Date of approval: December 1, 2006

FREEDOM OF INFORMATION SUMMARY

NADA 141-033

ANTISEDAN

atipamezole hydrochloride

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

Sponsored by:

Orion Corporation

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1. GENERAL INFORMATION:

a.	File Number:	NADA 141-033
b.	Sponsor:	Orion Corporation Orionintie 1 02200 Espoo Finland Drug Labeler Code: 052483
c.	Established Name:	atipamezole hydrochloride
d.	Proprietary Name:	ANTISEDAN
e.	Dosage Form:	Sterile injectable solution
f.	How Supplied:	ANTISEDAN is supplied in 10-mL, multidose vials containing 5.0 mg of atipamezole hydrochloride per mL.
g.	How Dispensed:	Rx
h.	Amount of Active Ingredients:	5 mg/mL
i.	Route of Administration:	Intramuscular
j.	Species/Class:	Canine
k.	Recommended Dosage:	ANTISEDAN is administered intramuscularly regardless of the route used for DEXDOMITOR (dexmedetomidine hydrochloride) or DOMITOR (medetomidine hydrochloride). The atipamezole dose for the reversal of intravenous DEXDOMITOR or DOMITOR is 3750 mcg/m^2. The atipamezole dose for the reversal of intramuscular DEXDOMITOR or DOMITOR is 5000 mcg/m^2. The concentration of ANTISEDAN is formulated so that the volume of injection is the same (mL for mL) as the recommended dose of DEXDOMITOR or DOMITOR.

The dosage of ANTISEDAN is calculated based on body surface area. Use the following tables to determine the correct injection volume or the correct ANTISEDAN dosage on

the basis of kilograms of body weight. **Note that the mcg/kg dosage <u>decreases</u> as body weight increases**.

Table 1: Atipamezole dosing for reversal of IV dexmedetomidine- or medetomidine-induced sedation/analgesia:

Dose table for ANTISEDAN (3750 mcg/m^2) when dexmedetomidine or medetomidine is given IV			
For # lb	**For # kg**	**dose = mcg/kg**	**volume = mL ANTISEDAN**
4-7	2-3	300	0.1
7-9	3-4	250	0.15
9-11	4-5	230	0.2
11-22	5-10	200	0.3
22-33	10-15	170	0.4
33-44	15-20	150	0.5
44-55	20-25	140	0.6
55-66	25-30	130	0.7
66-81	30-37	120	0.8
81-99	37-45	110	0.9
99-110	45-50	105	1.0
110-132	50-60	100	1.1
132-143	60-65	95	1.2
143-165	65-75	93	1.3
165-176	75-80	91	1.4
>176	>80	90	1.5

Table 2: Atipamezole dosing for reversal of IM dexmedetomidine- or medetomidine-induced sedation/analgesia:

Dose table for ANTISEDAN (5000 mcg/m^2) when dexmedetomidine or medetomidine is given IM			
For # lb	**For # kg**	**dose = mcg/kg**	**volume = mL ANTISEDAN**
4-7	2-3	400	0.15
7-9	3-4	350	0.2
9-11	4-5	300	0.3
11-22	5-10	250	0.4
22-29	10-13	230	0.5
29-33	13-15	210	0.6
33-44	15-20	200	0.7
44-55	20-25	180	0.8
55-66	25-30	170	0.9
66-73	30-33	160	1.0

73-81	33-37	150	1.1
81-99	37-45	145	1.2
99-110	45-50	140	1.3
110-121	50-55	135	1.4
121-132	55-60	130	1.5
132-143	60-65	128	1.6
143-154	65-70	125	1.7
154-176	70-80	123	1.8
>176	>80	120	1.9

l. Pharmacological Category: Alpha$_2$-adrenoreceptor antagonist

m. Indications: ANTISEDAN is indicated for the reversal of the sedative and analgesic effects of DEXDOMITOR (dexmedetomidine hydrochloride), and DOMITOR (medetomidine hydrochloride) in dogs.

n. Effect of Supplement: An additional indication for the reversal of the sedative and analgesic effects of DEXDOMITOR (dexmedetomidine hydrochloride).

2. EFFECTIVENESS

a. Dosage Characterization:

The dosage characterization for dexmedetomidine relies on the reasonable assumption that the dextrorotary enantiomer (dexmedetomidine) of the approved racemic compound, medetomidine, is the sole pharmacologically active ingredient of medetomidine.

