Date of Approval: December 1, 2006

FREEDOM OF INFORMATION SUMMARY

NADA 141-267

DEXDOMITOR

(dexmedetomidine hydrochloride)

DEXDOMITOR is indicated for use as a sedative and analgesic in dogs to facilitate clinical examinations, clinical procedures, minor surgical procedures, and minor dental procedures. DEXDOMITOR is also indicated for use as a preanesthetic to general anesthesia.

Sponsored by:
Orion Corporation
Orionintie 1,
02200 Espoo,
Finland

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1. GENERAL INFORMATION:

a.	File Number:	NADA 141267
b.	Sponsor:	Orion Corporation, Orionintie 1, 02200 Espoo, Finland Drug Labeler Code: 052483
c.	Established Name:	dexmedetomidine hydrochloride
d.	Proprietary Name:	DEXDOMITOR
e.	Dosage Form:	sterile injectable solution
f.	How Supplied:	10 mL, multidose vials
g.	How Dispensed:	Rx
h.	Amount of Active Ingredients:	each mL contains 0.5 mg dexmedetomidine hydrochloride
i.	Route of Administration:	Intravenous (IV) or intramuscular (IM)
j.	Species/Class:	dog
k.	Recommended Dosage:	**Sedation and Analgesia Dose:** The dexmedetomidine intravenous (IV) dose is 375 mcg per square meter of body surface area. The dexmedetomidine intramuscular (IM) dose is 500 mcg per square meter of body surface area. **Preanesthetic Dose:** The dexmedetomidine intramuscular (IM) doses are 125 mcg/m^2 or 375 mcg/m^2 of body surface area. The choice of preanesthetic dose depends on the duration and severity of the procedure, as well as the anesthetic regimen.

The following dosing tables should be used to determine the correct dexmedetomidine IV or IM dosage for sedation and analgesia (Table 1) and for preanesthesia (Table 2), and show the volume (mL) and the mcg per kilogram (mcg/kg) doses for different body weights. **Note that the mcg/kg dosage <u>decreases</u> as body weight <u>increases</u>.** For example, dogs weighing 2 kg are dosed at 30 mcg/kg dexmedetomidine IV, compared to dogs weighing 80 kg that receive a lower mcg/kg dose of 9 mcg/kg. It is recommended that dogs be fasted for 12 hours before treatment with DEXDOMITOR. Following injection of DEXDOMITOR, the dog should be allowed to rest quietly for 15 minutes.

Table 1: SEDATION/ANALGESIA DOSE TABLE: Intravenous (IV) and intramuscular (IM) dosing on the basis of body weight

Sedation/Analgesia					
Dog Weight		**Dexmedetomidine 375 mcg/m^2 IV**		**Dexmedetomidine 500 mcg/m^2 IM**	
lbs	**kg**	**mcg/kg**	**DEXDOMITOR, mL**	**mcg/kg**	**DEXDOMITOR, mL**
4-7	2-3	28.1	0.12	40.0	0.15
7-9	3-4	25.0	0.15	35.0	0.20
9-11	4-5	23.0	0.20	30.0	0.30
11-22	5-10	19.6	0.29	25.0	0.40
22-29	10-13	16.8	0.38	23.0	0.50
29-33	13-15	15.7	0.44	21.0	0.60
33-44	15-20	14.6	0.51	20.0	0.70
44-55	20-25	13.4	0.60	18.0	0.80
55-66	25-30	12.6	0.69	17.0	0.90
66-73	30-33	12.0	0.75	16.0	1.00
73-82	33-37	11.6	0.81	15.0	1.10
82-99	37-45	11.0	0.90	14.5	1.20
99-110	45-50	10.5	0.99	14.0	1.30
110-121	50-55	10.1	1.06	13.5	1.40
121-132	55-60	9.8	1.13	13.0	1.50
132-143	60-65	9.5	1.19	12.8	1.60
143-154	65-70	9.3	1.26	12.5	1.70
154-176	70-80	9.0	1.35	12.3	1.80
>176	>80	8.7	1.42	12.0	1.90

Table 2: PREANESTHESIA DOSE TABLE: Intramuscular (IM) dosing on the basis of body weight.

Preanesthesia					
Dog Weight		**Dexmedetomidine 125 mcg/m^2 IM**		**Dexmedetomidine 375 mcg/m^2 IM**	
lbs	**kg**	**mcg/kg**	**DEXDOMITOR, mL**	**mcg/kg**	**DEXDOMITOR, mL**
4-7	2-3	9.4	0.04	28.1	0.12
7-9	3-4	8.3	0.05	25.0	0.15
9-11	4-5	7.7	0.07	23.0	0.20
11-22	5-10	6.5	0.10	19.6	0.29
22-29	10-13	5.6	0.13	16.8	0.38
29-33	13-15	5.2	0.15	15.7	0.44
33-44	15-20	4.9	0.17	14.6	0.51
44-55	20-25	4.5	0.20	13.4	0.60
55-66	25-30	4.2	0.23	12.6	0.69
66-73	30-33	4.0	0.25	12.0	0.75
73-82	33-37	3.9	0.27	11.6	0.81
82-99	37-45	3.7	0.30	11.0	0.90
99-110	45-50	3.5	0.33	10.5	0.99
110-121	50-55	3.4	0.35	10.1	1.06
121-132	55-60	3.3	0.38	9.8	1.13
132-143	60-65	3.2	0.40	9.5	1.19
143-154	65-70	3.1	0.42	9.3	1.26
154-176	70-80	3.0	0.45	9.0	1.35
>176	>80	2.9	0.47	8.7	1.42

l. Pharmacological Category: alpha$_2$-adrenoreceptor agonist

m. Indications: DEXDOMITOR is indicated for use as a sedative and analgesic in dogs to facilitate clinical examinations, clinical procedures, minor surgical procedures, and minor dental procedures. DEXDOMITOR is also indicated for use as a preanesthetic to general anesthesia.

2. EFFECTIVENESS:

a. Dosage Characterization:

Sedation and analgesia indication

Dexmedetomidine is the dextrorotary enantiomer of the approved racemic compound medetomidine. The results of the following study demonstrate that the pharmacological activity of medetomidine is primarily attributable to its dextrorotary enantiomer, dexmedetomidine. This study also shows that sedative and analgesic effects of dexmedetomidine are dose dependent for dexmedetomidine doses in the proposed dosage range.

Title: Kuusela E, Raekallio M, Anttila M, et al. Clinical Effects And Pharmacokinetics Of Medetomidine And Its Enantiomers In Dogs. *J Vet Pharmacol Therap* 2000; 23:15-20. Faculty of Veterinary Medicine, Department of Clinical Sciences, Hämeentie 57, University of Helsinki, 00014 Finland.

The masked, single-sequence, six-period study (placebo control) evaluated the clinical effects of the following dose groups (IV bolus) in six beagle dogs:

Medetomidine (40 mcg/kg)
Levomedetomidine (20 mcg/kg)
Levomedetomidine (10 mcg/kg)
Dexmedetomidine (20 mcg/kg)
Dexmedetomidine (10 mcg/kg)
Saline placebo

Sedative and analgesic effects (withdrawal reflex) were evaluated at 0, 10, 20, 40, 60, 90, and 120 minutes. Peak sedatory effects were clinically similar between medetomidine (40 mcg/kg), and dexmedetomidine (20 mcg/kg). The levomedetomidine isomer caused no apparent sedation, no effects on cardiorespiratory parameters, and no apparent analgesic effect.

Study conclusion: Dose dependent sedation and analgesic effects were due to dexmedetomidine and are clinically comparable to the effects of medetomidine.

The currently approved dosage for medetomidine (DOMITOR, NADA 140-999) is 750 mcg IV or 1000 mcg IM per square meter of body surface. Therefore, the following dexmedetomidine dosages are one half the currently approved dosage for racemic medetomidine (**Note:** the concentration of dexmedetomidine [0.5 mg/mL] is half that of medetomidine [1 mg/mL]; therefore, the dosage volumes are the same for both products).

The dexmedetomidine intravenous (IV) dosage is 375 mcg per square meter of body surface area (9 to 30 mcg/kg*).

The dexmedetomidine intramuscular (IM) dosage is 500 mcg per square meter of body surface area (12 to 40 mcg/kg*).

***Note that the mcg/kg dosage <u>decreases</u> as body weight increases**. For example, dogs weighing 2 kg are dosed at 30 mcg/kg dexmedetomidine IV, compared to dogs weighing 80 kg that are dosed at 9 mcg/kg.

Dosage tables (see Recommended Dosage under the General Information section of the FOI Summary) should be used to determine the correct dexmedetomidine IV or IM dosage on the basis of volume (mL) or mcg per kilogram (mcg/kg) of body weight.

<u>Preanesthesia indication</u>

A preanesthesia dosage of dexmedetomidine was evaluated in one published study on dexmedetomidine:

Title: Kuusela E, Vainio O, Short CE, et al. A comparison of propofol infusion and propofol/isoflurane anesthesia in dexmedetomidine premedicated dogs. *J Vet Pharmacol Therap* 2003;26:199-204. Department of Clinical Veterinary Sciences, University of Helsinki, 00014 Finland.

In this laboratory study, six beagle dogs were included twice in each of the following three treatment groups with at least 2 weeks between treatments:

1. Dexmedetomidine (10 mcg/kg [250 mcg/m^2] IM) (n = 12).
2. Dexmedetomidine (10 mcg/kg [250 mcg/m^2] IM) + propofol induction + propofol infusion (200 mcg/kg/min) for maintenance of anesthesia for 60 minutes (n = 12).
3. Dexmedetomidine (10 mcg/kg [250 mcg/m^2] IM) + propofol induction + isoflurane (1.0% end-tidal) for maintenance of anesthesia for 60 minutes (n = 12).

Dogs were premedicated with dexmedetomidine 50 minutes prior to induction of anesthesia. Time to sternal recumbency after dexmedetomidine premedication was recorded. The dose of propofol required for satisfactory intubation was recorded. Rectal temperature, heart rate, arterial blood pressure, and respiratory rate were recorded before induction, 2, 15, 30, 45, and 60 minutes after induction, after extubation, 90, 120, 150, 180, 210, and 240 minutes after induction. Recovery times from the end of anesthesia to extubation, first head lift, and first time standing were recorded.

Dexmedetomidine at 250 mcg/m^2 IM resulted in smooth onset of sternal recumbency in all dogs at a mean time of 12 minutes after injection. Induction was achieved with an average dose of 2.0 mg/kg of propofol (range 0.9 to 2.9 mg/kg), demonstrating the marked dose sparing effect of dexmedetomidine on induction drug requirements. Respiratory depression was more profound in dogs that received dexmedetomidine and propofol induction/propofol maintenance anesthesia compared to dexmedetomidine and propofol induction/isoflurane maintenance anesthesia. Compared to dexmedetomidine alone or with propofol

induction/propofol maintenance anesthesia, heart rate was significantly higher and blood pressure was significantly lower during the 60 minute anesthesia for dogs that had received the dexmedetomidine + propofol + isoflurane treatment. Recovery time was longest for dogs treated with dexmedetomidine and propofol induction/propofol maintenance anesthesia.

Conclusion: Premedication with dexmedetomidine (250 mcg/m^2, IM) lowered propofol requirements (2.0 mg/kg) for smooth induction of anesthesia.

