I. GENERAL INFORMATION

A. File Number

NADA 141-033

B. Sponsor

Pfizer
235 East 42nd Street
New York, N.Y. 10017

C. Proprietary Name

Antisedan®

D. Established Name

atipamezole hydrochloride

E. Dosage Form

Sterile solution for injection

F. Dispensing Status

Prescription

G. Dosage Regimen

Antisedan® is administered intramuscularly regardless of the route used for Domitor®. The concentration of Antisedan® has been formulated such that the volume of injection is the same (mL for mL) as the recommended dose volume of Domitor®, and may be given at any time following Domitor® administration. Although injection volumes are the same, the concentration of Antisedan® (5.0 mg/mL) is 5 times that of Domitor® (1.0 mg/mL). Dogs that are sedated but ambulatory may be treated with Antisedan®, if warranted.

The dosage of Antisedan® is calculated based upon body surface area. Use the table below to determine the proper injection volume based on body weight:

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

* The IM dose of Domitor is 1.0 mg/m2 and the IV dose is 0.75 mg/m2.

H. Route of Administration

Intramuscular injection

I. Species/Class

Dogs

J. Indication

ANTISEDAN® is indicated for the reversal of the clinical effects of the sedative and analgesic agent, DOMITOR® (medetomidine hydrochloride), in dogs.

K. Effect of Supplement

This supplement provides for <changes being approved> (Delete this section for Original approvals)

II. EFFECTIVENESS

A. PIVOTAL STUDIES

Atipamezole dose determination following intramuscular administration of medetomidine in dogs (CD-0001-91)

a. Type of Study: Dose Determination
b. Investigator:
    i. Dr. Stephen Kamerling
    School of Veterinary Medicine

Louisiana State University
Baton Rouge, LA 70803

c. General Design
   i. Purpose: The objective of the study was to determine the optimum dose of atipamezole to reverse the clinical effects of intramuscular medetomidine in dogs.
   ii. Test Animals: Sixteen adult, purpose-bred, hound-cross mix-breed dogs composed of equal numbers of males and females.
   iii. Control Drug: Placebo (same as other treatments except for active ingredients).
   iv. Dosage Form: All treatments were sterile injectable solutions which were the same as the proposed market formula except for differing atipamezole concentrations used to maintain blinding: 1.0 mg/mL, 5.0 mg/mL, 10.0 mg/mL. Medetomidine used was the same as the proposed market formulation, 1.0 mg/mL.
   v. Route of Administration:
      - Atipamezole - intramuscular injection
      - Medetomidine - intramuscular injection
   vi. Dosages used:
      - Medetomidine - 1.0 mg/m2 of body surface area
      - Atipamezole - 0, 1.0, 5.0 or 10.0 mg/m2 of body surface area
   vii. Parameters Measured: Recovery from medetomidine treatment was evaluated by six measurements. Three measurements were conducted at timed intervals: Time -30 minutes (immediately prior to medetomidine injection), Time 0 (immediately prior to atipamezole), 3, 6, 9, 12, 15, 20, 30, 45, 60, 90, 120, 180, and 240 minutes post-injection of atipamezole. The measurements made at timed intervals were: sedation assessment (0, normal, to 5, unresponsive), walking ability (0, normal, to 3, unable to walk) and heart rate. Three additional measurements (arousal time, standing time, and walking time) were made at time intervals from injection of the antagonist until the dog was able to attain a specific level of vigilance or physical ability.

d. Results: Results of sedation assessment and walking ability are listed in Table 1. Results of analysis of heart rates indicate no statistical difference ($p < 0.05$) between the 0 mg/m2 and 1 mg/m2 groups. The 5 mg/m2 and 10 mg/m2 groups were statistically significantly different ($p < 0.05$) from each other and from the 0 mg/m2 and 1 mg/m2 groups. Although dogs may have appeared clinically normal, reversal of heart rate lagged behind and did not return to baseline values during the 4 hour duration of the study. See Figure 3 for the rate and magnitude of heart rate changes. Sedation assessment, walking ability, heart rate, and the arousal, standing, and walking times are depicted graphically in Figures 1-4.

e. Statistical Analysis: The study was conducted using a randomized, four-way crossover design. A 14-day "washout" period between dosing intervals was observed. Areas under the curves, times to "almost normal" and arousal, standing and walking times were analyzed by ANOVA according to a crossover design model with preliminary tests for one-period carryover effects. (Cochran and Cox, 1956, Experimental Designs, 2nd ed. pp 127-138).

i. **Table 1.**Sedation and Walking Ability by Dosage Group. (The units for area-under-response-curve means are sedation scores x minutes and walking ability scores x minutes.)

	Treatment Group (mg/m2)	Area-Under-The-Response-Curve Mean	Time to "Almost Normal" Mean (minutes)
Sedation Assessment	0	601.8 (a)	178.1 (a)
	1	281.9(b)	67.3(b)
	5	32.1(c)	6.9(c)
	10	39.3(c)	7.5(c)
Walking Ability	0	418.8(a)	159.4(a)
	1	187.3(b)	55.4(b)
	5	17.1(c)	6.9(c)
	10	18.2(c)	6.9(c)

Note: means within each variable with different superscript letters are significantly different ($p<0.05$)

f. Conclusions: An analysis was conducted to confirm that the 14 day washout period was adequate to prevent previous treatments from affecting subsequent treatments. Carryover effects were non-significant for all variables. Statistical analysis of the two most relevant variables, sedation assessment and walking ability, were conducted for both area under the response curve (AUC) and time for each dog to return to "almost normal" (scores of 0 or 1). Results of these variables are presented in Table 1. AUC was also analyzed for heart rates, and findings were as stated in the "Results" section.

Means of the continuous time variables were analyzed. The parameters measuring the times to arousal, standing and walking were variable due to the spontaneous behavior of the dogs, but also followed a dose response trend (see Table 2 and Figure 4) supporting the recommended dose. Dogs treated with the recommended dose aroused from sedation, stood, and walked within 12.7 minutes with the minimum time to walking taking 2.6 minutes.