Relationship of medetomidine and dexmedetomidine: The concentration of dexmedetomidine (0.5 mg/mL) is half that of medetomidine (1 mg/mL); therefore, the sedation/analgesia dose of dexmedetomidine in mcg is half the mcg dose of medetomidine. However, the dosage volumes are the same for both products, because 1 mL of either dexmedetomidine or medetomidine contains 0.5 mg of the active dexmedetomidine isomer.

Relationship of atipamezole to both alpha$_2$-agonists: The concentration of atipamezole (5.0 mg/mL) is 5 times that of medetomidine (1.0 mg/mL) and 10 times that of dexmedetomidine (0.5 mg/mL). Therefore, the dose of atipamezole is 5 times the initial dose of medetomidine and ten times the initial dose of dexmedetomidine (mcg/m^2).

Because of these relationships, the injection volume of the atipamezole dose is the same as the injection volume of either alpha$_2$-agonist dose.

The following table illustrates these relationships, comparing the IM atipamezole doses for the reversal of IV and IM medetomidine and dexmedetomidine.

Table 3: IM Atipamezole Doses

drug	**concen-tration**	**IV dose**	**atipamezole reversal dose***	**IM dose**	**atipamezole reversal dose***
medetomidine	1 mg/mL	750 mcg/m^2	**3750 mcg/m^2**	1000 mcg/m^2	**5000 mcg/m^2**
dexmedetomidine	0.5 mg/mL	375 mcg/m^2	**3750 mcg/m^2**	500 mcg/m^2	**5000 mcg/m^2**

*Atipamezole concentration = 5 mg/mL

b. Substantial Evidence:

Study Title and Number: Dexmedetomidine In Dogs: Safety And Effectiveness of a Sedative and Analgesic Veterinary Product (Orion Pharma Study No. MPV9901; Klifovet Study No. 199040).

Type of Study: Field Study

Study Dates: October 15, 1999 to June 28, 2000

Locations and investigators:

United Kingdom:

Clifford E. Aldermann, VedMed, CertVD, MRCVS
Stewart, Piggott and Aldermann MRCVS
Gloucester

Gavin A. T. Dalton-Morgan, BVMS, MRCVS
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Germany:	Andreas Böhm, Dr. Med. Vet. Bremen
	Sibylle Lutz, Dr. Med. Vet. München
	Birgit Kraus, Dr. Med. Vet. Neubiberg
	Karin Meier, Dr. Med. Vet. München
	Petra Wittmann, Dr. Med. Vet. München

General Study Design:

This clinical study was a masked, balanced, controlled, randomized, multicenter and comparative field study testing dexmedetomidine hydrochloride. The effects were compared to medetomidine, an approved drug. The effects of atipamezole hydrochloride, for the reversal of the effects of dexmedetomidine and medetomidine treated dogs were also studied.

The study was carried out in 7 veterinary clinics in the United Kingdom and in 5 veterinary clinics in Germany according to the EU guideline Good Clinical Practice for the Conduct of Clinical Trials for Veterinary Medicinal Products adopted by the CVMP in July, 1994 and according to the FDA Guidance for Industry Good Target Animal Study Practices: Clinical Investigators and Monitors of May, 1997.

Dogs requiring sedation, analgesia or sedation and analgesia for clinical examinations and procedures were presented. They were randomly treated with either dexmedetomidine or medetomidine. Atipamezole was randomly administered to half of the dogs that had received dexmedetomidine and to half of the dogs that had received medetomidine.

Purpose of Study: To compare the safety and effectiveness of atipamezole as a reversal agent, in dogs that were sedated for surgical/medical procedures with either dexmedetomidine or medetomidine.

Description of Test Animals:

A total of 213 dogs were included in the study (157 pure bred and 56 cross bred dogs). One hundred and six dogs were given dexmedetomidine and 107 dogs were given medetomidine.

Age: The mean age was 6.1 years and varied from 16 weeks to 16 years.

Gender: Of 213 dogs, 111 were male and 102 were female.

Weight: The mean weight was 20.5 kg, ranging from 2.2 kg to 64.0 kg.

Control and Treatment Groups:

The study design used 8 parallel groups:

1. Dexmedetomidine, IV without atipamezole (25 dogs)
2. Medetomidine, IV without atipamezole (25 dogs)
3. Dexmedetomidine, IM without atipamezole (26 dogs)
4. Medetomidine, IM without atipamezole (28 dogs)
5. Dexmedetomidine, IV with atipamezole (27 dogs)
6. Medetomidine, IV with atipamezole (28 dogs)
7. Dexmedetomidine, IM with atipamezole (28 dogs)
8. Medetomidine, IM with atipamezole (26 dogs)

A total of 55 dogs received dexmedetomidine (IV or IM), followed by atipamezole (IM). A total of 54 dogs received medetomidine, followed by atipamezole.