Based on dexmedetomidine's dose dependent effects, the following IM preanesthetic doses of dexmedetomidine were chosen for field study investigation (see Substantial Evidence of Effectiveness: Preanesthesia Field Study below).

125 mcg/m^2 of body surface (approximately 3.5 to 7 mcg/kg*). This is appropriate for minor procedures requiring anesthesia.

375 mcg/m^2 of body surface (approximately 10 to 20 mcg/kg*) is appropriate for longer procedures or for surgical procedures resulting in greater postoperative pain.

***Note that the mcg/kg dosage <u>decreases</u> as body weight increases.** Dosage tables (see Recommended Dosage under the General Information section of the FOI Summary) should be used to determine the correct dexmedetomidine IM dosage on the basis of volume (mL) or mcg per kilogram (mcg/kg) of body weight.

b. Substantial Evidence of Effectiveness:

Sedation and analgesia indication

1. Type of study: field study

2. Investigators:

Clifford E. Aldermann, VedMed, CertVD., MRCVS Gloucester, United Kingdom	Gavin A. T. Dalton-Morgan, BVMS., MRCVS Bristol, United Kingdom
David P. Fisher, VetMed., CertSAC., MRCVS Worcester, United Kingdom	Patrick Von Heimendahl, Med Vet (Berlin), MRCVS Cambridge, United Kingdom
David Holmes, BVSc., MRCVS Nr. Bristol, United Kingdom	Elizabeth A. Watkins, BVSc., MRCVS Nr. Bristol, United Kingdom
Susan P. Yeo, BVetMed., PhD., MRCVS Nr. Bristol, United Kingdom	Andreas Böhm, Dr. Med. Vet. Bremen, Germany
Sibylle Lutz, Dr. Med. Vet. München, Germany	Birgit Kraus Dr. Med. Vet. Neubiberg, Germany
Karin Meier, Dr. Med. Vet. München, Germany	Petra Wittmann, Dr. Med. Vet. München, Germany

3. General design:

(a) *Purpose:*

The objective of this study was to evaluate the sedative and analgesic effects of dexmedetomidine, comparing them to those of the active control, medetomidine. The study also recorded adverse events due to the administration of dexmedetomidine, comparing their frequency with those produced by the approved drug medetomidine (NADA 140-999).

(b) *Test Animals:*

A total of 213 dogs were enrolled, ranging in age between 16 weeks and 16 years of age, and in size between 2.2 kg (5 lb) and 64 kg (141 lb) in body weight. One hundred and fifty-seven pure bred dogs were represented; remaining animals were mixed breed dogs. Participating dogs were classified as American Society of Anesthesiologists Class I (ASA normal healthy patient with no detectable disease) or Class II (slight or moderate systemic disease causing no obvious incapacity).

The dogs were randomly assigned to eight treatment groups: dexmedetomidine IV (with or without atipamezole) or medetomidine IV, (with or without atipamezole), or dexmedetomidine IM (with or without atipamezole) or medetomidine IM (with or without atipamezole).

Ninety-three dogs were used in the statistical analysis. Protocol deviations resulted in 13 dogs being eliminated from the original 213 dogs. Half of the remaining dogs (n = 100) received a reversal agent following completion of the procedure; therefore, observations for these dogs ceased immediately following administration of the reversal agent, and they were excluded from the statistical analysis. Only results from dogs that were evaluated for the entire 180 minute observation period were statistically analyzed. Of the remaining 100 dogs, seven were from sites with fewer than four dogs. Sites with fewer than four dogs were eliminated from the statistical analysis because they did not allow for the replication of complete blocks that included treatment (dexmedetomidine or medetomidine) and administration route (IV or IM). Therefore, 93 dogs were included in the statistical analysis of effectiveness (as reflected in the tables in the Results section).

(c) *Control Drug:*

The active control treatment was medetomidine in the approved formulation of DOMITOR 1 mg/mL solution for injection.

(d) *Reason for treatment:* All dogs were presented at the clinic for minor clinical examinations and/or procedures requiring restraint, sedation, or sedation and analgesia.

Procedures by numbers of dogs:

Procedure performed	**N**	**Procedure performed**	**N**
Anal sac treatment	4	Laryngoscopy	1
Anal sac treatment, skin tumor removal	1	Microchip removal	1
Applying a cast	1	Ophthalmic	1
Bathing	1	Ophthalmic, radiography	1
Clipping claws	4	Otitis treatment	12
Clipping and grooming	1	Placing of feeding tube	1
Clipping hair from sore perineum	1	Radiography	44
Curettage of third eyelid	1	Radiography, clipping claws	1
Cutting back torn nail	1	Radiography, cryosurgery of wart on tail	1
Suture removal	1	Radiography, fine needle aspiration	1
Dental	61	Radiography, hips	1
Dental, anal sac treatment	4	Radiography, punch biopsy of dorsal skin	1
Dental, brushing, inserting microchip, clipping	1	Radiography, tattooing	1
Dental, clipping claws	2	Radiography, tattooing, lancing abscess	1
Dental, lancing abscess	1	Radiography, ultrasound	1
Dental, ophthalmic	2	Enema	2
Dental, ophthalmic, otitis treatment, skin tumor removal	1	Removal of drain	1
Dental, radiography	4	Removal of warts	2
Dental, skin tumor removal	7	Removal of foreign body from foot pad	1
Dental, skin tumor removal, tattooing	1	Skin biopsy	2
Dental, tattooing	1	Skin scrapings	8
Examination of ear canal	1	Skin scrapings + ear cleaning	1
Examination of oronasal fistula	1	Skin tumor removal	5
Examination of the stifle joint	1	Suturing wounds	2
Extraction of sutures after otitis surgery	1	Tattooing	4
Fine needle aspiration	2	Tattooing, curettage of third eyelid	1
Flushing after bone constipation	1	Tattooing, wound debridement, suturing wounds	1
Intra-articular injection	1	Trimming and removal of torn dew claw	1
Lancing abscess	2	Wound debridement	2
		Total number of dogs	**213**

(e) *Dosage form:* Injectable solution, 0.5 mg dexmedetomidine/ mL. The formulation used in this study contained 1.4 mg/mL methylparaben. This differs from the intended market formulation that contains 1.6 mg/mL methylparaben, but had no impact on the results of the study.

(f) *Routes of administration:* intravenous (IV) or intramuscular (IM)

(g) *Dosages:*

DEXDOMITOR:
Intravenous route of administration:
375 mcg/square meter body surface area

Intramuscular route of administration:
500 mcg/square meter body surface area

DOMITOR:
Intravenous route of administration:
750 mcg/square meter body surface area

Intramuscular route of administration:
1000 mcg/square meter body surface area

(h) *Test duration*: October 15, 1999 to June 28, 2000

(i) *Variables:*

Duration and quality of sedation:
Posture
Response to noise
Muscle tone of jaw
Ability to perform procedures

An overall subjective evaluation of the quality of sedation was also performed by the investigator at the end of the study.

Duration and quality of analgesia:

Pedal reflex induced by toe pinching

An overall subjective evaluation of the quality of analgesia was also performed by the investigator at the end of the study.

Respiratory and cardiovascular parameters:
appearance of mucous membranes
heart rate (bpm)
heart rhythm
respiratory rate (breaths/minute)
rectal temperature

Tolerance during injection was assessed (mild, moderate, or severe reaction).

Adverse events were monitored throughout the study.

4. Statistical methods: Continuous variables were analyzed using mixed effect modeling and it was of primary interest to examine if there were significant treatment by time effects or treatment effects. Additionally, means and ranges of continuous variables over time were stratified by treatment and route of administration. Responses for categorical variables were stratified by treatment and route of administration, tabulated, and presented as frequency tables. Ordinal categorical variables were analyzed using Mantel Haenszel tests for association. Furthermore, categorical variables were analyzed comparing the two treatment groups stratified by the route of administration. Significant results of tests comparing the two treatment groups are presented, with the frequency tables of categorical variables in which treatment effects were detected.

5. Results:

(a) Duration and quality of sedation/analgesia: Table 1 summarizes the times for peak sedative and analgesic effects for all variables in IV and IM groups (dexmedetomidine and medetomidine):

Table 1:

Variable	**Peak effect (minutes)**
Posture	15 min in IV and 30 min in IM groups
Response to noise	15 min in IV and 30 min in IM groups
Muscle tone of jaw	15 min in IV and 15-30 min in IM groups
Ability to perform procedure	15-30 min in IV and 30 min in IM groups
Pedal reflex	15-30 min in IV and 15-30 min in IM groups

DEXDOMITOR induced sedation and analgesia after both IV and IM administration. The onset of sedation was evident within five minutes after administration, regardless of route of administration. The peak effect occurred at approximately 15 minutes after IV administration, and at approximately 30 minutes after IM administration.

●Posture

Table 2a: Number of dogs with each posture response over time for the IV route:

DESCRIPTION OF POSTURE OVER TIME									
Posture	Drug	Time (minutes after treatment)							
		0	5	15	30	60	90	120	180
normal	DEXDOMITOR IV	22	0	0	0	0	0	1	10
	DOMITOR IV	21	0	0	0	0	1	3	9
standing sedation	DEXDOMITOR IV	0	4	0	1	2	7	13	11
	DOMITOR IV	2	3	1	1	5	7	8	12
recumbent, able to achieve sternal	DEXDOMITOR IV	1	4	5	2	9	9	6	0
	DOMITOR IV	0	7	5	4	4	9	11	2
recumbent, difficulty rising	DEXDOMITOR IV	0	3	2	7	6	4	0	0
	DOMITOR IV	0	4	3	5	6	2	0	0
unable to rise	DEXDOMITOR IV	0	12	16	12	4	1	1	0
	DOMITOR IV	0	9	14	13	8	4	1	0
Number of dogs	DEXDOMITOR IV	23	23	23	22	21*	21*	21*	21*
	DOMITOR IV	23	23	23	23	23	23	23	23

*Asterisks indicate missing values.

Intravenous route: Approximately half the dogs were not able to rise after 5 minutes. At 15 minutes after treatment the peak effect was seen. After 30 minutes animals started to recover and by 180 minutes after treatment, all had risen, and approximately half showed normal behavior.

Table 2b: Number of dogs with each posture response over time for the IM route:

DESCRIPTION OF POSTURE OVER TIME									
Posture	Drug	Time (minutes after treatment)							
		0	5	15	30	60	90	120	180
normal	DEXDOMITOR IM	23	5	1	0	0	0	1	1
	DOMITOR IM	23	3	1	1	1	1	1	3
standing sedation	DEXDOMITOR IM	0	8	2	3	3	3	4	13
	DOMITOR IM	1	10	1	3	2	6	12	16
recumbent, able to achieve sternal	DEXDOMITOR IM	0	8	8	4	7	11	12	6
	DOMITOR IM	0	5	9	5	7	9	6	4
recumbent, difficulty rising	DEXDOMITOR IM	0	1	4	4	3	4	4	1
	DOMITOR IM	0	2	5	6	8	4	2	0
unable to rise	DEXDOMITOR IM	0	1	8	12	10	5	2	2
	DOMITOR IM	0	4	8	9	6	4	3	1
Number of dogs	DEXDOMITOR IM	23	23	23	23	23	23	23	23
	DOMITOR IM	24	24	24	24	24	24	24	24

Intramuscular route: Approximately one-third of the dogs were not able to rise after 15 minutes. By 30 minutes the peak effect was seen. After 180 minutes, more than half of the dogs were sedated but could stand; some dogs were still unable to rise at 180 minutes.

