in the cardiopulmonary, sedative or analgesic effects between asymptomatic heartworm-infected and heartworm-negative dogs treated with medetomidine at doses of 1000 µg/m² i.m. (1X) and 750 µg/m² i.v. (1X).

**D. Fourth Pivotal Study:**

1. Type of Study: Safety study of medetomidine when administered to puppies.

2. Investigator: Dr. Edward Schwartz, White Eagle Toxicology Laboratories, 2003 Lower State Road, Doylestown, PA 18901.

3. General Design of the Study:

   a. Purpose: To compare the safety of the sedative and analgesic effects of medetomidine hydrochloride when administered to puppies by the intravenous and intramuscular routes according to body surface area.

   b. Test Animals: Twelve beagle pups (6M,6F), 12 weeks of age, were assigned to two treatment groups containing an equal number of each sex.

   c. Dosage Form: All treatments were sterile injectable solutions.

   d. Dosages Used: Medetomidine hydrochloride was administered at 750µg/M² of body surface area intravenously and 1000 µg/$M^2$ of body surface intramuscularly.

e. Routes of Administration: In this two stage study, one group received the dosage intravenously and the other group intramuscularly. After a one-week washout the routes were reversed for each group.

f. Test Duration: Data collection occurred at 0, 15, 30, 60 and 90 minutes, and at 2 and 3 hours after injection. One week later the same procedures were followed.

g. Parameters Measured: The following parameters were measured and scored at the specified data collection times:

(i) Posture (0 = normal to 4 = unable to rise)

(ii) Response to Noise (0 = hypersensitive to 3 = no reaction)

(iii) Cardiopulmonary Assessments: heart rate, pulse quality, ECG tracings

(iv) Mock Radiographic Procedures (0 = cannot be performed to 4 = no resistance)

(v) Toe Pinch Pedal Reflex (0 = normal to 3 = absent)

(vi) Times from injection until dog is unable to stand, is able to attain sternal recumbency, is able to stand

(vii) Miscellaneous Observations (e.g., vomiting, dyspnea)

4. Statistical Analysis: Data on each variable were statistically analyzed by analysis of variance (ANOVA), along with multiple comparisons of means, to evaluate the differences between the IV and IM routes of administration. In particular, data on each variable collected at several times following treatment initiation were statistically evaluated via the analysis of variance procedure appropriate for repeated-measurements within the context of a two-period crossover design; the mean difference between IV and IM routes of medetomidine administration within both male and female dogs was evaluated at each measurement time via application of the lease-significant-difference (LSD) procedure with the appropriately pooled mean-square error. Data on each variable collected at only one time within each administration were also statistically analyzed by an ANOVA procedure appropriate for a two-period crossover design with a "single measurement" rather than repeated-measurements over time.

5. Results: Body weight increased significantly ($p<0.001$) from study day -1 to study day 8. Male and female puppies did not differ significantly either in the overall mean body weight during this 9-day period or in the increase in body weight ($p = 0.749$ and $p = 0.658$, respectively). Similarly, Groups I and II differed significantly neither in the overall mean body weight nor in the change in body weight from study day -1 through study day 8 ($p = 0.915$ and $p = 0.139$, respectively). Mean heart rate was found to be significantly different between IV and IM administration of medetomidine ($p = 0.015$). The difference between IV and IM administration was similar for male and female puppies ($p = 0.547$). The variation in heart rate over time was highly significant ($p < 0.001$) and was significantly different between IV and IM administration ($p < 0.029$). However, based on the LSD procedure, the mean

difference in heart rate between IV and IM administration was statistically significant at only 120 minutes post-treatment-initiation (PTI) and for only the male dogs; this mean difference at 120 minutes PTI, after adjustment for the difference at baseline, did not exceed the LSD critical value. Whereas the mean noise-response score, the mean posture score, and the mean pedal reflex score were each significantly different ($p < 0.02$) overall between IV and IM administration of medetomidine. The mean procedure score was not significantly different overall between IV and IM administration ($p = 0.796$). The IV administration was found to have a significantly higher mean than the IM administration in each of these four scores at one or more PTI times for either male or female puppies: the noise score for male dogs at 30 minutes; the posture and pedal reflex scores for male dogs and the noise, posture, pedal reflex, and procedure scores for female dogs at 60 minutes; and the posture and procedure scores for female dogs at 90 minutes. Male and female puppies did not differ significantly overall in any of these scores, and, except for the noise score, the differences in these scores between the two routes of administration were not significantly different between male and female dogs.