Masking:

The study was fully masked for dexmedetomidine and medetomidine. At the time of administration of atipamezole, the investigator remained masked for dexmedetomidine and medetomidine treatments but was unmasked for treatment with atipamezole. The investigators, the monitor and the person responsible for entering data into the database did not have access to the treatment codes.

Inclusion Criteria:

1. Dogs of any sex or breed, more than 12 weeks of age, presented for routine medication for the following indications: restraint, sedation and analgesia associated with clinical examinations and procedures, including minor surgery.

2. Prior to inclusion, the following parameters were evaluated in a physical examination on day 0 or day -1: body temperature, pulse and respiration, auscultation of heart and lung sounds, palpation of peripheral pulse, evaluation of mucous membrane color, evaluation of state of hydration and suitability for the study. Only animals categorized according to the American Society of Anesthesiologists class I (normal healthy patient with no detectable disease) or II (slight or moderate systemic disease causing no obvious incapacity) were included.
3. The owners gave written informed consent for their dogs to participate in the study.

Exclusion Criteria:

1. Body weight less than 2.0 kg
2. Pregnancy
3. Congestive heart failure
4. Signs of mitral regurgitation (cough, dyspnea)
5. Severe endotoxic or traumatic shock
6. Stress conditions such as extreme heat, cold or fatigue
7. Significantly depressed respiration
8. Severe debilitation
9. Use of any other tranquilizer, anesthetic, or anesthetic/analgesic drugs
10. Use of anticholinergic agents administered prior to, concurrent with, or following the administration of the dexmedetomidine or medetomidine.

Drug Product:

Atipamezole:

Trade name: ANTISEDAN

Dosage form: Injectable solution

Concentration: 5.0 mg atipamezole per mL

Dexmedetomidine:

Trade name: DEXDOMITOR

Dosage form: Injectable aqueous solution

Concentration: 0.5 mg dexmedetomidine hydrochloride per mL

Medetomidine:

Trade name: DOMITOR

Dosage form: Injectable aqueous solution

Concentration: 1.0 mg medetomidine hydrochloride per mL

Drug Administration:

1. **Table 4: Dosage Amount, Frequency, and Duration:**

Product	**Dose**	**Frequency**	**Route of Administration**
Dexmedetomidine	375 mcg/m^2	once	IV
Medetomidine	750 mcg/m^2	once	IV
Dexmedetomidine	500 mcg/m^2	once	IM
Medetomidine	1000 mcg/m^2	once	IM
Atipamezole	3750 mcg/m^2	once	IM (dose if agonist is given IV)
Atipamezole	5000 mcg/m^2	once	IM (dose if agonist is given IM)

Atipamezole following medetomidine: Both drugs were used at dosages approved by FDA in NADA 141-033 and NADA 140-999, respectively.

2. Relationship to feeding:

Animals were fasted for 12 hours prior to treatment with dexmedetomidine or medetomidine.

Variables measured:

Duration and quality of reversal from sedation:
- Posture (0 to 4)
- Response to noise (0 to 3)
- Muscle tone of jaw (0 to 3)
- Ability to perform procedures (0 to 4)

Duration and quality of reversal from analgesia:
- Pedal reflex induced by toe pinching (0 to 4)

Respiratory and cardiovascular parameters: Heart rate, heart rhythm, pulse character, respiratory rate, body temperature, and the appearance of mucous membranes were monitored.

Adverse events were followed throughout the study.

Criteria for Success/Failure:

Reversal of physiological and sedation parameters was evaluated by comparing values and scores from medetomidine and dexmedetomidine treated dogs (without reversal) with values and scores from sedated dogs following treatment with atipamezole.

Procedures:

The most frequently performed procedures were dental care (n=85), radiography (n=57), skin tumor removal (n=15) and treatment of otitis (n=13). In some cases, more than one procedure was performed during sedation.

Results:

One hundred and nine dogs were evaluated in the groups treated with ANTISEDAN (55 dogs received DEXDOMITOR, and 54 received DOMITOR). Atipamezole was administered at the completion of the procedure, within a range of 39-57 minutes after administration of either dexmedetomidine or medetomidine.

1. Posture:

At 5 minutes, signs of reversal effects of atipamezole were seen in all 4 treatment groups (medetomidine IM or IV; dexmedetomidine IM or IV).