Table 2. Mean Times to Arousal, Standing, and Walking

Dosage Group (mg/m2)	Mean Arousal Time (min.)	Mean Standing Time (min.)	Mean Walking Time (min.)
0	59.93(a)	84.75(a)	90.30(a)
1	12.93(b)	25.02(b)	27.37(b)
5	5.09(b)	5.90(c)	6.08(c)
10	5.31(b)	6.26(c)	6.53(c)

Note: means within each column with different superscript letters are significantly different ($p<0.05$) Dogs in the 5.0 mg/m2 and 10.0 mg/m2 groups exhibited rapid and complete clinical recovery from sedation, without relapse into sedation during the 240 minute recording period. Dogs in the 1.0 mg/m2 group also recovered from medetomidine-induced sedation, but responded more slowly than the other treatment groups. Placebo-treated dogs

required the full four-hours for all dogs to return to normal vigilance and activity. Medetomidine-induced bradycardia was quickly corrected in the 5.0 mg/m2 and 10.0 mg/m2 groups, but values did not return to the pre-medetomidine rate.

The results of the study demonstrate that the optimum intramuscular dosage of atipamezole, when reversing the clinical effects of 1.0 mg/m2 intramuscular medetomidine, is 5.0 mg/m2.

g. Side Effects: Urination was a common side effect of medetomidine treatment, and was seen to a lesser extent in the 10.0 mg/m2 atipamezole dosage group. Emesis was another reported side effect related to medetomidine, with occurrences in three of the 16 dogs participating in the study.

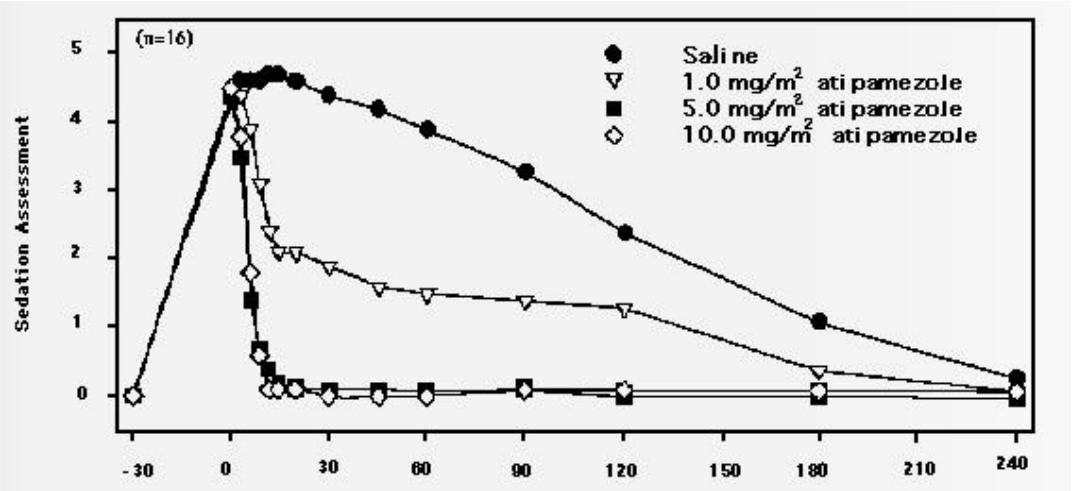
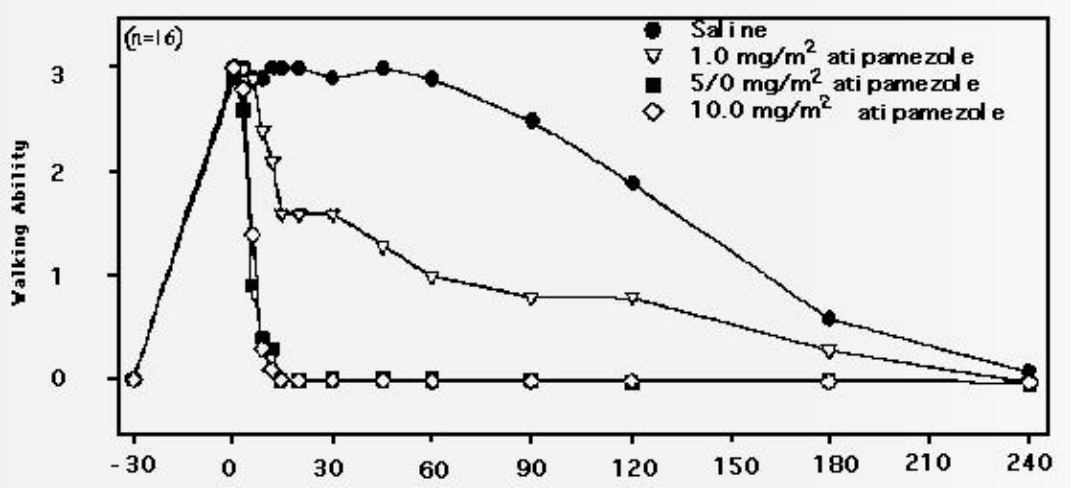


Figure 1 Atipamezole dose determination following intramuscular administration of medetomidine (1 mg/m2) in dogs - Sedation Assessment.

Sedation Assessment Scale 0 - No Sedation Present 1 - Slight Sedation - almost normal; able to stand easily, but appears somewhat fatigued, subdued or somnolent. 3 - Moderate Sedation - able to stand but prefers to be recumbent; sluggish,; ataxic or uncoordinated. 4 - Profound Sedation - unable to rise, but can exhibit some awareness of environment; responds to stimuli through body movement; may be lateral or sternal recumbency. 5 - Unresponsive - in a state of coma or semi-coma from which little or no response can be elicited; remains in lateral recumbency.

Figure 2: Atipamezole dose determination following intramuscular administration of medetomidine (1 mg/m2) in dogs - Walking Ability.