●Response to noise: Noise was generated by dropping metal artery forceps onto a metal surface in close proximity to, but out of sight of the animal (an audible noise that would normally stimulate the animal to respond).

Table 3a: Number of dogs with each response to noise over time for the IVroute:

DESCRIPTION OF RESPONSE TO NOISE OVER TIME									
Response to noise	Drug	Time (minutes after treatment)							
		0	5	15	30	60	90	120	180
sensitive	DEXDOMITOR IV	2	1	2	2	1	0	0	1
	DOMITOR IV	6	0	1	1	1	1	2	1
normal	DEXDOMITOR IV	20	3	1	0	3	5	9	17
	DOMITOR IV	15	2	0	1	6	8	8	16
weak	DEXDOMITOR IV	1	8	5	11	12	14	11	3
	DOMITOR IV	1	10	6	8	8	10	11	4
no reaction	DEXDOMITOR IV	0	11	15	9	5	2	1	0
	DOMITOR IV	1	11	16	13	8	4	2	2
Number of dogs	DEXDOMITOR IV	23	23	23	22*	21*	21*	21*	21*
	DOMITOR IV	23	23	23	23	23	23	23	23

*Asterisks indicate missing values.

Intravenous route: At 15 minutes after treatment, approximately three-quarters of the animals in showed no response to noise. By 180 minutes, most dogs showed normal responses.

Table 3b: Number of dogs with each response to noise over time for the IM route:

DESCRIPTION OF RESPONSE TO NOISE OVER TIME									
Response to noise	Drug	Time (minutes after treatment)							
		0	5	15	30	60	90	120	180
sensitive	DEXDOMITOR IM	3	2	2	1	0	0	1	2
	DOMITOR IM	5	2	2	1	1	1	2	2
normal	DEXDOMITOR IM	20	15	4	3	4	5	5	10
	DOMITOR IM	19	6	2	1	1	5	7	12
weak	DEXDOMITOR IM	0	5	10	9	9	12	11	9
	DOMITOR IM	0	10	12	11	14	13	12	9
no reaction	DEXDOMITOR IM	0	1	7	10	10	6	6	2
	DOMITOR IM	0	5	7	10	7	4	2	0
Number of dogs	DEXDOMITOR IM	23	23	23	23	23	23	23	23
	DOMITOR IM	24	23*	23*	23*	23*	23*	23*	23*

*Asterisks indicate missing values.

Intramuscular route: Most dogs showed weak or no response to noise after 15 minutes; peak effects were seen at 30 minutes. After 180 minutes, approximately half of the dogs were normal.

●Jaw muscle tone

Table 4a: Number of dogs with each jaw tone response over time for the IV route:

DESCRIPTION OF JAW TONE OVER TIME									
Jaw tone	Drug	Time (minutes after treatment)							
		0	5	15	30	60	90	120	180
normal	DEXDOMITOR IV	21	1	0	1	2	7	10	18
	DOMITOR IV	22	1	0	1	3	13	18	20
slightly weak	DEXDOMITOR IV	2	4	4	6	11	10	10	3
	DOMITOR IV	1	3	2	2	8	3	3	3
weak	DEXDOMITOR IV	0	9	5	7	6	4	1	0
	DOMITOR IV	0	16	14	14	10	7	2	0
absent	DEXDOMITOR IV	0	9	14	8	2	0	0	0
	DOMITOR IV	0	3	7	6	2	0	0	0
Number of dogs	DEXDOMITOR IV	23	23	23	22*	21*	21*	21*	21*
	DOMITOR IV	23	23	23	23	23	23	23	23

*Asterisks indicate missing values.

Intravenous route: The maximum effect on muscle tone of jaw was seen at 15 minutes after treatment. After 180 minutes, most dogs were normal.

Table 4b: Number of dogs with each jaw tone response over time for the IM route:

DESCRIPTION OF JAW TONE OVER TIME									
Jaw tone	Drug	Time (minutes after treatment)							
		0	5	15	30	60	90	120	180
normal	DEXDOMITOR IM	21	8	2	2	2	3	7	15
	DOMITOR IM	22	8	3	4	8	12	15	18
slightly weak	DEXDOMITOR IM	1	11	7	6	6	12	11	6
	DOMITOR IM	0	9	6	3	3	7	6	4
weak	DEXDOMITOR IM	1	2	10	9	10	8	4	1
	DOMITOR IM	0	5	8	12	12	5	2	1
absent	DEXDOMITOR IM	0	2	4	6	5	0	1	1
	DOMITOR IM	0	1	7	5	1	0	0	0
Number of dogs	DEXDOMITOR IM	23	23	23	23	23	23	23	23
	DOMITOR IM	22*	23*	24	24	24	24	23*	23*

*Asterisks indicate missing values.

Intramuscular route: The maximum effect on muscle tone of jaw was seen at 30 minutes after treatment (in approximately two-thirds of the dogs). By 180 minutes after treatment, two-thirds to three-quarters of the dogs were normal.

●Ability to perform procedure

Procedures could not be performed in seven dogs treated with dexmedetomidine and in one dog treated with medetomidine.

(b) Duration and quality of analgesia:

●Pedal reflex (toe pinch): The scores were used in response to extension of a hind leg and pinching of a digit or the interdigital webbing of the extended limb. The same limb and site for the application of the nociceptive pressure was used throughout the periods of assessment for a given animal.

Table 5a: Number of dogs with each pedal reflex over time for the IV route:

DESCRIPTION OF PEDAL REFLEX OVER TIME									
Pedal reflex	Drug	Time (minutes after treatment)							
		0	5	15	30	60	90	120	180
hyper-sensitive	DEXDOMITOR IV	1	0	1	1	0	1	2	3
	DOMITOR IV	2	0	0	0	0	0	1	0
normal	DEXDOMITOR IV	19	1	0	0	1	5	9	13
	DOMITOR IV	21	0	0	0	3	5	12	17
slightly impaired	DEXDOMITOR IV	3	1	0	3	7	8	4	1
	DOMITOR IV	0	7	1	1	6	9	5	5
clearly weak	DEXDOMITOR IV	0	4	3	2	4	1	1	1
	DOMITOR IV	0	7	8	8	8	3	3	1
absent	DEXDOMITOR IV	0	17	19	16	8	5	4	2
	DOMITOR IV	0	9	14	14	6	6	2	0
Number of dogs	DEXDOMITOR IV	23	23	23	22*	20*	20*	20*	20*
	DOMITOR IV	23	23	23	23	23	23	23	23

* Asterisks indicate missing values.

Intravenous route: More dogs in the dexmedetomidine group presented an absent pedal reflex after 5 minutes compared with the medetomidine group. By 30 minutes, maximum analgesia had been achieved (measured as the response to toe pinch). By 60 minutes, analgesia had diminished in two-thirds of the dogs, and was totally absent in nearly all dogs at 180 minutes.

Table 5b: Number of dogs with each type of pedal reflex over time for the IM route:

DESCRIPTION OF PEDAL REFLEX OVER TIME									
Pedal reflex	Drug	Time (minutes after treatment)							
		0	5	15	30	60	90	120	180
hyper-sensitive	DEXDOMITOR IM	2	0	1	0	2	2	2	2
	DOMITOR IM	2	0	2	0	0	0	0	0
normal	DEXDOMITOR IM	20	11	2	3	3	2	5	12
	DOMITOR IM	22	8	2	3	6	9	10	18
slightly impaired	DEXDOMITOR IM	0	7	7	3	3	10	8	7
	DOMITOR IM	0	7	5	4	6	8	11	6
clearly weak	DEXDOMITOR IM	1	3	5	7	6	6	5	1
	DOMITOR IM	0	7	6	7	7	4	1	0
absent	DEXDOMITOR IM	0	2	8	10	9	3	3	1
	DOMITOR IM	0	2	9	10	5	3	2	0
Number of dogs	DEXDOMITOR IM	23	23	23	23	23	23	23	23
	DOMITOR IM	24	24	24	24	24	24	24	24

Intramuscular route: The weakening of pedal reflex was comparable in both groups with peak effect at 30 minutes after treatment.

●Results of the overall, subjective investigator evaluation of sedation and analgesia:

Intravenous and intramuscular routes: For the IV dexmedetomidine groups, sedation was evaluated as good or excellent in approximately two-thirds of the animals. For the IV medetomidine groups, approximately three-quarters were evaluated as good or excellent. Approximately two-thirds of all dogs treated IM were scored as good or excellent.

(c) Physiological variables:

●Mucous membranes were normal or pale in most cases after administration of DEXDOMITOR or DOMITOR from treatment until the end of the study (180 minutes).

Table 6a: Number of dogs with each type of mucous membrane appearance over time for the IV route:

DESCRIPTION OF MUCOUS MEMBRANE APPEARANCE OVER TIME									
Mucous membrane	Drug	Time (minutes after treatment)							
		0	5	15	30	60	90	120	180
normal	DEXDOMITOR IV	20	11	13	13	15	15	18	21
	DOMITOR IV	21	14	12	15	17	18	21	21
pale	DEXDOMITOR IV	2	10	8	7	5	4	2	0
	DOMITOR IV	1	5	8	7	5	4	1	1
pale (slightly cyanotic)	DEXDOMITOR IV	0	2	2	2	1	2	1	0
	DOMITOR IV	0	4	3	1	1	1	0	0
cyanotic	DEXDOMITOR IV	0	0	0	0	0	0	0	0
	DOMITOR IV	0	0	0	0	0	0	0	0
hyperemic	DEXDOMITOR IV	1	0	0	0	0	0	0	0
	DOMITOR IV	1	0	0	0	0	0	1	1
Number of dogs	DEXDOMITOR IV	23	23	23	22*	21*	21*	21*	21*
	DOMITOR IV	23	23	23	23	23	23	23	23

* Asterisks indicate missing values.

Table 6b: Number of dogs with each type of mucous membrane appearance over time for the IM route:

DESCRIPTION OF MUCOUS MEMBRANE APPEARANCE OVER TIME									
Mucous membrane	Drug	Time (minutes after treatment)							
		0	5	15	30	60	90	120	180
normal	DEXDOMITOR IM	22	15	16	13	15	20	18	21
	DOMITOR IM	21	17	15	17	19	19	20	20
pale	DEXDOMITOR IM	1	6	5	5	3	1	3	2
	DOMITOR IM	1	4	7	4	3	5	3	2
pale (slightly cyanotic)	DEXDOMITOR IM	0	2	2	5	5	1	2	0
	DOMITOR IM	0	1	1	3	2	0	1	1
cyanotic	DEXDOMITOR IM	0	0	0	0	0	1	0	0
	DOMITOR IM	0	1	1	0	0	0	0	0
hyperemic	DEXDOMITOR IM	0	0	0	0	0	0	0	0
	DOMITOR IM	2	1	0	0	0	0	0	1
Number of dogs	DEXDOMITOR IM	23	23	23	23	23	23	23	23
	DOMITOR IM	24	24	24	24	24	24	24	24

- The respiratory rate (RR) decreased markedly within 5 minutes (IV) and within 15 minutes (IM), returning toward baseline values by 180 minutes.