Intravenous route: 56.5% of the dogs in the dexmedetomidine group and 50% of the dogs in the medetomidine group were normal or slightly sedated, and could stand 5 minutes after atipamezole administration. At 15 minutes, the corresponding figures were 95.5 % for the dexmedetomidine group and 92 % for the medetomidine group. All the dogs in both groups had normal posture at 120 minutes.

Intramuscular route: 70.9% of the dogs in the dexmedetomidine group and 69.6% of the dogs treated with medetomidine were normal or slightly sedated, and could stand 5 minutes after atipamezole. At 15 minutes the corresponding figures were 95.8% for the dexmedetomidine group and 91.3% for the medetomidine group. All dogs but one in the dexmedetomidine group and all dogs in the medetomidine group had normal posture 120 minutes after atipamezole treatment. The single dexmedetomidine dog had attained sternal recumbency by 120 minutes.

2. Response to noise:

Intravenous route: Fifteen (of 23) dogs that received either dexmedetomidine or medetomidine IV, responded normally to noise at 5 minutes. Fifteen minutes after atipamezole treatment, all but one of the dogs in the dexmedetomidine group and all dogs in the medetomidine group responded to noise with a normal or exaggerated response.

Intramuscular route: Fifteen (of 24) dogs that received either dexmedetomidine or medetomidine IM, responded normally to noise at 5 minutes. Fifteen minutes after atipamezole treatment, 91.7% of the dogs in the dexmedetomidine group and 86.9% of the dogs in the medetomidine group responded to noise with a normal or exaggerated response.

3. Jaw muscle tone:

In all 4 groups, muscle tone of jaw had increased by 5 minutes after atipamezole administration.

Intravenous route: 86.4% of the dogs in the dexmedetomidine group and 100% of the dogs in the medetomidine group were normal at 15 minutes after treatment with atipamezole.

Intramuscular route: 91.7% of the dogs in the dexmedetomidine group and 82.6% of the dogs in the medetomidine group were normal after 15 minutes.

4. Evaluation of pedal reflex:

Fifteen minutes after administration of atipamezole the pedal reflex was normal or hypersensitive (reversal of analgesia) in more than 90% of the dogs treated either IV or IM with dexmedetomidine or medetomidine.

5. Heart rate:

Intravenous route: Heart rate increased between 0 and 5 minutes after the administration of atipamezole in both IV groups (dexmedetomidine dogs from 60 to 85 bpm, and medetomidine dogs from 51 to 67 bpm).

Intramuscular route: Heart rate increased between 0 and 5 minutes after the administration of atipamezole in both IM groups (dexmedetomidine dogs from 45 to 73 bpm, and medetomidine dogs from 52 to 79 bpm). Ultimately, bradycardia resolved more slowly in IM treated dogs.

6. Body temperature:

Intravenous and intramuscular route: Up to 120 minutes after administration of atipamezole, there were no major changes in body temperature.

7. Respiratory rate:

Respiratory rates increased between 0 and 5 minutes after the administration of atipamezole in all 4 groups.

8. Mucous membranes:

Intravenous route: After 5 minutes, the membranes were described as normal in 91.3% of dogs of the dexmedetomidine group and in 73.1% of the medetomidine group. After 120 minutes, membranes of 95.7% of dogs in the dexmedetomidine group and 88.5% in the medetomidine group were described as normal.

Intramuscular route: After 5 minutes, the mucous membranes were described as normal in 91.7% of dogs in the dexmedetomidine group and in 82.6% of dogs in the medetomidine group. After 120 minutes, all dogs treated either with dexmedetomidine or medetomidine showed normal mucous membranes.

9. Adverse events:

Adverse events in general were associated with the administration of alpha$_2$-agonists, not the reversal agent. One dog treated with IM medetomidine showed 4 instances of sinus arrest at the 5 minute timepoint after atipamezole administration; all other timepoints after atipamezole reversal were negative for arrhythmias. Sinus arrest was most likely due to, but cannot be definitively correlated with, administration of the alpha$_2$-agonist rather than atipamezole.

Descriptive statistics:

Heart rates increased toward normal following atipamezole reversal of the effects of IV medetomidine or dexmedetomidine, with slightly higher heart rates in the IV dexmedetomidine treated dogs, compared to IV medetomidine treated dogs. Also, dogs

treated with either IV or IM dexmedetomidine showed improved posture scores following atipamezole reversal; and IV dexmedetomidine treated dogs showed slightly improved mucous membrane color following reversal with atipamezole, compared to medetomidine treated dogs.