Walking Ability Scale 0 - Normal 1 - Good - able and willing to walk with only slight missteps. 2 - Poor - can manage to walk but is markedly ataxic, staggers and falls. 3 - Unable to walk - no purposeful forward movement is achieved.

Figure 3: Atipamezole dose determination following intramuscular administration of medetomidine (1 mg/m2) in dogs - Heart Rate

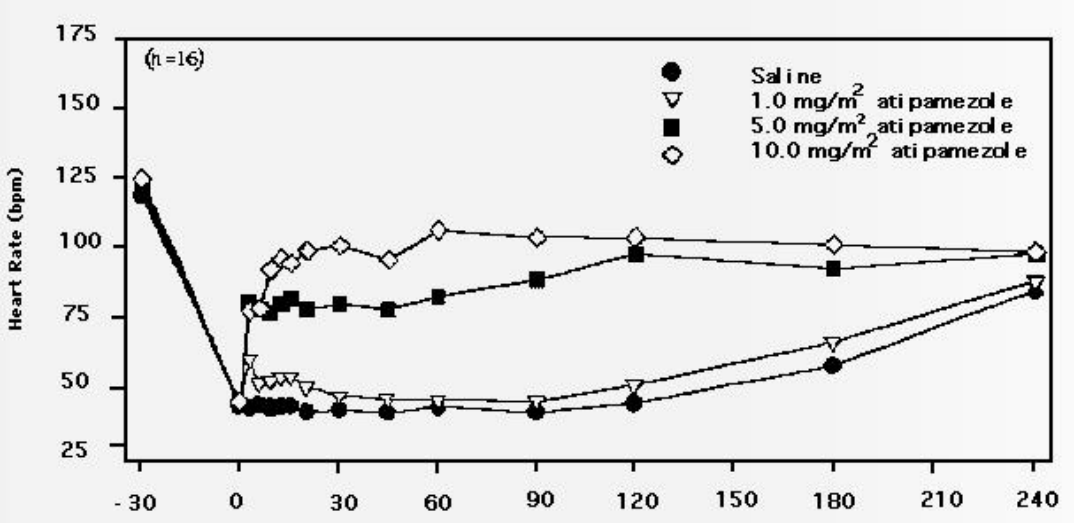
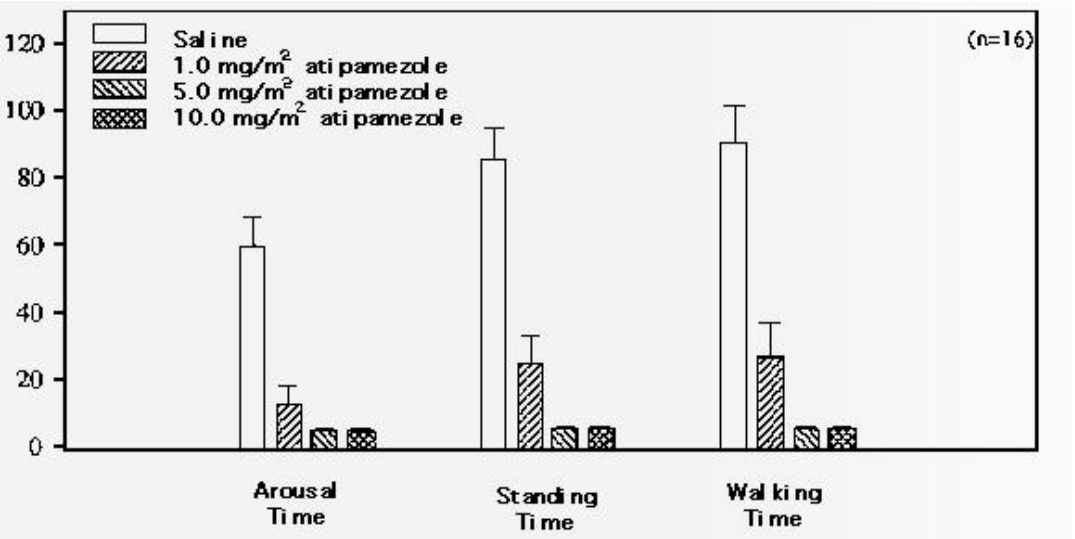


Figure 4: Atipamezole dose determination following intramuscular administration of medetomidine (1 mg/m2) in dogs - Arousal, Standing, and Walking Times.



Error Bar = SEM Arousal Time (AT): The time interval between injection of atipamezole and first signs of increased awareness (e.g. a willingness and ability to lift the head for five seconds). Standing Time (ST): The time interval between atipamezole injection and the point at which the dog is able to stand for five seconds. Walking Time (WT): The time interval between atipamezole injection and ambulation (purposeful forward movement).

Confirmation of atipamezole dose following intravenous administration of medetomidine in dogs (CD-0073-91)

a. Type of Study: Dose confirmation

b. Investigator:
   i. Dr. Stephen Kamerling
   School of Veterinary Medicine
   Louisiana State University
   Baton Rouge, LA 70803

c. General Design:
   i. Purpose: The previous dose determination study concluded that the optimum dosage of the antagonist, atipamezole, was five times that of the agonist, medetomidine, when administered intramuscularly. The recommended dosage of medetomidine, when administered intravenously, is less than that given intramuscularly. The objective of the present study was to confirm that the same atipamezole:medetomidine ratio is safe and effective to reverse the clinical effects of intravenous medetomidine.
   ii. Test Animals: Sixteen adult, purpose-bred, hound-cross, mix-breed, dogs composed of equal numbers of males and females.
   iii. Control Drug: Placebo (same as atipamezole formula except the active ingredients)

iv. Dosage Form: The test formula was a sterile injectable solution which was the same as proposed market formula.