The mean times from injection until the dog was unable to stand, until sternal recumbency was attained, and until the dog was able to stand again were all significantly higher under IM administration than under IV administration ($p = 0.003$, $p = 0.036$, and $p = 0.047$, respectively). Male and female beagle puppies were not significantly different with respect to each of these time durations. Also, the mean difference between IV and IM administration in each of these three time durations following injection was found to be similar for male and female puppies.

In this study, the effects of medetomidine were found to be significantly different overall between IV and IM routes of administration with respect to heart rate, the noise, posture, and pedal reflex scores, and the times from injection until the dog was unable to stand, until sternal recumbency was attained, and until the dog was able to stand again. The overall mean procedure score was not significantly different between IV and IM administration of medetomidine. Neither the overall mean nor the mean difference between IV and IM administration with respect to each of the eight response variables reported in this study was significantly different between male and female beagle puppies.

6. Conclusions: Medetomidine hydrochloride was safe when used at the 1X dose (1000 µg/m² i.m., 750 µg/m² i.v.) as a sedative and analgesic in twelve week old puppies. There was also no difference in response between female and male puppies.

**E. Corroborative Study:**

1. Type of Study: Intramuscular irritation of medetomidine hydrochloride in dogs.

2. Investigator: Lauri Nieminen, Ph.D., Orion Corporation FARMOS, Turku, Finland.

3. Animal Species and Number per Group: Four young adult female beagles were used, two for each test group.

4. This study was well controlled, using physiological saline as negative control in all dogs and xylazine injectable solution as positive control in two of the four dogs.

5. Dosages Used and Route: A solution containing 0.8 mg/mL medetomidine hydrochloride was used (Note: the market formulation contains 1.0 mg/mL medetomidine hydrochloride); 0.1 mL/kg body weight was injected intramuscularly into the same location on the right hind leg daily for five consecutive days. The concentration of the xylazine control solution was 30 mg/mL; 0.1 mL/kg was injected intramuscularly into the same location on the right hind leg daily for five consecutive days. Physiological saline was administered in a similar volume and manner in the left hind leg.

6. Other Information: All animals were euthanized three days after last dosing and subcutis and muscular tissue from all injection sites were examined macroscopically and histologically.

7. Results and Conclusions: Small foci of muscular degeneration and focal leucocytic infiltrations were observed at the injection sites in the histological studies; however, these changes were also seen in the muscles injected with physiological saline and were therefore believed to have been caused by the repeated injections (27 gauge needle). On the basis of this study, the intramuscular irritation potential of medetomidine hydrochloride is considered to be very weak.

## IV. HUMAN FOOD SAFETY

### A. Drugs for Use in Non-Food Animals:

1. Drugs for Use in Dogs: Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this NADA. The drug is to be labeled for use in dogs, which are non-food animals.

### B. Human Safety Considerations Other than Food Safety:

Keep out of reach of children. Not for human use.

Avoid contact with eyes, skin and mucous membranes. In case of eye contact flush with plenty of water for 15 minutes. Wash skin with soap and plenty of water. If irritation persists, seek medical attention. Precaution should be taken while handling and using filled syringes. In case of accidental oral exposure or injection, seek medical attention.

Users receiving treatment for hypertension should take special precaution to avoid any exposure to this product. To report adverse reactions in users, obtain emergency medical assistance and/or to obtain a copy of the material safety data sheet, call 1-800-366-5288.

NOTE TO PHYSICIAN: This product contains an α-2-adrenoreceptor agonist and can be absorbed by the oral and dermal routes.

## V. AGENCY CONCLUSIONS

Data in support of this NADA comply with the requirements of Section 512 of the Act and Section 514.111 of the implementing regulations. It demonstrates that Domitor® injectable (medetomidine hydrochloride), when used under labeled conditions of use, is safe and effective.

Domitor® is restricted to use by or on the order of a licensed veterinarian because professional expertise is required to determine the level of sedation required for various veterinary techniques that may be employed with the use of this drug. It is also necessary to provide a differential diagnosis of the pain-causing pathology which only a trained professional can accomplish.

Under Section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for five years of marketing exclusivity beginning on the date of approval because no active ingredient (including any ester or salt of the active ingredient) of the drug has been approved in any other application.

## VI. ATTACHMENTS

Package Insert
Vial label
Box label
Shipper label

Copies of applicable 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.