Conclusions:

It was concluded that IM ANTISEDAN, when administered after IV or IM DEXDOMITOR or DOMITOR, is effective and safe in reversing either DEXDOMITOR or DOMITOR induced sedation and analgesia. Based on field study results, the following recommendations are proposed for use of ANTISEDAN to reverse the effects induced by DEXDOMITOR:

1. The route of administration of ANTISEDAN is intramuscular (IM).
2. ANTISEDAN should be administered approximately 15-60 minutes after DEXDOMITOR.
3. The atipamezole dose (mcg/m^2) is 10 times the initial DEXDOMITOR dose (mcg/m^2).
4. The formulations have been designed so that ANTISEDAN should be used at the same dose volume as the initial dose volume of DEXDOMITOR.

3. TARGET ANIMAL SAFETY:

a. **Note:** Information contained in the FOI Summary for atipamezole's original approval (NADA 141-033, approval date August 6, 1996), examines target animal safety (TAS) data for atipamezole only, when administered to dogs in the absence of an alpha$_2$-agonist.

b. **Study Title and Number:** Toxicity of DEXMEDETOMIDINE in Beagle Dogs Following Intravenous (IV) or Intramuscular (IM) Administration (WEL Study No. 00-008)
Note: As part of the dexmedetomidine TAS study design, 2 groups of dogs received the reversal agent, atipamezole.

Type of Study: Target animal safety (TAS); the study was conducted under Good Laboratory Practice (GLP) regulations.

Study Dates: December 20, 2000 to January 5, 2001

Location of Study: White Eagle Toxicology Laboratories
Doylestown, Pennsylvania

General Design and Treatment Groups:

Two groups of 3 beagle dogs/sex/group were given a 3X dose of dexmedetomidine either IV or IM followed by 3 sequential 1X doses of atipamezole (ANTISEDAN), administered every 30 minutes after dexmedetomidine administration. The following table summarizes the study design. The 1X atipamezole dose following IM

dexmedetomidine is 5000 mcg/m^2 IM; following IV dexmedetomidine, the atipamezole dose is 3750 mcg/m^2 IM.

Table 5: Treatment Groups

No. of dogs	Dose of dexmedetomidine (mcg/m2/day)	Multiple of recommended dose	Route of administration	No. of doses
6*	1125	3X	IV	1
6**	1500	3X	IM	1

* Dogs received 3750 mcg/m^2 atipamezole IM 3 consecutive times (every 30 minutes).
** Dogs received 5000 mcg/m^2 atipamezole IM 3 consecutive times (every 30 minutes).

The 3X dexmedetomidine dose (IV and IM) was followed by a 1X dose of atipamezole administered intramuscularly 0.5, 1, and 1.5 hours after dosing. Dogs were observed for evidence of sedation approximately 15 minutes after dosing and then continually for approximately 90 minutes, following the first dose of atipamezole.

Objective:

The objective of the TAS study was to evaluate the effects of the administration of three 1X doses of atipamezole after administration of a 3X dose of IV and IM dexmedetomidine. These safety data were generated to assess possible drug interactions and to evaluate the effect of repeated doses of atipamezole on dogs that have been heavily sedated with the dexmedetomidine.

Inclusion Criteria:

All animals were acclimated 7 to 8 days prior to the start of the study. Healthy dogs were selected for inclusion in the study based on the results of the pretest physical examination and clinical pathology results.

Dosage Form: The approved atipamezole product was used during the study.

Drug Administration, Dosage Amount, Duration, and Route of Administration:

Dogs received a single dose of 3X dexmedetomidine. IV doses were administered as a bolus dose into the cephalic vein using a needle and syringe, and IM doses were administered into the lateral, proximal hind limbs using a needle and syringe.

Approximately 30 minutes after dosing with dexmedetomidine at 3X, dogs received 3 sequential doses of 1X atipamezole administered intramuscularly into the lateral, proximal hind limb at approximately 0.5 hour intervals. The doses of atipamezole were administered in the leg not used for administration of dexmedetomidine.

Relationship to Feeding:

Dogs were fed between 8 - 9 am, and dosing occurred between 10 am and 2:45 pm.

Variables Measured:

Clinical observations, physical examination, body weight, clinical pathology, urinalysis, and fecal examinations were evaluated.

Body weight, hematology, blood coagulation, blood chemistry, urinalysis, and fecal examination were performed on each animal pretest and approximately 24 hours following the dose. Body weight was also recorded prior to dosing. Animals were not necropsied.