v. Route of Administration:
- Atipamezole - intramuscular injection
- Medetomidine - intravenous injection

vi. Dosages used:
- Medetomidine -0.75 mg/m2 of body surface area
- Atipamezole -0 or 3.75 mg/m2 of body surface area

vii. Parameters Measured: Observations were conducted exactly as in the previous dose determination study. Recovery from medetomidine treatment was evaluated by six measurements. Three measurements were conducted at timed intervals: Time -20 minutes (immediately prior to medetomidine injection), Time 0 (immediately prior to atipamezole), 3, 6, 9, 12, 15, 20, 30, 45, 60, 90, 120, 180, and 240 minutes pose-injection of atipamezole. The measurements made at timed intervals were: sedation assessment (0, normal, to 5, unresponsive), walking ability (0, normal, to 3, unable to walk) and heart rate. Three additional measurements (arousal time, standing time, and walking time) were made at time intervals from injection of the antagonist until the dog was able to attain a specific level of vigilance or physical ability.

d. Results: Sedation assessment, walking ability, heart rate, and the arousal, standing, and walking times are depicted graphically in Figures 1-4.

e. Statistical Analysis: Results were unequivocal and did not require statistical analysis for proper interpretation.

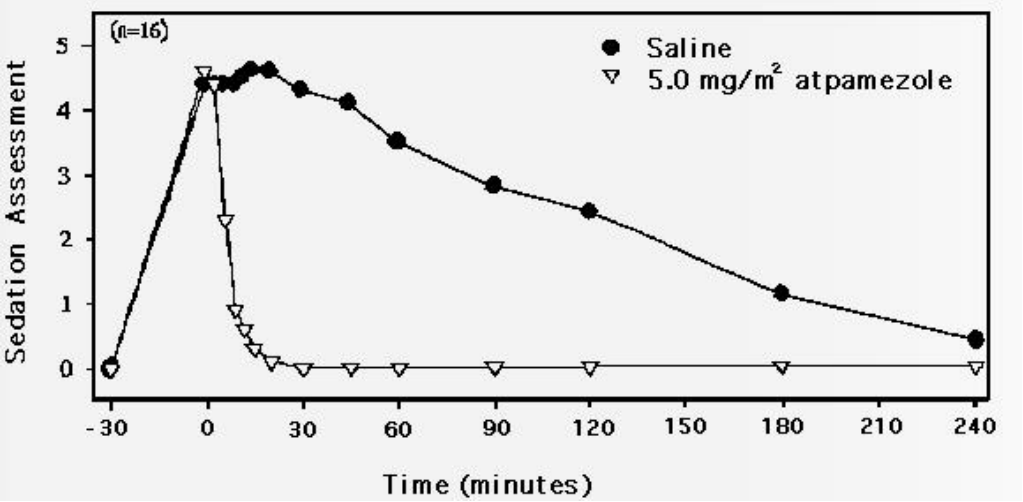
f. Conclusions: Atipamezole completely reversed the clinical sedation produced by medetomidine. At the time of atipamezole injection, all dogs were heavily sedated. Between 6 and 15 minutes after atipamezole injection, all dogs returned to normal or near-normal sedation assessment and remained so for the subsequent four-hour recording period. Walking times mirrored sedation scores. Placebo-treated dogs gradually returned to normal during the same period.

Atipamezole produced a rapid (generally within 3 minutes) antagonism of medetomidine-induced bradycardia. Reversal of this variable occurred more quickly than observed for the other variables, but did not return to the pre-medetomidine value.

These data support the clinical efficacy and safety of atipamezole when used intramuscularly and used at the recommended multiple of five times the previously administered medetomidine (3.75 mg/m2 medetomidine) dose to reverse the clinical effects of intravenous medetomidine in the dog. The intravenous route of medetomidine administration, with the concomitant dosage reduction, did not influence the ratio of atipamezole dosage to medetomidine dosage in the dog.

Side Effects: Urination was a common side effect of medetomidine treatment.

Figure 1: Confirmation of atipamezole dose following intravenous administration of medetomidine (0.75 mg/m2) in dogs - Sedation Assessment.



Sedation Assessment Scale 0 - No Sedation Present 1 - Slight Sedation - almost normal; able to stand easily, but appears somewhat fatigued, subdued or somnolent. 3 - Moderate Sedation - able to stand but prefers to be recumbent; sluggish,; ataxic or uncoordinated. 4 - Profound Sedation - unable to rise, but can exhibit some awareness of environment; responds to stimuli through body movement; may be lateral or sternal recumbency. 5 - Unresponsive - in a state of coma or semi-coma from which little or no response can be elicited; remains in lateral recumbency.

Figure 2: Confirmation of atipamezole dose following intravenous administration of medetomidine (0.75 mg/m2) in dogs - Walking Ability. Walking Ability Scale 0 - Normal 1 - Good - able and willing to walk with only slight missteps. 2 - Poor - can manage to walk but is markedly ataxic, staggers and falls. 3 - Unable to walk - no purposeful forward movement is achieved.

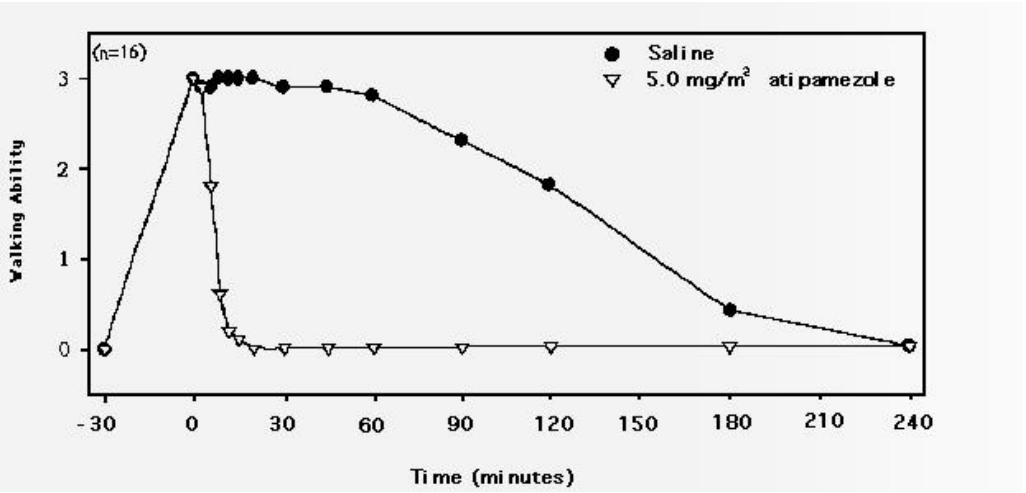


Figure 3: Confirmation of atipamezole dose following intravenous administration of medetomidine (0.75 mg/m2) in dogs - Heart Rate.