Table 7: Mean respiratory rate over time (range in parentheses):

Route	Drug	Number of dogs	Time							
			0	5	15	30	60	90	120	180
IV	DEXDOMITOR	23	35.1 (12-140)	22.7 (3-52)	17.5 (9-32)	17.3 (4-38)[1]	17.3 (8-52)[2]	15.6 (8-28)[2]	17.0 (7-32)[2]	19.8 (12-36)[2]
	DOMITOR	23	35.4 (16-120)[2]	21.8 (9-44)	23.6 (7-60)	19.4 (6-44)	20.3 (7-60)	19.6 (5-60)	21.2 (8-80)	23.7 (7-88)
IM	DEXDOMITOR	23	39.9 (20-90)[2]	30.0 (12-80)	27.1 (10-108)	19.0 (8-50)	17.4 (7-42)	18.2 (9-36)	17.5 (5-42)	19.9 (10-48)
	DOMITOR	24	52.9 (12-200)	31.3 (9-120)	21.9 (7-40)[1]	21.5 (4-128)	18.0 (4-84)	16.4 (8-45)	16.4 (4-40)	17.6 (8-40)

[1,2]Superscript 1 indicates that one dog had an unrecorded value for that timepoint; superscript 2 indicates that two dogs had an unrecorded value for that timepoint.

●The heart rate (HR) decreased after administration of DEXDOMITOR to approximately half of baseline values. HR returned toward, but did not reach, baseline values by 180 minutes.

Table 8: Mean heart rate over time (range in parentheses):

Route	Drug	Number of dogs	Time 0	5	15	30	60	90	120	180
IV	DEXDOMITOR	23	104.3 (60-150)	50.8 (12-110)	49.0 (28-96)	49.6 (28-90)[1]	50.8 (30-80)[2]	51.3 (32-108)[2]	51.4 (32-100)[2]	60.3 (32-120)[2]
	DOMITOR	23	111.3 (46-180)	59.0 (28-108)	52.1 (30-116)	53.8 (24-92)	52.0 (28-96)	52.1 (36-116)	56.9 (34-120)	63.1 (32-120)
IM	DEXDOMITOR	23	109.9 (56-148)	65.7 (36-112)	49.5 (30-84)	45.0 (32-76)	44.2 (28-72)	46.4 (27-92)	50.7 (36-80)	52.2 (24-106)
	DOMITOR	24	115.0 (56-180)	64.7 (28-160)	54.0 (32-108)	53.0 (28-140)[1]	50.4 (24-115)	51.8 (22-125)[1]	54.5 (20-138)[1]	61.3 (24-162)

[1,2]Superscript 1 indicates that one dog had an unrecorded value for that timepoint; superscript 2 indicates that two dogs had an unrecorded value for that timepoint.

●Cardiac rhythms were described using routine auscultation.

Table 9a: Number of dogs with each type of heart rhythm (auscultation) over time for IV route:

DESCRIPTION OF HEART RHYTHM OVER TIME									
Description of Heart Rhythm	Drug	Time (minutes after treatment) 0	5	15	30	60	90	120	180
Physiologic	DEXDOMITOR IV	20	7	7	7	10	10	9	11
	DOMITOR IV	20	6	6	6	7	7	9	11
Tachycardia	DEXDOMITOR IV	2	0	0	0	0	0	0	0
	DOMITOR IV	2	0	0	0	0	0	0	0
Bradycardia	DEXDOMITOR IV	1	16	16	15	11	11	12	9
	DOMITOR IV	1	15	15	15	15	15	14	12
Arrhythmia	DEXDOMITOR IV	0	0	0	0	0	0	0	1
	DOMITOR IV	0	2	2	2	1	1	0	0
Number of dogs	DEXDOMITOR IV	23	23	23	22*	21*	21*	21*	21*
	DOMITOR IV	23	23	23	23	23	23	23	23

* Asterisks indicate missing values.

Table 9b: Number of dogs with each type of heart rhythm (auscultation) over time for IM route:

DESCRIPTION OF HEART RHYTHM OVER TIME									
Description of Heart Rhythm	Drug	Time (minutes after treatment)							
		0	5	15	30	60	90	120	180
Physiologic	DEXDOMITOR IM	21	15	7	4	4	4	5	7
	DOMITOR IM	24	17	12	11	10	11	11	11
Tachycardia	DEXDOMITOR IM	2	0	0	0	0	0	0	0
	DOMITOR IM	0	0	0	0	0	0	0	0
Bradycardia	DEXDOMITOR IM	0	7	14	17	17	18	16	16
	DOMITOR IM	0	6	9	8	11	11	10	11
Arrhythmia	DEXDOMITOR IM	0	1	2	2	2	1	2	0
	DOMITOR IM	0	1	3	4	3	1	2	2
Number of dogs	DEXDOMITOR IM	23	23	23	23	23	23	23	23
	DOMITOR IM	24	24	24	23*	24	23*	23*	24

* Asterisks indicate missing values.

●Cardiac rhythm data were obtained by ECG for 4 medetomidine treated dogs: 2 received medetomidine by the IM route with subsequent atipamezole administration, 1 received medetomidine by the IM route without subsequent atipamezole administration, and 1 received the drug by the IV route without subsequent atipamezole administration. The frequency of arrhythmias observed by ECG follows:

Table 10:

Arrhythmias from ECG	Number of dogs (total dogs = 4)
Sinus arrest	4
Sinus bradycardia	3
Sinus pause	1
First degree AV block	3
Second degree AV block	2
Supraventricular premature complex	1 (transient)

The most noteworthy ECG finding was the frequent presence of abnormalities associated with depression of the heart rate and slowing of conduction.

Arrhythmias in general were associated with the administration of alpha$_2$-agonists, not the reversal agent. One dog treated with IM medetomidine showed four instances of sinus arrest 5 minutes after atipamezole administration; all other timepoints after atipamezole reversal were negative for arrhythmias.

●Body temperature decreased slowly to below pretreatment values during the 180 minute evaluation period. Dexmedetomidine IV caused a mean decrease in temperature of 2.1°F (from 101.4 to 99.3°F). Dexmedetomidine IM caused a mean decrease in temperature of 2.5°F

(from 101.6 to 99.1°F). Medetomidine IV caused a mean decrease in temperature of 2.0 °F (from 101.7 to 99.6°F). Medetomidine IM caused a mean decrease in temperature of 2.7 °F (from 101.7 to 99.0°F).

(d) Recovery: At 60 minutes after treatment, sedation and analgesia were still evident in most dogs. Between 60 and 180 minutes, dogs recovered from sedation and the analgesic effects of dexmedetomidine disappeared. By 180 minutes after IV administration of dexmedetomidine, most dogs had recovered. Recovery was slower following IM dexmedetomidine.

(e) Response to injection: All 213 dogs were evaluated for their response to injection. For IM dexmedetomidine, the response during injection was evaluated as excellent in 37 (of 54) dogs. For the medetomidine groups, the corresponding figure is 29 (of 54). Injection response using the IV route was evaluated as excellent in 46 (of 52) of the dexmedetomidine, and 47 (of 53) of the medetomidine treated dogs.

6. Adverse reactions:

A total of 213 dogs of 49 breeds, 16 weeks to 16 years old were included in the field safety clinical analysis. The following table shows the number of dogs displaying each adverse reaction. These observations reflect the pharmacological effects of the alpha$_2$-agonists and most of these observations were not reported as serious adverse reactions by the investigators.

Table 11:

Adverse reactions reported during field study		
	Dexmedetomidine Total n= 106	Medetomidine Total n=107
Arrhythmia, unspecified	19	16
1st or 2nd degree heart block	0	3*
Intermittent sinus arrest	0	4*
Bradycardia	1	1*
Apnea	1	0
Slow onset of sedation	1	1
Ineffectiveness (nonrecumbent)	3	2
Hypothermia	2	0
Prolonged recovery	1	4

*ECG recorded arrhythmia (see Cardiac rhythm section above)

Investigators reported 9 of these dogs as serious adverse reactions (5 received dexmedetomidine and 4 received medetomidine):

Following dexmedetomidine, atipamezole was administered for apnea (1 dog) and for prolonged hypothermia and prolonged recovery (2 dogs that were unable to rise at 180 minutes after sedative treatment). A fourth dog with severe bradycardia was treated with atropine and atipamezole. The fifth dog was reported as an adverse reaction due to gastric dilatation, resulting in surgery nine hours after receiving dexmedetomidine, and subsequent death. The adverse reaction was not considered drug related. The apneic dog received IV dexmedetomidine. Heart rate decreased from baseline 60 bpm to 32 bpm within 15 minutes and severe bradycardia was reported at 32 minutes. The duration of apnea was not recorded. The dog was intubated, given oxygen, and atipamezole IV. The dog recovered within 5 to 10 minutes. Dexmedetomidine was the cause of the adverse reaction.

Following medetomidine, one dog received atipamezole to reverse persistent bradycardia in conjunction with prolonged sedation. Two other dogs experienced prolonged recoveries. The fourth dog showed a slow onset of sedation, followed by slow recovery.

7. Conclusions:

The study showed that DEXDOMITOR administered at 375 mcg/m^2 by the intravenous (IV) or at 500 mcg/m^2 by the intramuscular (IM) route of administration induces effects suitable for use as a sedative and analgesic in dogs. The effects were similar to those induced by DOMITOR at approved doses. The rate and quality of recovery from sedation was satisfactory and consistent for dexmedetomidine IV or IM. Physiological effects and transient arrhythmias were acceptable for sedated dogs, and IM or IV injections were well-tolerated.

Preanesthesia indication

1. Type of study: field study

2. Investigators:

Sam Geller, VMD Quakertown Veterinary Hospital Quakertown, PA	Mark Lapierre, DVM North East Veterinary Hospital Greensboro, NC
Corinne Thomas, VMD Atglen Veterinary Hospital Christiana, PA	Chuck Miller, DVM Triangle Veterinary Hospital Durham, NC

3. General design:

(a) *Purpose:*

The main objectives of the study were to demonstrate the dose-sparing effect of dexmedetomidine at dose levels of 125 and 375 mcg/m^2 on the amount of propofol or thiopental needed for successful induction of anesthesia; to demonstrate a dose sparing effect of dexmedetomidine on the concentration of isoflurane required for maintenance anesthesia during a major procedure; to demonstrate an improvement in postoperative analgesia and pain control when dexmedetomidine is administered as a preanesthetic prior to minor or major procedures; and to confirm that the use of dexmedetomidine as a preanesthetic is safe under these conditions.

(b) *Test Animals:*

A total of 192 dogs were enrolled, ranging in age between 5 months and 15 years of age, and in size between 2 kg (4 lb) and 89 kg (196 lb) in body weight. Of the 43 dog breeds enrolled in the study, Labrador Retrievers and crossbreds were the most common. Participating dogs were classified as American Society of Anesthesiologists Class I (ASA normal healthy patient with no detectable disease) or Class II (slight or moderate systemic disease causing no obvious incapacity).