Blood samples were obtained by jugular venipuncture following an overnight fast (water only). Urine and fecal samples were collected overnight. Fecal samples were examined for consistency, blood, excessive cellular debris, parasites and other abnormalities. Complete blood count (CBC) and serum chemistry variables were analyzed.

Animals were observed for evidence of sedation approximately 15 minutes after dosing and then continually for approximately 90 minutes beginning with the first dose of atipamezole. The time of onset of reversal of sedation and time of complete recovery was recorded. Other findings were recorded when observed. Observations ceased 30 minutes after the final atipamezole dose.

Results:

Signs of sedation and reversal:

No animals died. Following administration of dexmedetomidine, the animals became rapidly sedated, showing pale mucous membranes, ataxia, and lateral recumbency. Following the first dose of atipamezole, the animals were able to stand within 4 to 18 minutes, and sedated behaviors gradually resolved over the next 90 minutes of observation time.

All dogs were recorded as normal at the time of the final clinical observation (2 hours after administration of dexmedetomidine IV or IM). The times when individual variables became (and remained) normal are listed below:

Mucous membranes:

IV dexmedetomidine (3X): Mucous membranes were noted as normal from 4 to 27 minutes after the first dose of atipamezole (5 of 6 dogs). Mucous membranes were noted as normal 11 minutes after the second IV dose of atipamezole in the sixth dog.

IM dexmedetomidine (3X): All 6 dogs had normal colored mucous membranes between 2 and 22 minutes after the first atipamezole dose.

Sedation:

IV dexmedetomidine (3X): Four dogs were reported as normal (sedation resolved) between 5 and 30 minutes after the second atipamezole injection. The other 2 dogs had recovered from sedative effects between 0 and 9 minutes after the third atipamezole injection.

IM dexmedetomidine (3X): All 6 dogs had recovered from sedation between 3 and 13 minutes after the second atipamezole dose.

Lateral recumbency:

IV dexmedetomidine (3X): All 6 dogs stood after the first atipamezole injection (between 4 and 18 minutes later).

IM dexmedetomidine (3X): All 6 dogs stood after the first atipamezole injection (between 4 and 16 minutes later).

Ataxia:

IV dexmedetomidine (3X): Ataxia resolved within 5 to 26 minutes after the second atipamezole dose in 4 (of 6) dogs, and within 0 to 9 minutes after the third atipamezole dose in the remaining 2 dogs.

IM dexmedetomidine (3X): All 6 dogs had recovered from ataxia after the second atipamezole injection (between 3 and 13 minutes later).

Body weight:

There were no significant effects on body weight following dosing. Slight decreases in body weights were noted in all animals, but these were considered to be within normal limits.

Clinical pathology:

Clinical pathology results remained within the ranges considered normal for animals of this age at this laboratory. Mild elevations in creatine kinase were associated with repeated IM injections.

Adverse Reactions:

One dog vomited after receiving 3X dexmedetomidine, with no reoccurrence during the 3 atipamezole injections.

Conclusion:

The clinical effects of a 3X dose of dexmedetomidine administered either IV or IM were rapidly reversed by the first 1X dose of atipamezole. Following dexmedetomidine overdosage, sedation relapse occurred (abnormal mucous membrane color, ataxia,

sedated behavior), until the second or third atipamezole injection. There were no toxicological effects of administration of 3 atipamezole reversal injections.

c. **Study Title and Number:** Dexmedetomidine and Atipamezole. Evaluation of the effects of intramuscular (IM) administration of atipamezole in the presence of IM or intravenous (IV) dexmedetomidine on cardio-respiratory variables in dogs (CERB Study No. 20040011PCC).

Type of Study: Target animal safety (TAS); the study was conducted under Good Laboratory Practice (GLP) regulations.

Study Dates: January 20, 2004 to February 11, 2004

Location of Study: Centre de Recherches Biologiques
Baugy, France

General Design and Treatment Groups:

Five beagle dogs (3 females and 2 males) were included in a study using a crossover design involving randomization to 2 treatment sequences. Dogs were administered either an IM or an IV dose of dexmedetomidine, followed 45 minutes later by atipamezole (ANTISEDAN). Atipamezole is always administered by the IM route. A minimum washout of 48 hours was used between periods. The following table summarizes the study design and doses.