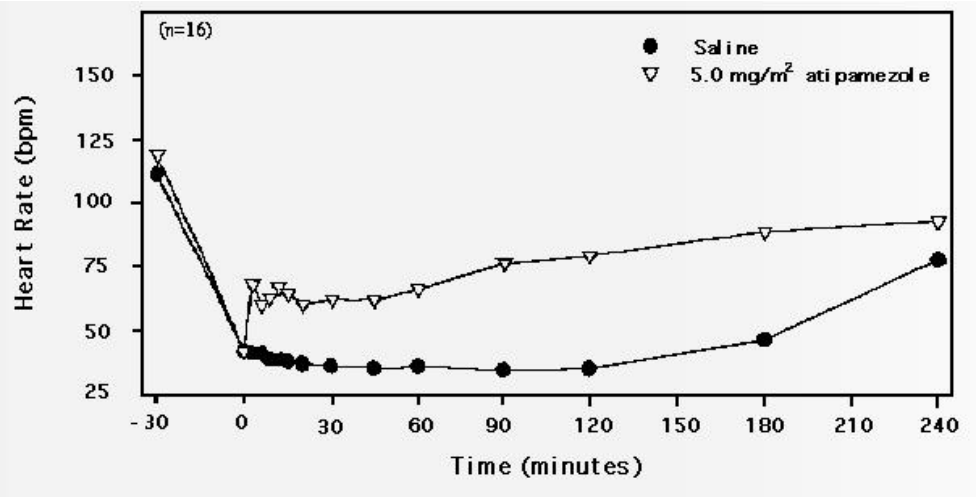
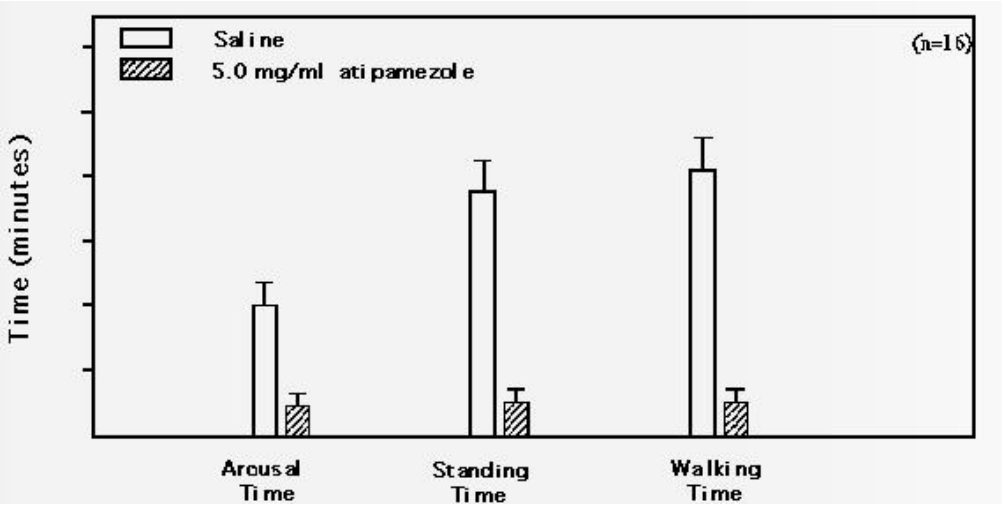


Figure 4: Confirmation of atipamezole dose following intravenous administration of medetomidine (0.75 mg/m2) in dogs - Arousal, Standing, and Walking Times.



Error Bar = SEM Arousal Time (AT): The time interval between injection of atipamezole and first signs of increased awareness (e.g. a willingness and ability to lift the head for five seconds). Standing Time (ST): The time interval between atipamezole injection and the point at which the dog is able to stand for five seconds. Walking Time (WT): The time interval between atipamezole injection and ambulation (purposeful forward movement).

Atipamezole Reversal of Medetomidine Sedation in Dogs: A Multicentered Clinical Field Study (CD-0112-91)

a. Type of Study: Multicentered Clinical Field Study

b. Investigators:

Name	Cases	Name	Cases
Dr. Danielle Garrison Bay Springs, MS	39	Dr. Dietrich Franczuszki Malvern, PA	2
Dr. Lee Tyner College of Vet. Medicine Mississippi State University Mississippi State, MS	35	Dr. Raymond Ewing Christiana, PA	32
Dr. Lynn Buzhardt Zachary, LA	31	Dr. Kevin Todd Big Rapids, MI	35
Dr. Lucie Berryhill Baton Rouge, LA	22	Dr. Marc Leven Grand Rapids, MI	37

c. General Design

i. Purpose: The objective of the study was to evaluate, under field conditions, the efficacy and safety of atipamezole as an antagonist of the sedative effects of medetomidine in dogs.

ii. Test Animals:

- Of the 233 cases which could be used to evaluate atipamezole, 115 were treated with atipamezole while 118 were treated with placebo. Dogs were well-balanced and well-represented across both treatment groups with regard to age, sex, weight, breed, the length of procedure and the severity of the procedure to which they were subjected. Dogs ranged from four to 129 lb body weight, and from three months to 14 years of age.
- Dogs were randomly assigned to either atipamezole or placebo treatment groups and were treated intravenously or intramuscularly with medetomidine. A clinical procedure(s) and/or examination was conducted. The dogs were then blindly administered atipamezole or placebo and recovery from the effects of medetomidine was then measured.