Dogs that were enrolled for minor (n = 96) or major (n = 96) clinical procedures were randomly assigned to 6 preanesthetic by induction drug treatment groups:

Procedure	*Preanesthetic-induction drug group*	*Randomized number of dogs*	*Preanesthetic dose level (mcg/m^2)*	*Induction drug*	*Maintenance anesthesia*
Minor	1	16	0 (saline)	propofol	-
	2	16	125	propofol	-
	3	16	375	propofol	-
	4	16	0 (saline)	thiopental	-
	5	16	125	thiopental	-
	6	16	375	thiopental	-
Major	1	16	0 (saline)	propofol	isoflurane
	2	16	125	propofol	isoflurane
	3	16	375	propofol	isoflurane
	4	16	0 (saline)	thiopental	isoflurane
	5	16	125	thiopental	isoflurane
	6	16	375	thiopental	isoflurane

Procedure types and frequency:

Minor procedures	**Number of dogs**
Anal sac expression and/or infusion	10
Dental: cleaning, scaling, polishing	17
Dental: tooth extraction	5
Ear cleaning and/or flushing	9
Growth, cyst, lump, wart removal and/or biopsy	30
Nail trimming	5
Radiographs and/or orthopedic examination	20
	Total = 96
Major procedures (isoflurane maintenance)	**Number of dogs**
Castration	28
Ovariohysterectomy	23
Umbilical hernia repair	1
Dental: cleaning, scaling, polishing	18
Dental: tooth extraction	1
Ear cleaning and/or flushing	1
Growth, cyst, lump, wart removal and/or biopsy	24
	Total = 96

Similar procedures were classified as major or minor because they differed in length, difficulty, and associated pain for each case. Major procedures required isoflurane maintenance for these reasons.

(c) *Control Drug:* The negative control treatment was saline.

(d) *Reason for treatment:* All dogs were presented at the clinic for minor or major clinical procedures requiring general anesthesia.

(e) *Dosage form:* Injectable solution, DEXDOMITOR 0.5 mg dexmedetomidine/mL, final market formulation.

(f) *Routes of administration:* intramuscular (IM)

(g) *Dosages:*

DEXDOMITOR: 125 or 375 mcg/square meter of body surface
Propofol: administered IV to effect
Thiopental: administered IV to effect
Isoflurane: administered by endotracheal tube to effect

(h) *Test duration*: October 07, 2003 to April 01, 2004

(i) *Variables:*

Amount of induction drug required for intubation

Concentration of isoflurane during major procedures

Duration and quality of analgesia:
Analgesia score (0 to 6) = pedal reflex induced by toe pinching (0 to 3) + response to palpation of the procedure site (0 to 3)

Quality of pain control:
Pain score (0 to 9) = relaxation score (0 to 3) + vocalization score (0 to 3) + activity score (0 to 3)

Quality of sedation:
Sedation score (0 to 10) = posture (0 to 4) + response to noise (0 to 3) + muscle tone of jaw (0 to 3)

Physiological parameters:
heart rate (beats/minute)
respiratory rate (breaths/minute)
heart rhythm
oxygen saturation (pulse oximetry)
rectal temperature (° F)

Time to extubation, sternal recumbency, and standing (from the end of the procedure)

Response to injection of the preanesthetic (none, slight, moderate, strong).

Adverse events were monitored throughout the study.

4. Statistical methods: Separate analyses were conducted for the minor and major procedures, respectively. Dose sparing effects were evaluated for propofol and thiopental separately. Continuous variables were analyzed using mixed effect modeling and it was of primary interest to examine if there were significant treatment effects. Additionally, means and ranges of continuous variables over time were stratified by treatment and induction drug. Responses for categorical variables were stratified by treatment and induction drug, tabulated, and presented as frequency tables. Ordinal categorical variables were analyzed using Fisher's exact tests for association.

5. Results:

(a) Induction drug dose sparing (amount of induction drug required for intubation): Compared to saline controls, induction drug requirements for intubation were reduced on average between 30 and 61%, depending on preanesthetic dose and on induction drug.

Table 1. Reduction (%) in the amount of induction drug required for intubation compared to saline controls:

Procedure	Dexmedetomidine dose (mcg/m^2)	Induction drug	
		Propofol	Thiopental
Minor	125	-30.1	-29.5
	375	-38.1	-43.3
Major	125	-36.2	-31.9
	375	-42.9	-61.4

(b) Maintenance anesthetic dose sparing (concentration of isoflurane during major procedures):
Compared to saline controls, mean isoflurane concentration during a major procedure was lower by 40-60% for dexmedetomidine-treated dogs depending on preanesthetic dose.

Table 2. Mean isoflurane concentration (%) during major procedures:

Procedure	Dexmedetomidine dose (mcg/m^2)	Induction drug	
		Propofol	Thiopental
Major			
	0	2.9	2.4
	125	1.8	1.6
	375	1.1	1.1

(c) Duration and quality of analgesia:
Compared to saline controls, mean postprocedural analgesia scores were greater (increased analgesia) for the 375 mcg/m^2 dose group, but not for the 125 mcg/m^2 dose group for both procedure groups.

Table 3. Mean analgesia score (0 to 6) during 0 to 4 hours after the procedure:

Procedure	Dexmedetomidine dose (mcg/m^2)	Induction drug	
		Propofol	Thiopental
Minor	0	3.5	3.5
	125	3.7	3.9
	375	4.3	4.7
Major			
	0	3.5	3.7
	125	3.3	3.9
	375	4.3	4.7

(d) Quality of pain control:

Compared to saline controls, mean postprocedural pain scores were lower (less pain) for dexmedetomidine treated dogs, depending on preanesthetic dose and on induction drug. The number and percentage of dogs with a postprocedural pain score ≥ 2 at any time point from 0 to 4 hours after the procedure was highest for saline controls in both the minor and major procedure groups.

Table 4. Number and percentage of dogs with a postprocedural pain score ≥ 2:

Procedure	Dexmedetomidine dose (mcg/m^2)	Induction drug			
		Propofol		Thiopental	
Minor	0	3 (of 14)	21 %	2	13 %
	125	2 (of 15)	13 %	0	0 %
	375	1 (of 16)	6 %	0	0 %
Major					
	0	5 (of 16)	31 %	6	38 %
	125	2 (of 16)	13 %	0	0 %
	375	0 (of 16)	0 %	0	0 %

(e) Quality of sedation:

Compared to saline controls, mean preprocedural sedation scores observed 15 minutes after preanesthetic treatment were higher (more sedated) for dexmedetomidine-treated dogs, depending on preanesthetic dose.

Table 5. Mean preprocedural sedation scores at 15 minutes after dexmedetomidine treatment:

Procedure	Dexmedetomidine dose (mcg/m^2)	Sedation score (0 to 10)
Minor	0	0
	125	2.0
	375	4.1
Major	0	0.3
	125	2.9
	375	4.7

(f) Physiologic parameters:

Heart rate (HR): Compared to saline controls, heart rate was lower for dexmedetomidine-treated dogs and remained lowest for the 375 mcg/m^2 dose level until approximately 4 hours after both the minor and major procedures (Tables 9a and 9b, respectively). Heart rate at 24 hours after the procedure did not differ between treatments and was similar to pretreatment values.

Table 6a: Summary of mean heart rate (beats/minute) by time point for the minor procedures (n = 16 dogs per dexmedetomidine dose by induction drug combination; total dogs = 96):

Dose level	Induction drug	Time point										
		A	C	E	F	J	K	L	M	N	O	P
0	Propofol	120	106	119	123	126	126	120	113	109	112	107
	Thiopental	127	124	154	157	153	154	142	135	129	118	120
125	Propofol	125	79	78	83	77	64	66	72	89	110	116
	Thiopental	120	79	89	85	83	72	83	92	107	125	118
375	Propofol	122	58	68	71	56	55	56	53	58	92	113
	Thiopental	110	61	92	100	80	66	59	61	63	78	115

Time points: A = 5 min prior to preanesthesia, C = 15 min after preanesthesia, E = 25 min after preanesthesia, F = start of procedure, J = end procedure (0 hr after procedure), K = 0.5 hr after procedure, L = 1 hr after procedure, M = 1.5 hr after procedure, N = 2 hr after procedure, O = 4 hr after procedure, P = 24 hr after procedure.

Table 6b: Summary of mean heart rate (beats/minute) by time point for the major procedures (n = 16 dogs per preanesthetic dose level (mcg/m^2) by induction drug combination; total dogs = 96):

Dose level	Induction drug	Time point													
		A	C	E	F	G	H	I	J	K	L	M	N	O	P
0	Propofol	122	117	140	132	123	121	-	125	113	110	100	103	106	114
	Thiopental	137	120	160	165	145	135	130	141	145	119	113	108	122	123
125	Propofol	126	70	77	75	84	79	76	84	79	82	91	100	108	114
	Thiopental	124	93	95	96	102	95	87	94	93	95	99	111	130	124
375	Propofol	117	66	59	60	64	64	60	62	60	64	67	69	96	117
	Thiopental	118	66	82	95	77	74	72	67	51	57	65	70	85	112

Time points: A = 5 min prior to preanesthesia, C = 15 min after preanesthesia, E = 25 min after preanesthesia, F = gas on, G = 15 min during procedure, H = 30 min during procedure, I = 45 min during procedure, J = end procedure (0 hr after procedure), K = 0.5 hr after procedure, L = 1 hr after procedure, M = 1.5 hr after procedure, N = 2 hr after procedure, O = 4 hr after procedure, P = 24 hr after procedure.

Table 6c: Minimum HR by dose, procedure, and induction drug during the study:

Dose (mcg/m^2)	**minor procedure/ propofol induction**	**minor procedure/ thiopental induction**	**major procedure/ propofol induction**	**major procedure/ thiopental induction**
0	40	60	44	40
125	24	34	40	36
375	32	16	30	24

- Respiratory rate (RR): Compared to saline controls, respiratory rate was lower for dexmedetomidine-treated dogs and remained lowest for the 375 mcg/m^2 dose level until approximately 4 hours after both the minor and major procedures (Tables 7a and 7b, respectively). Respiratory rate at 24 hr after the procedure did not differ between treatments and was similar to pretreatment values. The lowest minimum respiratory rates observed in at least one dog for the minor or major procedure groups, regardless of treatment combination, were between 2 and 4 breaths/minute.

Table 7a: Summary of mean respiratory rate (breaths/minute) by time point for the minor procedures (n = 16 dogs per preanesthetic dose level (mcg/m^2) by induction drug combination):

Dose level	Induction drug	Time point										
		A	C	E	F	J	K	L	M	N	O	P
0	Propofol	60	63	29	33	47	50	43	46	48	55	35
	Thiopental	40	42	29	24	21	30	33	32	30	32	34
125	Propofol	43	36	17	17	16	25	27	24	30	35	31
	Thiopental	31	27	13	11	13	17	25	27	27	28	30
375	Propofol	37	22	12	11	13	18	18	19	18	25	33
	Thiopental	35	27	14	15	17	20	17	18	20	24	26

Time points: A = 5 min prior to preanesthesia, C = 15 min after preanesthesia, E = 25 min after preanesthesia, F = start of procedure, J = end procedure (0 hr after procedure), K = 0.5 hr after procedure, L = 1 hr after procedure, M = 1.5 hr after procedure, N = 2 hr after procedure, O = 4 hr after procedure, P = 24 hr after procedure.