Table 6: Experimental Design

Trial	Period	Dog	Sequence	Dexmedetomidine at T = 0		Atipamezole at T = 45 min	
				Dose (mcg/m^2)	Route	Dose (mcg/m^2)	Route
1	1	1	1	375	IV	3750	IM
2	1	2	1	375	IV	3750	IM
3	1	3	2	500	IM	5000	IM
4	1	4	2	500	IM	5000	IM
5	1	5	2	500	IM	5000	IM
6	2	1	2	500	IM	5000	IM
7	2	2	2	500	IM	5000	IM
8	2	3	1	375	IV	3750	IM
9	2	4	1	375	IV	3750	IM
10	2	5	1	375	IV	3750	IM

Objective:

The aim of the TAS study was to evaluate the effects of atipamezole, in the presence of dexmedetomidine (IV or IM), on arterial blood pressure (BP), heart rate (HR), heart

rhythm, cardiac conduction times, respiration rate (RR), and body temperature (T) in dogs.

Inclusion/Exclusion Criteria:

Five, healthy, previously instrumented, beagles with normal cardiovascular (CV) measurements were included. Before starting, the study CV variables and body temperature (T) were checked. Dogs with at least one variable outside the following normal ranges were not included and a replacement was used.

Table 7: Values For Inclusion/Exclusion

Variables	*Threshold of exclusion*
mean arterial pressure (map)	<70 or >120 mmHg
diastolic arterial pressure (dap)	<50 or >100 mmHg
systolic arterial pressure (sap)	<100 or >160 mmHg
heart rate (HR)	<60 beats per minute (bpm)

Dosage Form: DEXDOMITOR (IV or IM sterile solution, 0.5 mg/mL, final market formulation) and ANTISEDAN (approved IM sterile solution, 5 mg/mL) were administered.

Drug Administration, Dosage Amount, Duration, and Route of Administration: Each dog received both treatments in a randomized crossover design. Atipamezole is administered only by the IM route.

1. IV Dexmedetomidine 375 mcg/m^2 at timepoint T 0 minutes, followed by atipamezole 3750 mcg/m^2 at T 45 minutes.

2. IM Dexmedetomidine 500 mcg/m^2 at timepoint T 0 minutes, followed by atipamezole 5000 mcg/m^2 at T 45 minutes.

Variables Measured:

These variables included: mean, systolic, diastolic arterial pressure, heart rate, respiratory rate, body temperature, and cardiac arrhythmias (ventricular ectopic beats, run, ventricular tachycardia, 2nd degree atrioventricular block, 3rd degree atrioventricular block, premature junctional or ventricular contraction, ventricular escape beats, and sinus arrhythmia). Arrhythmias were attributed to atipamezole only if arrhythmias were persistent through several time points, or were seen in several ECG strips close to the time point at which an arrhythmia was initially detected.

Variables were recorded before administration of dexmedetomidine (pre-dose), and at 5, 10, 15, 30, 50, 55, 60, 90, 120, 180 and 240 minutes after dosing with dexmedetomidine (T 0). Atipamezole was administered at T 45 minutes. Dogs were observed for signs of sedation relapse after administration of atipamezole (T 50 to 240 minutes). Adverse events were recorded from T 0 to 240 minutes.

Statistical Methods:

Change from baseline at each time point was analyzed using the analysis of variance (AOV) with the following factors: treatment group, period, sequence, and subject (nested within sequence). In cases where significant factor effects were detected at more than one time point for a specific variable, the relevant mean contrasts were presented to aid in further examining the differences. The post-hoc test determined whether the change from baseline for each treatment was significantly different from zero. A p-value < 0.10 was used to identify differences that may warrant further clinical examination. No adjustments for multiple testing were made in the post-hoc analysis.

Results:

1. Clinical observations: Dexmedetomidine (IV or IM) resulted in drowsiness, loss of locomotor activity, sedation, and muscle twitching. All dogs stood up within 5 minutes of atipamezole administration. All clinical signs of sedation induced by dexmedetomidine (IV or IM) were successfully reversed within 5 to 10 minutes following atipamezole administration, and no observation of sedation relapse was observed in any dog (monitored for 3 hours). Following reversal, all dogs appeared ataxic when they first stood up.

   Dexmedetomidine without atipamezole: One dog vomited 4 minutes after dexmedetomidine IM (prior to atipamezole). One dog did not become sedated following dexmedetomidine IM (ineffective).

   After atipamezole: One dog showed slight trembling from 10 to 15 minutes after atipamezole. One dog vomited after dexmedetomidine IV (45 minutes after atipamezole), and also vomited after dexmedetomidine IM at the same timepoint (45 minutes after atipamezole).

2. Cardiorespiratory variables:

   Heart rate (HR):

   Dexmedetomidine (IM and IV) resulted in a decrease in HR during the T 5 to T 30 minutes time period compared to pre-dosing values (T -15 minutes).