iii. Control Drug: Placebo (same as other treatments except for active ingredients)

iv. Dosage Form: The atipamezole and medetomidine study drugs were sterile injectable solutions which were the same as the proposed market formulas except the atipamezole was provided in 2 mL vials (one vial/one dog) for blinding.

v. Route of Administration:
- Atipamezole - intramuscular injection
- Medetomidine - intravenous and intramuscular injection

vi. Dosages used:

- Medetomidine:
    a. 0.75 mg/m2 of body surface area, intravenously
    b. 1.0 mg/m2 of body surface area, intramuscularly
- Atipamezole:
    a. 3.75 mg/m2 of body surface area, intramuscularly
    b. 5.0 mg/m2 of body surface area, intramuscularly

Atipamezole was administered intramuscularly, at five times the dosage of the previously administered medetomidine.

vii. Parameters Measured: Three observations were made at 15 minute intervals for one hour following injection of the reversal agent: heart rate, sedation score, and ability to walk. Sedation scores were rated from 0 to 5, with 0 as normal and 5 as a maximum (unresponsive). Assessment of the ability to walk was rated 0 to 3, with 0 as normal and 3 designating an inability to walk. In addition, the time necessary for the dog to walk unassisted was recorded as a measurable clinical endpoint of physical ability.

A general, or overall, assessment of the reversal of sedation was recorded summarizing response to treatment according to the following ratings: excellent, good, poor or none. For a period of at least four hours following sedation injection, the dogs were observed to ensure that a relapse into sedation did not occur.

d. Results: Results of the atipamezole and placebo treatments are provided in Table 1. Immediately prior to reversal injection, at post-reversal Time 0, the atipamezole treatment group had an average sedation score of 3.8 of a possible 5. Profound sedation or unresponsiveness was exhibited in 76.5% of the dogs. Though some dogs were able to walk prior to reversal, the ability to walk scores indicated that 85.2% of the dogs were unable to walk, with an average walking score of 2.8 of a possible 3. Heart rate averaged 40% of the pretreatment rate (single-sample).

At the first scoring interval, 15 minutes following atipamezole injection, the average sedation score dropped to 0.4, with 91.3% of the subjects rated normal or almost normal. By 30 minutes post-reversal, 99.1% of the dogs were rated normal or almost normal. The mean walking score 15 minutes after reversal was 0.3 with 95.6% walking normally or with only slight missteps. Dogs which were scored completely normal in their walking represented 74.8% and 97.4% of the group at the 15 minute and 30 minute intervals, respectively. Within 15 minutes of treatment, the average heart rate returned to 83% of the pre-treatment rate, with a slight increase at subsequent intervals. Table 1 illustrates the distribution of cases according to heart rate.

Table 1. Distribution of Heart Rates Expressed As a Percent of "Baseline" Heart

Rate	Percent of Atipamezole-treated Dogs According to Time Interval Following Treatment			
Percent of Basline Heart Rate	15 minute	30 minute	45 minute	60 minute
<= 79%	45%	36%	41%	33%
80-119%	47%	53%	50%	63%
>=120%	8%	11%	10%	4%

By comparison, the percentage of placebo-treated dogs with normal or almost normal sedation scores at the 15 and 30 minute intervals were 4.2% and 8.5%, respectively. The percentage of dogs in the placebo group which were walking normally or with slight missteps at the same intervals were 7.6% and 12.7%, respectively. Heart rates in the placebo group remained between 40% and 44% of the baseline value during the hour of measurement.

Table 2. Summary of Reversal Therapy by Treatment Group (CD-0112-91)

		Average Post-Reversal Scores by Minutes							
Treatment Group	Parameter	0	15	30	45	60	Average Min. to Walking	No. Cases: Reversal Assessment	Percent Clinical Success
Atipamezole (n=115)	Sedation	3.8	0.4	0.1	0	0	7.9	Excel: 105 Good: 9 Poor: 0 None: 1	99.1
	Walking	2.8	0.3	0	0	0			
	H.R. (%)	40	83	88	87	86			
Placebo (n=118)	Sedation	3.8	3.5	3.3	3.0	2.7	73.5	Excel: 2 Good:6 Poor:18 None: 92	5.9
	Walking	2.8	2.6	2.5	2.3	2.1			
	H.R. (%)	39	40	41	42	44			

Note: Heart Rate (H.R.(%)) is expressed as a percent of pretreatment baseline.

The overall assessment in the atipamezole group was rated as excellent or good in all dogs except one, which was rated "none." Closer examination of this case revealed that the sedation and walking scores progressed from 4 and 3, respectively, to normal (0) within thirty minutes, suggestive of significant reversal. However, recovery was slower than expected, which may have had a bearing on the investigator's overall assessment. Recovery of the placebo group was slow and more gradual than with atipamezole by all parameters.

A clinical success rating was determined by combining "excellent" or "good" overall assessments of reversal with absence of relapse. All cases but one in the atipamezole group were clinical successes. Conversely, the clinical

success rate in the placebo-treated group was 7 of 118, or 5.9%. It is noted that one placebo animal that initially reversed, relapsed.

a. Statistical Analysis: Rates of being evaluated as normal, in terms of sedation and rates of walking normally, were significantly higher ($p<0.001$) in the atipamezole-treated group from 15 minutes post-treatment onward. The associated average sedation and walking assessment scores reflect the treatment effect. Clinical success rates and reversal assessment scores were significantly higher ($p<0.001$) in the atipamezole-treated group.

b. Conclusions: In diverse clinical settings, utilizing an adequate and well-controlled design, atipamezole was shown to be a rapidly-acting, safe and effective agent for the reversal of sedation and bradycardia induced by intravenous or intramuscular administration of medetomidine to dogs. Clinically, animals administered atipamezole had total reversal of signs, yet heart rate measurements indicated a slower return to baseline. No conclusions can be made on the potential for drug interactions, although no untoward effects were noted in this study. Additionally, this study does not address use of the drug in animals intended for breeding.

c. Side Effects: Atipamezole side effects were infrequent and mild. Rarely, dogs exhibited brief excitement or apprehensiveness upon reversal.