Table 7b: Summary of mean respiratory rate (breaths/minute) by time point for the major procedures (n = 16 dogs per preanesthetic dose level (mcg/m^2) by induction drug combination):

Dose level	Induction drug	Time point													
		A	C	E	F	G	H	I	J	K	L	M	N	O	P
0	Propofol	70	52	29	29	22	19	-	29	42	42	38	35	32	38
	Thiopental	32	48	24	25	16	10	9	15	27	33	36	32	29	29
125	Propofol	44	23	14	12	16	13	11	15	21	20	22	25	29	28
	Thiopental	48	38	17	15	16	16	19	15	25	22	22	28	38	31
375	Propofol	46	21	13	13	15	14	18	16	21	23	23	22	25	30
	Thiopental	40	26	13	10	11	16	8	11	21	15	17	19	22	28

Time points: A = 5 min prior to preanesthesia, C = 15 min after preanesthesia, E = 25 min after preanesthesia, F = gas on, G = 15 min during procedure, H = 30 min during procedure, I = 45 min during procedure, J = end procedure (0 hr after procedure), K = 0.5 hr after procedure, L = 1 hr after procedure, M = 1.5 hr after procedure, N = 2 hr after procedure, O = 4 hr after procedure, P = 24 hr after procedure.

- Heart rhythm: Compared to saline controls, the number of dogs observed with at least one arrhythmia after preanesthetic treatment administration was greater for dexmedetomidine-treated dogs (Table 8).

Table 8: Summary of the number of dogs with at least one observation of arrhythmia after preanesthetic treatment (n = 16 dogs in each dexmedetomidine IM dose level by induction drug and type of procedure):

Procedure	arrhythmia	Treatment Group					
		Propofol			Thiopental		
		saline	125 mcg/kg	375 mcg/kg	saline	125 mcg/kg	375 mcg/kg
Minor	bradycardia	1	10	14	0	10	13
	1st degree heart block	2	9	11	1	12	9
	2nd degree heart block	0	3	6	0	1	5
	3rd degree heart block	0	0	1	0	0	0
	VPC	0	1	0	3	3	1
	SVPC (supraventricular)	0	0	0	3	0	0
	sinus arrest	2	12	14	5	14	14
	sinus pause	1	2	1	1	3	0
	long QT interval	2	7	8	2	13	9
Major	bradycardia	3	12	15	2	7	13
	1st degree heart block	6	8	13	3	9	12
	2nd degree heart block	0	2	8	0	1	10
	3rd degree heart block	0	0	1	0	0	0
	VPC	0	1	2	2	0	0
	SVPC (supraventricular)	1	0	1	1	0	2
	sinus arrest	2	14	15	5	8	15
	sinus pause	1	4	3	1	4	2
	long QT interval	2	10	13	6	12	14

- Oxygen Saturation: Mean oxygen saturation did not differ between treatments and ranged between 92 and 99%. The lowest minimum oxygen saturation observed in at least one dog for the minor procedure group that received propofol was 80, 74, and 85% for the 0, 125, and 375 mcg/m^2 dexmedetomidine treatments, respectively. The lowest minimum oxygen saturation observed in at least one dog for the minor procedure group that received thiopental was 91, 87, and 85% for the 0, 125, and 375 mcg/m^2 dexmedetomidine treatments, respectively. The lowest minimum oxygen saturation observed in at least one dog for the major procedure group that received propofol was 91, 91, and 40% for the 0, 125, and 375 mcg/m^2 dexmedetomidine treatments, respectively. The lowest minimum oxygen saturation observed in at least one dog for the major procedure group that received thiopental was 88, 90, and 80% for the 0, 125, and 375 mcg/m^2 dexmedetomidine treatments, respectively.

  Nine dogs experienced oxygen saturations lower than 90%. One dog in the high dose dexmedetomidine, propofol induction, major procedure group had the lowest oxygen saturation value (40%) at 15 minutes after the start of the procedure. The low oxygen saturation was associated with low respiratory rate (6 breaths/minute), and responded to lowering the isoflurane concentration, thereby relieving respiratory depression.

- Temperature: For all treatment combinations, body temperature decreased slowly to below pretreatment values during the procedure and for at least 2 hours after both the minor and major procedures (Tables 9a and 9b, respectively). Body temperature at 24 hours after the procedure did not differ between treatments and was similar to pretreatment values. The lowest minimum rectal temperature observed in at least one dog for the minor procedure group that received propofol was 97.3, 97.2, and 97.3 °F for the 0, 125, and 375 mcg/m^2 dexmedetomidine treatments, respectively. The lowest minimum rectal temperature observed in at least one dog for the minor procedure group that received thiopental was 96.1, 97.2, and 94.3 °F for the 0, 125, and 375 mcg/m^2 dexmedetomidine treatments, respectively. The lowest minimum rectal temperature observed in at least one dog for the major procedure group that received propofol was 96.6, 95.5, and 89.8 °F for the 0, 125, and 375 mcg/m^2 dexmedetomidine treatments, respectively. The lowest minimum rectal temperature observed in at least one dog for the major procedure group that received thiopental was 94.8, 93.8, and 94.6 °F for the 0, 125, and 375 mcg/m^2 dexmedetomidine treatments, respectively.

Table 9a: Summary of mean body temperature (°F) by time point for the minor procedures (n = 16 dogs per preanesthetic dose level (mcg/m^2) by induction drug combination):

Dose level	Induction drug	Time point										
		A	C	E	F	J	K	L	M	N	O	P
0	Propofol	101.7	102.1	101.5	101.5	100.7	100.4	100.7	100.9	100.9	101.0	101.4
	Thiopental	102.2	102.4	102.1	101.9	101.3	100.9	101.4	101.9	101.8	101.2	101.5
125	Propofol	101.5	102.1	101.8	101.7	101.3	100.4	100.1	99.6	99.9	100.6	101.1
	Thiopental	101.3	102.0	101.7	101.8	101.1	100.3	100.0	100.0	100.1	101.0	101.2
375	Propofol	101.2	102.5	102.2	102.2	101.9	101.2	100.9	100.4	100.0	100.7	101.6
	Thiopental	101.6	102.1	102.1	101.9	101.6	101.0	100.1	99.8	99.6	100.1	101.2

Time points: A = 5 min prior to preanesthesia, C = 15 min after preanesthesia, E = 25 min after preanesthesia, F = start of procedure, J = end procedure (0 hr after procedure), K = 0.5 hr after procedure, L = 1 hr after procedure, M = 1.5 hr after procedure, N = 2 hr after procedure, O = 4 hr after procedure, P = 24 hr after procedure.

Table 9b: Summary of mean body temperature (°F) by time point for the major procedures (n = 16 dogs per preanesthetic dose level (mcg/m^2) by induction drug combination):

Dose level	Induction drug	Time point													
		A	C	E	F	G	H	I	J	K	L	M	N	O	P
0	Propofol	101.7	102.0	101.7	101.5	100.6	99.9	32.0	100.4	100.9	100.8	100.8	100.8	100.8	101.1
	Thiopental	101.5	101.8	101.5	101.1	100.2	99.7	99.7	99.7	99.7	100.0	100.2	100.4	100.6	100.9
125	Propofol	101.5	101.7	101.3	101.1	100.2	99.1	99.0	99.5	99.1	99.1	99.3	99.7	100.4	100.8
	Thiopental	101.3	102.0	101.5	101.5	100.8	99.9	99.0	99.9	99.3	99.3	99.7	100.0	101.5	101.3
375	Propofol	101.7	102.2	101.8	101.8	100.9	100.6	98.6	100.2	99.7	99.3	99.1	98.8	100.8	101.1
	Thiopental	101.5	101.7	101.8	101.7	100.8	100.4	95.9	100.4	99.9	99.3	99.1	98.8	99.5	100.6

Time points: A = 5 min prior to preanesthesia, C = 15 min after preanesthesia, E = 25 min after preanesthesia, F = gas on, G = 15 min during procedure, H = 30 min during procedure, I = 45 min during procedure, J = end procedure (0 hr after procedure), K = 0.5 hr after procedure, L = 1 hr after procedure, M = 1.5 hr after procedure, N = 2 hr after procedure, O = 4 hr after procedure, P = 24 hr after procedure.

(g) Recovery: Times for the end of the procedure to extubation, sternal recumbency and standing were longer for dexmedetomidine-treated dogs compared to saline controls and the effect appeared to be dose-dependent (Tables 10a, 10b, and 10c). Dogs induced with thiopental had longer recovery times than dogs induced with propofol.

Time from the end of procedure to extubation was on average 21 and 16 minutes for the minor (range 0 to 110 minutes) and major (range 0 to 72 minutes) procedure groups, respectively. Time from the end of procedure to lateral recumbency was on average 52 and 40 minutes for the minor (range 3 to 214 minutes) and major (range 3 to 176 minutes) procedure groups, respectively. Time from the end of procedure to standing was on average 90 and 82 minutes for the minor (range 6 to 279 minutes) and major (range 7 to 237 minutes) procedure groups, respectively.

Table 10a. Mean time (minutes) to extubation relative to the end of the procedure:

Procedure	Preanesthetic dose (mcg/m^2)	Induction drug	
		Propofol	Thiopental
Minor	saline	4	11
	125	11	22
	375	28	45
Major			
	saline	9	10
	125	11	16
	375	17	34

Table 10b. Mean time (minutes) to sternal recumbency relative to the end of the procedure:

Procedure	Preanesthetic dose (mcg/m^2)	Induction drug	
		Propofol	Thiopental
Minor	saline	14	42
	125	28	46
	375	70	107
Major			
	saline	18	24
	125	24	42
	375	53	77

Table 10c. Mean time (minutes) to standing relative to the end of the procedure:

Procedure	Preanesthetic dose (mcg/m^2)	Induction drug	
		Propofol	Thiopental
Minor	saline	28	82
	125	64	77
	375	113	167
Major			
	saline	37	72
	125	51	89
	375	106	137

(h) Response to injection of the preanesthetic treatment: Ninety-six (of 192) dogs exhibited no reaction. The second most common reaction was graded slight in 36% of all dogs (n = 69, subtle change in posture). Fourteen dogs were graded with a moderate reaction (attention directed to injection site); 13 dogs were graded with a severe reaction to the injection (aggression).

6. Adverse reactions:

A total of 192 dogs from 43 breeds between 5 months and 15 years of age were included in the field safety analysis. The following table (Table 11) shows the number of dogs displaying each adverse reaction. These observations reflect the pharmacological effects of dexmedetomidine. One saline-treated control group dog died due to atrial hemangiosarcoma associated with severe hemopericardium that caused a fatal arrhythmia while the dog was under propofol anesthesia. Another dog was withdrawn from the study due to intermittent premature ventricular complexes 15 minutes after receiving 125 mcg/m^2 dexmedetomidine. The dog recovered uneventfully following treatment with atipamezole.

7. Conclusions:

The study showed that DEXDOMITOR administered at 125 or 375 mcg/m^2 by the intramuscular (IM) route of administration induces effects suitable for use as a preanesthetic in dogs. Physiological effects were acceptable for anesthetized dogs, IM injection was well-tolerated, and recovery times were satisfactory.