   Except for one dog, by T 240, dogs in both dexmedetomidine dose groups (IV and IM) showed increases in HR compared to HR at the time of maximum dexmedetomidine effects (T 5 to T 30), demonstrating atipamezole's reversal of dexmedetomidine's effects on HR.

   Following atipamezole (at T 45), HR increased (higher when dexmedetomidine was given by the IV route), but was not completely restored to pre-dexmedetomidine values (remained statistically significantly different). Atipamezole immediately increased HR, but levels were not sustained. HR decreased slightly between timepoints 120 and 240 minutes.

Cardiac conduction times:
Dexmedetomidine lengthened the duration of the PR interval, resulting in increased AV conduction time, as a result of the decrease in HR. In spite of the effects on conduction times, no arrhythmias developed during the 4 hour study.

For dogs treated with dexmedetomidine IV, values at timepoints between 50 and 180 minutes (post-atipamezole) showed PR duration statistically significantly longer compared to baseline values. By T 240, PR duration returned to approximately baseline levels. For dogs treated with dexmedetomidine IM, all timepoints after administration of atipamezole showed statistically significantly longer PR duration compared to baseline.

For both dexmedetomidine dose groups (IV and IM), by T 240, PR durations were shorter compared to the timepoints at maximum dexmedetomidine effect (T 5 to T 30), demonstrating atipamezole's partial reversal of dexmedetomidine's effects on cardiac AV conduction time.

Similar findings were noted for PQ and PT intervals, which also reflect cardiac conduction times. Cardiac AV conduction times decreased but did not return completely to pre-dexmedetomidine values.

3. Other cardiorespiratory variables:

   Dexmedetomidine IV or IM resulted in an increase in arterial blood pressure (followed by a decrease) and a decrease in heart rate and respiratory rate during the T 5 to T 30 minutes time period compared to pre-dosing values (T -15 minutes).

   Following atipamezole (at T 45 minutes), mean values for arterial blood pressure and respiratory rate returned to pre-dexmedetomidine values between the T 50 to T 240 minutes.

4. Body temperature did not change dramatically during the 45 minutes between dexmedetomidine IV or IM and atipamezole; however, mean temperatures were slightly lower by the end of the study.

5. Arrhythmias: No arrhythmias were observed in dogs treated with dexmedetomidine and atipamezole at any time point.

Conclusion:

Atipamezole was used safely and successfully for the reversal of clinical and cardiorespiratory effects induced by dexmedetomidine IV or IM. All clinical signs of sedation induced by dexmedetomidine were successfully reversed within 5 to 10 minutes following atipamezole administration, and no observation of sedation relapse was observed in any dog during the 3.5 hour period following treatment with atipamezole.

4. HUMAN SAFETY:

This drug is intended for use in dogs, which are non-food animals. Because this new animal drug is not intended for use in food-producing animals, data on human safety pertaining to drug residues in food were not required for approval of this NADA.

Human Warnings are provided on the product label as follows:

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

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 reaction occurs (for example, increased heart rate, tremor, muscle cramps), seek medical attention. In case of accidental oral exposure or injection, seek medical attention. Caution should be used while handling and using filled syringes.

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

The material safety data sheet (MSDS) contains more detailed occupational safety information.

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

Note to Physician: This product contains an alpha$_2$-adrenergic antagonist.

5. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that ANTISEDAN when used under the labeled conditions of use is safe and effective. ANTISEDAN is indicated for the reversal of the sedative and analgesic effects of DEXDOMITOR (dexmedetomidine hydrochloride), and DOMITOR (medetomidine hydrochloride) in dogs.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is needed to determine when a dog should be reversed from the sedative effects of the prescription drugs, DEXDOMITOR and DOMITOR.

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of approval. The three years of marketing exclusivity applies only to the new indication for which this supplement is approved. The supplemental application contains substantial evidence of the effectiveness of the drug involved, and studies of animal safety, that were

required for the approval of the application, and were conducted or sponsored by the applicant.

According to the Center's supplemental approval policy (21 CFR 514.106), this is a Category II change. The approval of this change is not expected to have any adverse effect on the safety or effectiveness of this new animal drug. Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.

ANTISEDAN is under the following U.S. patent numbers:

U.S. Patent Number	Date of Expiration
4,689,339	August 6, 2010
4,933,359	May 14, 2007

6. ATTACHMENTS:

Facsimile labeling is attached as indicated below:

Package insert
Carton
Vial
Shipping carton