B. CORROBORATIVE STUDIES

Study to determine the antagonistic activity of atipamezole against medetomidine induced cardiovascular and respiratory changes(Study No. Atip 5/2)

a. Type of Study/Objective: The objective was to determine the ability of atipamezole to reverse medetomidine-induced cardiovascular and respiratory changes in dogs. A randomized complete block design was used with at least 6 days between treatments.

b. Investigator:

Dr. Outi Vainio
Farmos Research Center
Farmos Group, Ltd.
Turku, Finland

c. Test Animals: Six laboratory beagles

d. Control: Placebo

e. Dosage and Route of Administration: Atipamezole was tested at five-and ten-fold multiples of a range of medetomidine doses (20, 40, 80 micrograms per kilogram), yielding a total of nine different combinations of medetomidine and atipamezole, including placebo. All doses were given intramuscularly. (The five fold multiple of atipamezole following 40 mcg/kg of medetomidine intramuscularly is roughly equivalent to the proposed optimum dosage.)

f. Results and Conclusions: Atipamezole was able to reverse medetomidine-induced bradycardia, respiratory depression and decrease in pO2. Following doses which approximated recommended doses of medetomidine and atipamezole, a transient decrease in systolic blood pressure of approximately 10% was seen during the first 10 minutes after injection of atipamezole, but thereafter the effects on blood pressure were negligible. There were no significant differences in the overall efficacy of the two tested doses of atipamezole in antagonizing medetomidine-induced effects. No adverse reactions were reported.

Pharmacokinetics of intramuscular atipamezole in the dog (Study No. Atip 4/41)

a. Type of Study/Objective: The objective was to determine the pharmacokinetics of intramuscular atipamezole.

b. Investigator:

i. Jarmo S. Salonen, Ph.D.
Farmos Research Center
Farmos Group, Ltd.
Turku, Finland

c. Test Animals: Six (3 male, 3 female) laboratory beagles, weighing 8.0 to 14.8 kg

d. Control: Not applicable

e. Dosage and Route of Administration: Each dog received a single dose of 500 mcg/kg atipamezole intramuscularly. Serum drug concentrations from 0 to 72 hr after dosing were based on the use of radiolabeled atipamezole.

f. Results and Conclusions: Atipamezole was absorbed rapidly with Tmax calculated to be 0.17 hr. The apparent distribution volume was 2.5 L/kg. Elimination half-life was 2.6 hr. No adverse reactions were reported.

III. TARGET ANIMAL SAFETY

A. PIVOTAL STUDIES

Target safety study of atipamezole (Antisedan®) in beagle dogs (Study no. AT-I-1001-91)

a. Type of Study: Target animal safety and acute toxicity

b. Investigator:

Clare M. Salamon
Hazelton Wisconsin Laboratory
Madison, WI

c. General Design:

i. Purpose: The purpose of this study was to assess the target animal safety and acute toxicity of atipamezole when administered intramuscularly to dogs.
ii. Test Animals: Thirty-six male and female laboratory beagles, approximately 5 months old at study initiation, weighing from 5.3 to 7.8 kg.
iii. Control Drug: Placebo (identical to proposed market formulation except for absence of atipamezole)
iv. Dosage Form: Sterile solutions for injection, proposed market formulations
v. Route of Administration: intramuscular injection
vi. Dosages used: Test groups are outlined below:

			Number of Animals	
Group	Number of Doses	Atipamezole Dose (mg/m2)	M	F
1 Controls	3	0	3	3
2 1X	3	5	3	3
3 3X	3	5	3	3
4 5X	3	5	3	3
5 10X	1	5	3	3
6 medetomidine 1X and atipamezole 3X	3	5	3	3

vii. Parameters Measured: Clinical observations: mortality, morbidity, body weight, food consumption, water consumption
Electrocardiography
Ophthalmoscopy
Laboratory parameters: hematology, clinical chemistry
Necropsy, pathology and histopathology

Animals were observed twice daily for mortality and moribundity. On the days of dosing, animals were observed continuously for approximately 4 hours post dose. Body weights were recorded on the day before initiation of the treatment, on each day of dosing, approximately 24 hours after the last dose, and on the day of necropsy. Animals were observed daily for qualitative food and water consumption. Physical examinations were done before initiation of treatment, daily during treatment (before dosing), approximately 24 hours after the last dose, and before necropsy. Electrocardiographic measurements and ophthalmic examinations were done before

initiation of treatment and approximately 24 hours after the last dose. Hematology and clinical chemistry parameters were evaluated twice before initiation of treatment and approximately 24 hours after the last dose. All animals were necropsied two days after the last dose.

e. Results: Dogs injected with atipamezole exhibited clinical signs suggestive of having been dosed with a stimulant. All male and female dogs in the 10X group showed one or more effects (hyperactivity, panting, tremors, salivation, soft or liquid feces, injected sclera, etc.) of stimulation. Signs were also noted among three of three male dogs and two of three female dogs in the 5X group. Of the male dogs in the 3X and 1X groups, only one dog in the 3X group exhibited any significant changes (injected sclera). Hyperactivity was noted in three of three females in the 1X group and two of three females in the 3X group. Vomiting was observed in two of three female dogs in the 1X group and one of three females in the 3X group. Medetomidine-sedated dogs showed either no effects of atipamezole administration or very mild effects similar to those observed in the 1X and 3X groups.