Table 11. Summary of the number of dogs with adverse reactions during the preanesthetic field study:

Adverse Reaction	Treatment Combination					
	Propofol			Thiopental		
	saline	125	375	saline	125	375
Minor procedure group (no maintenance anesthetic)						
VPCs	0	1	0	3	1	0
cardiac arrest; death*	1	0	0	0	0	0
diarrhea	0	0	0	2	0	0
emesis	1	2	0	2	0	2
disc prolapse	0	0	1	0	0	0
seizures	1	0	0	0	0	0
urinary incontinence	0	0	0	0	0	1
cough	0	0	0	1	0	0
erythema	0	0	1	0	0	0
self trauma	0	1	1	1	0	0
hyperthermia	0	0	0	1	0	0
lethargy	0	0	0	1	0	0
pyrexia	0	0	0	1	0	0
Major procedure group (with isoflurane maintenance anesthetic)						
VPCs	0	1	0	1	0	0
bradycardia	0	0	1	0	0	1
tachycardia	0	0	0	1	1	0
diarrhea	1	0	0	1	1	1
emesis	3	5	4	0	3	4
hypersalivation	1	0	0	0	0	0
muscle tremor	1	0	0	0	0	0
cough	1	0	0	0	0	0
sneezing	0	0	0	0	0	1
dermatitis	1	0	0	0	0	0
erythema	1	0	0	0	0	0
self trauma	0	1	0	1	1	0
pyrexia	0	0	1	0	0	0

* Death under propofol anesthesia caused by arrhythmias resulting from hemangiosarcoma and severe hemopericardium.

3. TARGET ANIMAL SAFETY: Four Studies

A. Safety study of dexmedetomidine in beagle dogs following intravenous or intramuscular administration (study no. 00-008)

1. Type of study: GLP multiple dose laboratory safety study

2. Study director: C. Steven Godin, PhD, DABT

3. Location: Provident Preclinical, Inc. (formerly White Eagle Toxicology Laboratories), Doylestown, PA

4. General design:

(a) *GLP compliance:* The study was conducted in compliance with the U.S. Food and Drug Administration Good Laboratory Practice regulations as set forth in the Code of Federal Regulations (21 CFR part 58) and the Animal Welfare Act of 1970.

(b) *Purpose:* The objective of the study was to assess the safety of DEXDOMITOR 0.5 mg/ml when administered once daily to 48 dogs equally divided into 8 groups (3 males and 3 females per group) by the intravenous (IV) route at 0, 375, 1125 or 1875 mcg/square meter of body surface area, or by the intramuscular (IM) route at 0, 500, 1500, or 2500 mcg/square meter of body surface area, on three consecutive days.

(c) *Test animals:* Forty-eight (24 male and 24 female), healthy laboratory beagles, ranging between 9 to 17 months of age, weighing from 7.9 to 13.3 kg.

(d) *Treatment groups:*

Table 1. Dose levels, dosing route and number of dogs:

0 (saline)	0X IV	6 dogs (3 male; 3 female)
375 mcg/m^2/day	1X IV	6 dogs (3 male; 3 female)
1125 mcg/m^2/day	3X IV	6 dogs (3 male; 3 female)
1875 mcg/m^2/day	5X IV	6 dogs (3 male; 3 female)
0 (saline)	0X IM	6 dogs (3 male; 3 female)
500 mcg/m^2/day	1X IM	6 dogs (3 male; 3 female)
1500 mcg/m^2/day	3X IM	6 dogs (3 male; 3 female)
2500 mcg/m^2/day	5X IM	6 dogs (3 male; 3 female)

(e) *Control drug:* physiological saline

(f) *Dosage form:* injectable solution; final market formulation

(g) *Test duration:* August 16, 2000 to March 20, 2001

(h) *Variables:*

Physical examination: Performed on each animal pretest and 24 hours after the last dose.
Clinical observations: Performed on each animal on each day predose, 5 minutes, 0.25, 0.5, 1, 1.5, 2, 4 and 8 hours post-dosing. Any abnormal finding was recorded, with particular attention paid to sedation-related changes, muscle twitches, corneal opacities, qualitative estimate of pupillary changes, vomiting and signs of injection site irritation and pain.
Respiratory rate: Recorded on each animal on each day predose, 0.25, 0.5, 1, 1.5, 2, 4 and 8 hours post-dosing.
Rectal temperature: Recorded on each animal on each day predose, 0.25, 0.5, 1, 1.5, 2, 4 and 8 hours post-dosing.
Body weight: Recorded on each animal pretest, prior to each dose and about 24 hours after the last dose.
Food and water consumption: Recorded daily.
Heart rate: Recorded on each animal on each day of dosing predose, 0.25, 0.5, 1, 1.5, 2, 4 and 8 hours post-dosing.
Electrocardiogram: Recorded on each animal on each day predose, 0.25, 0.5, 1, 1.5, 2, 4 and 8 hours post-dosing.
Blood pressure (BP): Indirect BP, recorded on each animal on each day predose, 0.25, 0.5, 1, 1.5, 2, 4 and 8 hours post-dosing.
Hematology: Performed on each animal twice pretest and about 24 hours after the first and last dose.
Blood coagulation: Performed on each animal twice pretest and about 24 hours after the first and last dose.
Blood chemistry: Performed on each animal twice pretest and about 24 hours after the first and last dose.
Urinalysis and faecal examination: Performed on each animal twice pretest and about 24 hours after the first and last dose.
Necropsy: Performed on each animal on the day after the last dosing.
Gross pathology: Performed on each animal during necropsy.
Histopathology: Performed on each control and high-dose animal. Gross lesions and the following known or suspected target organs were examined: eyes, heart, injection sites, liver and lung.

5. Results:

Table 2. Results from a target animal safety study for IV administration of dexmedetomidine or saline in 24 beagles

Dose ($mcg/m^2/day$)	0	375	1125	1875
Dogs /group Male + female	6 3 + 3	6 3 + 3	6 3 + 3	6 3 + 3
Mortality	0	0	0	0
Clinical signs	-	Sedation (duration < 3 h). Muscle twitches intermittently during sedation. Slow pupil response to light (1/6 dogs), (duration up to 0.25 h).	Sedation (duration up to 2-8 h). Muscle twitches intermittently during sedation. Slow pupil response to light (3/6 dogs), (duration up to 1.5h).	Sedation(duration up to 4-8 h). Muscle twitches intermittently during sedation. Slow pupil response to light (0/6 dogs) (duration up to 1.5 hr)
Respiratory rate	-	↓ to 11-14 breaths/min (duration < 4 h).	↓ to 11-14 breaths/min (duration < 8 h).	↓ to 11-14 breaths/ min (duration < 8 h).
Rectal temperature	-	↓ to 96-98 °F (duration < 4 h).	↓ to 92-95 °F (duration < 8h).	↓ to 92-95 °F (duration ≤ 8 h).
Ophthalmology	-	NF	NF	NF
Body Weight	-	NF	NF	NF
Food Consumption	-	NF	NF	NF
Water Consumption	-	NF	NF	NF
Heart rate	-	↓ to 33-45 beats/min (duration < 4 h).	↓ to 33-45 beats/min (duration < 8 h).	↓ to 33-45 beats/min (duration < 8 h).
ECG	-	QT time↑ due to decreased heart rate.	QT time↑ due to decreased heart rate. First and second degree A-V-block (1/6 dogs). Second degree A-V-block (2/6 dogs).	QT time↑ due to decreased heart rate.
Blood pressure	-	Results unreliable due to the indirect method used	Results unreliable due to the indirect method used	Results unreliable due to the indirect method
Hematology	-	NF	NF	NF
Blood coagulation	-	NF	NF	NF
Clinical Chemistry	-	NF	NF	↑ ALT values outside the normal range (2/6 dogs).
Urinalysis	-	NF	NF	NF
Fecal examination	-	NF	NF	NF
Gross pathology	-	NF	NF	NF
Histopathology	-	NF	NF	NF
NF = no drug-related findings - = normal				

Table 3. Results from a target animal safety for IM dexmedetomidine or saline in 24 beagles

Dosage (microg/m^2/day)	0	500	1500	2500
Dogs /group Male + female	6 3 + 3	6 3 + 3	6 3 + 3	6 3 + 3
Mortality	0	0	0	0
Clinical signs	-	Sedation (duration up to 4 h). Muscle twitches intermittently during sedation. Normal pupil response to light (6/6 dogs),	Sedation (duration up to 4 h). Muscle twitches intermittently during sedation. Vomiting after dosing (2/6 dogs). Slow pupil response to light (1/6 dogs), (duration up to 0.5h).	Sedation(duration up to 4-8 h). Muscle twitches intermittently during sedation. Vomiting after dosing (1/6 dogs). Slow pupil response to light (2/6 dogs), (duration up to 1 h).
Respiratory rate	-	↓ to 10-21 breaths/min (duration < 8 h).	↓ to10-21 breaths/min (duration < 8 h).	↓ to 10-14 breaths/min (duration < 8 h).
Rectal temperature	-	↓ to 96-98 ˚F (duration < 4 h).	↓ to 93-95 ˚F (duration < 8h).	↓ to 93-95 ˚F (duration < 8 h).
Ophthalmology	-	NF	NF	NF
Body Weight	-	NF	NF	NF
Food Consumption	-	NF	NF	NF
Water Consumption	-	NF	NF	NF
Heart rate	-	↓ to 37-48 beats/min (duration < 4 h).	↓ to 37-48 beats/min (duration < 8 h).	↓ to 37-48 beats/min (duration ≥ 8 h).
Electrocardiogram	-	QT time ↑ due to decreased heart rate. . Second degree A-V-block (1/6 dogs).	QT time ↑ due to decreased heart rate. Second degree A-V-block (1/6 dogs).	QT time ↑ due to decreased heart rate. First and second degree A-V-block (1/6 dogs).
Blood pressure	-	Results unreliable due to the indirect method used	Results unreliable due to the indirect method used	Results unreliable due to the indirect method used
Hematology	-	NF	NF	NF
Blood coagulation		NF	NF	NF
Clinical Chemistry	-	NF	↑ ALT values outside the normal range (1/6 dogs).	↑ ALT values outside the normal range (1/6 dogs).
Urinalysis	-	NF	NF	NF
Fecal examination	-	NF	NF	NF
Gross pathology	-	NF	NF	NF
Histopathology	-	NF	NF	NF
NF = no drug related findings - = normal				

Clinical observations: No mortality occurred during the study. Intravenous or IM dexmedetomidine induced sedation during 2 to 8 hours post-dosing on each dosing day at all three dose levels. The duration of sedation was dose related. Muscle twitches and a sporadically sluggish pupillary response were seen during the sedative periods. Two (of 6) dogs in the middle dose group and 1 (of 6) in the high dose group vomited after administration of dexmedetomidine, all

immediately after IM administration. There was expected mild irritation of the IM injection site.

Respiratory rate: The respiratory rate decreased in all groups on each day. The respiratory rate returned to normal within 4 hours in the low dose group and within 8 hours in the middle and high dose groups.

Rectal temperature: The rectal temperature decreased in all groups on each day. IV groups: In the low dose group, the rectal temperature declined to 96-98°F, then returned to normal within 4 hours. In the middle group, temperature decreased to 92-95°F, returning to normal within 8 hours. In the high dose group, temperature decreased to 92-95°F, and were still recovering at 8 hours.

IM groups: Following administration of IM dexmedetomidine, rectal temperatures decreased by a similar amount, took longer to reach their lowest point (approximately 4 hours) and returned to normal by 8 hours.

Body weight: Unaffected by treatment

Food and water consumption: Unaffected by treatment

Heart rate: The results showed a dose dependent decrease in heart rate following IV and IM administration of dexmedetomidine on all three days of the study.