   There were no atipamezole-related effects on body weight, food consumption, hydration, physical examination results, or electrocardiographic data. Mean creatine kinase and aspartate aminotransferase values were increased in dogs administered the 10X dose of atipamezole. Mean creatine kinase in 10X males was 1760 iu/L, which was 5.9X higher than the control group males while the mean value (1353 iu/L) for 10X females was 4.4X that of controls. 3X males had a mean creatine kinase value of 654 iu/L, which was 2.2X that of the controls. The mean aspartate aminotransferase value among male dogs in the 10X group was 62 iu/L, which was 1.7X that of control males. The value for females was 1.8X that of controls. Females in the 10X group had a mean alanine transferase value of 50 iu/L, which was 2.1X that of control females. There were no systemic anatomical pathology changes observed in dogs given atipamezole. At intramuscular injection sites, localized skeletal muscle degeneration and necrosis occurred in all dogs given atipamezole. However, dogs exhibited no test material-related pain during injection compared with the placebo group, and there was no post-injection pain, swelling or other clinically evident injection site abnormalities. The microscopic injection site lesions reported in this study were considered relatively mild, clinically insignificant and a common sequella to the process of drug administration by intramuscular injection.

f. Conclusions: Based on this study, the administration of atipamezole was not associated with any life threatening toxicity when given in a single dose at 10X the anticipated use rate or when given daily for three consecutive days at 1X, 3X or 5X the anticipated use rate, both without prior administration of medetomidine, and at 3X the anticipated dose rate following the administration of medetomidine. Atipamezole was well tolerated and is not expected to produce significant signs of toxicity when used as directed.

Target safety study of atipamezole (Antisedan®) in medetomidine sedated beagle dogs given acute multiple doses (Study no. AT-I-1002-91).

a. Type of Study: Target animal safety of multiple doses following sedation.

b. Investigator:

Clare M. Salamon
Hazelton Wisconsin Laboratory
Madison, WI

c. General Design

i. Purpose: The purpose of this study was to assess the target animal safety and acute toxicity of atipamezole when administered intramuscularly in repeated doses to dogs heavily sedated with medetomidine.
ii. Test Animals: Twelve male and female laboratory beagles, approximately 5 months old at study initiation, weighing from 5.8 to 8.1 kg
iii. Control Drug: Placebo (identical to proposed market formulation except for absence of atipamezole).
iv. Dosage Form: Sterile solutions for injection, proposed market formulations.
v. Route of Administration: intramuscular injection (both drugs)
vi. Dosages used: Test groups are outlined below:

			Number of Animals	
Group	Medetomidine Dose (mg/m2)	Atipamezole Dose (mg/m2)	M	F
1 Controls	3.0	0	3	3
2 Medetomidine 3X single injection followed by three atipamezole 1X injections at 30 minute intervals	3.0	5.0 (given 3 times)	3	3

vii. Parameters Measured: Clinical observations: mortality, morbidity, body weight, food consumption, water consumption, physical examination

Electrocardiography

Ophthalmoscopy

Laboratory parameters: hematology, clinical chemistry

The animals were observed continuously through six hours after the last dose of atipamezole. Body weights were taken before treatment and approximately 24 hours after the last dose. Animals were observed daily for qualitative food and water consumption. Physical examinations

and electrocardiograms were done approximately 24 hours before study initiation and approximately one and 24 hours after the last dose of atipamezole. Clinical chemistry and hematology information was obtained twice before study initiation and approximately 24 hours after the last dose. Ophthalmic examinations were done once before study initiation and approximately 28 hours post dose.

d. Results: All dogs in Group 1 appeared sedated for 2 to 3 hours after medetomidine administration and exhibited hypoactivity, uncoordinated movement, and unsteadiness for up to 5 additional hours. All dogs in Group 2 were showing signs of arousal from sedation approximately 5 to 6 minutes after the first injection of atipamezole. Trembling was observed after the second and third doses. Five of six dogs in Group 2 exhibited some degree of hypoactivity for approximately 2 hours after the medetomidine administration (or approximately 30 minutes after the last atipamezole dose).

   There were no test material-related changes in body weights, food consumption or hydration observed. Expected decreases in body temperature, respiration rates and heart rates were observed among the dogs not treated with atipamezole due to the sedative effects of medetomidine. Prolonged Q-T intervals due to bradycardia were also noted on ECG examinations of dogs not receiving atipamezole. All dogs given atipamezole had electrocardiographic results (except heart rate) which were similar to baseline values. A complete return to basal heart rate was not observed in ten of twelve dogs one hour after reversal with atipamezole or placebo, although the placebo-treated animals achieved heart rates only approaching 50% of the atipamezole-treated animals. There were no test material-related changes in hematological or clinical chemical results.

e. Conclusions: Based on the results of this study, administration of medetomidine at 3X the anticipated use rate followed by three successive intramuscular injections of atipamezole at the anticipated dose rate was well-tolerated and did not result in any unexpected effects.

IV. HUMAN FOOD SAFETY

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.

V. USER SAFETY

Keep out of reach of children. Not for human use. Atipamezole hydrochloride can be absorbed and may cause irritation following direct exposure to skin, eyes, or mouth. In case of accidental eye exposure, flush with water for 15 minutes. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing. If irritation or other adverse reactions occur (e.g., increased heart rate, tremor, muscle cramps), seek medical attention. In case of accidental oral exposure or injection, seek medical attention. Precaution should be used while handling and using filled syringes.

Users with cardiovascular disease (e.g., hypertension or ischemic heart disease) should take special precautions to avoid any exposure to this product.

To report adverse reactions in users or to obtain a copy of the material safety data sheet (MSDS) for this product call 1-800-366-5288.

This product contains an alpha-2-andrenergic antagonist.

VI. 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 Antisedan® (atipamezole hydrochloride), when used under labeled conditions of use, is safe and effective.

Antisedan® is restricted to use by or on the order of a licensed veterinarian because professional expertise is required to determine when a dog should be reversed from the sedative effects of the prescription drug, Domitor® (medetomidine).

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.

VII. LABELING:

1. Package insert
2. Vial label
3. Box label
4. Shipper label

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

Freedom of Information Office
Center for Veterinary Medicine, FDA
7500 Standish Place
Rockville, MD 20855