IV: The mean heart rates declined at all doses to between 33 and 45 beats/minute within 15 minutes of dosing and remained depressed through 1.5 to 4 hours following dosing. The mean heart rate of animals receiving the 1X dose of test article gradually returned to normal between 2 and 4 hours after dosing; the mean heart rates of animals receiving the 3X and 5X doses remained depressed through 4 hours after dosing, returning to normal by 8 hours after dose administration.

IM: The mean heart rates declined at all doses to between 37 and 48 beats/minute within 15 minutes of dosing and remained depressed through 2 to 4 hours following dosing. The mean heart rate of animals receiving the lowest dose of test article gradually returned to normal between 2 and 4 hours after dosing. The mean heart rate of animals receiving the middle and highest dose of test article remained depressed 4 hours after dosing. In the middle dose group, the mean heart rate values returned to baseline 8 hours after dosing, whereas in the high-dose group the mean heart rate values were still slightly depressed.

Electrocardiogram: Dexmedetomidine caused bradycardia and prolongation of the QT interval. First and second degree atrioventricular block was noted sporadically in all dose groups. The effects were dose related and also related to the route of administration. In the 1X dose groups, these effects persisted through 4 hours in most dogs in the IM group, compared to dogs in the IV group that showed the effects for up to 2 hours. In spite of prolonged QT intervals,

sometimes in the presence of first and second degree heart block, no ventricular arrhythmias occurred during the time of maximal drug effect (through 4 hours in the IM group; through 2 hours in the IV group). One dog showed ventricular extrasystoles pretest, and at hours 4 and 8; however, these did not occur during the time when dexmedetomidine exerted its maximum pharmacological effects, and were not considered to be drug related.

Blood pressure: Blood pressure was recorded indirectly using a Critikon Dynamap Vital Signs Monitor and tail cuff. This indirect measurement, however, resulted in unreliable BP values, due to peripheral vasoconstriction and bradycardia caused by alpha$_2$-agonists.

Hematology and blood coagulation: Unaffected by treatment.

Blood chemistry: Most dogs in the 3X and 5X dose groups showed gradually increasing ALT values well within the normal range between predose values and day 3 values. The two dogs in the 5X IV dose group showed the highest ALT values; dogs in the IM treatment groups showed mildly elevated ALT values on day 3.

Urinalysis and fecal examination: Decreased specific gravity was related to treatment with dexmedetomidine. This response to treatment with an alpha$_2$-agonist is temporary and responds to water deprivation. Alpha$_2$-agonists cause an increase in the production of urine (dogs frequently urinate as they recover from sedation), that is believed to be due to the inhibition of antidiuretic hormone.

Gross pathology and histology: No test article effects were evident, except for mild irritation of the IM injection site.

6. Adverse reactions:

Adverse reactions reflect the pharmacological action of alpha$_2$- agonists: hypothermia, bradycardia, arrhythmias, prolonged sedation and vomition. Two (of 6) dogs in the middle dose group and 1 (of 6) in the high dose group vomited within minutes after administration of dexmedetomidine, immediately after IM administration. The dog in the high dose group vomited on 2 (of the 3) days. There was mild irritation of the IM injection site. Cardiac changes associated with the administration of dexmedetomidine were predictable (bradycardia, 1st and 2nd degree AV block, dose-related effects), and did not cause dangerous or fatal arrhythmias at the recommended dose in healthy dogs.

7. Conclusion:

When administered alone at 375, 1125 and 1875 mcg/m^2/day IV or 500, 1500 and 2500 mcg/m^2/day IM on three consecutive days,

DEXDOMITOR was well tolerated, and adverse effects on physiology were related to the pharmacology of the drug. There were no toxicological effects on body weight, clinical variables, or gross and microscopic pathology. DEXDOMITOR demonstrates a satisfactory margin of safety when administered IV or IM at doses as high as 5X the recommended dose.

B. **Dexmedetomidine tolerance study: daily intramuscular (IM) administration to male dogs for four weeks.** (TOX-90006, 1997).

1. Type of study: target animal safety study

2. Investigators: Nieminen L, Hakulinen P, Watson B, Nieminen K, Hirsimäki Y, Karlsson S., at Orion Corporation ORION PHARMA, Finland.

3. General design:

(a) *Purpose:* to assess the toxicity of dexmedetomidine HCl when administered intramuscularly (IM) once daily for 4 weeks to male dogs.

(b) *Test animals:* laboratory beagles, 12 males, 10-27 months old.

(c) *Dosages:* 0, 10, 50, 250 mcg/kg; 3 males in each dose group. The doses used in the study were about 0.5X, 2.5X and 12.5X the recommended clinical dose.

(d) *Control drug:* physiological saline

(e) *Dosage form:* injectable solution

(f) *Duration:* four weeks

(g) *Variables:* Clinical signs and mortality daily. Body weight once a week, food consumption daily. Ophthalmoscopy: pretest and at the end of study. Hematology, blood chemistry, and urinalysis: pretest and at the end of the study. Necropsy, gross pathology, organ weights and histopathology.

4. Results:

Dosage (mcg/kg/day)	0	10	50	250
Male dogs /group	3	3	3	3
Mortality	0	0	0	0
Clinical signs	-	sedation	sedation	sedation, muscle twitches, reddish eyes, irregular or ↑ respiratory rate
Body Weight	-	NF	NF	↓
Food Consumption	-	NF	NF	NF
Hematology	-	NF	NF	NF
Clinical Chemistry	-	NF	alk. phosp. ↑	alk. phosp. ↑ ALT ↑
Urinalysis	-	NF	NF	NF
Ophthalmology	-	NF	NF	corneal opacities
Organ Weights	-	NF	NF	NF
Histopathology	-	NF	hepatocellular eosino-philic cytoplasmic inclusions (1/3 dogs)	hepatocellular eosino-philic cytoplasmic inclusions (3/3 dogs), tissue damage at the injection site

NF = no findings judged drug-related
↑ = slight increase
↓ = slight decrease

5. Adverse reactions: Dose-related hepatic intracytoplasmic eosinophilic inclusions, a slight increase in alanine aminotransferase and alkaline phosphatase, and injection site necrosis at the high dose were noted. Also at the high dose, irregular respiratory rate, reddish conjunctiva, transient corneal opacity, and muscle twitching were noted.

6. Conclusions: The doses were well tolerated by dogs during 4 weeks of treatment. Dose-related changes included hepatic intracytoplasmic eosinophilic inclusions, slight increases in alkaline phosphatase and increases in alanine aminotransferase. These observed changes were mild and considered to be related to the repeated hemodynamic effects of dexmedetomidine. Injection site damage was minimal over 4 weeks for the lower doses (0, 10, and 50 mcg/kg/day).

C. **Dexmedetomidine tolerance study: daily intramuscular (IM) administration to <u>female</u> dogs for four weeks.** (TOX-90013, 1997).

1. Type of study: target animal safety study

2. Investigators: Nieminen L, Hakulinen P, Watson B, Nieminen K, Hirsimäki Y, Karlsson S., at Orion Corporation ORION PHARMA, Finland.

3. General design:

   (a) *Purpose:* to assess the toxicity of dexmedetomidine HCl when administered intramuscularly (IM) once daily for 4 weeks to female dogs.

   (b) *Test animals:* laboratory beagles, 12 females, 11-23 months old.

   (c) *Dosages:* 0, 10, 50, 250 mcg/kg; 3 females in each dose group. The doses used in the study were approximately 0.5X, 2.5X and 12.5X the recommended clinical dose.

   (d) *Control drug:* physiological saline

   (e) *Dosage form:* injectable solution

   (f) *Duration:* four weeks

   (g) *Variables:* Clinical signs and mortality daily. Body weight once a week, food consumption daily. Ophthalmoscopy: pretest and at the end of study. Hematology, blood chemistry, and urinalysis: pretest and at the end of the study. Necropsy, gross pathology, organ weights and histopathology.

4. Results:

Dosage (mcg/kg/day)	0	10	50	250
Female dogs /group	3	3	3	3
Mortality	0	0	0	0
Clinical signs	-	sedation	sedation	sedation, muscle twitches, irregular respiratory rate
Body weight	-	NF	NF	↓
Food Consumption	-	NF	NF	↓
Hematology	-	NF	NF	NF
Clinical chemistry	-	NF	NF	alanine aminotransferase ↑
Urinalysis	-	NF	NF	NF
Ophthalmology	-	NF	NF	corneal opacities
Organ Weights	-	NF	NF	NF
Histopathology	-	NF	hepatocellular eosino-philic cytoplasmic inclusions (1/3 dogs)	hepatocellular eosino-philic cytoplasmic inclusions (3/3 dogs), tissue damage at the injection site

NF = no findings judged drug-related
↑ = slight increase
↓ = slight decrease

5. Adverse reactions:

Dose-related hepatic intracytoplasmic eosinophilic inclusions, a slight increase in alanine aminotransferase, and injection site necrosis at the high dose were noted. Also at the high dose, irregular respiratory rate, transient corneal opacity, and muscle twitching were noted.

6. Conclusions:

The doses were well tolerated by dogs during 4 weeks of treatment. Dose-related changes included hepatic intracytoplasmic eosinophilic inclusions, increases in alkaline phosphatase and increases in alanine aminotransferase. These observed changes were mild and considered to be related to the repeated hemodynamic effects of dexmedetomidine. Injection site damage was minimal over 4 weeks for the lower doses (0, 10, and 50 mcg/kg/day).

D. **Cardiovascular effects of three doses of atropine when administered before, with, or after dexmedetomidine (MPV 03 01).**

1. Type of study: laboratory safety study

2. Investigator: Robert D. Keegan, DVM, MS, Diplomat ACVA
Washington State University, College of Veterinary Medicine,
Department of Veterinary Clinical Sciences, Pullman, WA 99163

3. General design:

(a) *Purpose:* To determine the relative safety of atropine given for the prevention or treatment of low heart rate, when atropine is administered prior to, concurrently, or after the administration of dexmedetomidine in dogs.

(b) *Test animals:* Eighteen (9 males and 9 females, all intact) purpose-bred, instrumented laboratory hound dogs with a mean age of 10 months (range of 8 to 13 months)

(c) *Dosages:* 0.01, 0.02, or 0.04 mg/kg atropine IM
500 mcg/m^2 dexmedetomidine IM

(d) *Control drug:* saline

(e) *Dosage form:* sterile injectable

(f) *Duration:* The study was designed as a randomized, unmasked, crossover experiment with treatments administered once weekly for 4 weeks. Atropine doses were administered at either 10 minutes prior to (T -10), concurrently with (T 0), or 15 minutes after (T 15) IM administration of dexmedetomidine. Control data (no atropine) were collected for all dogs during week 0.

(g) *Relationship to feeding:* Dogs were fasted (with access to water) for at least 12 hours prior to the first injection.

(h) *Variables:*

Directly measured variables:

Non-categorical: heart rate (HR), respiratory rate (RR), systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), cardiac output measured in triplicate (CO1, CO2, and CO3), mean pulmonary arterial pressure (PAP), pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), pulmonary arterial temperature

(TEMP), arterial pH (pH), arterial CO_2 tension (PaCO2), arterial O_2 tension (PaO2), and mixed venous O_2 tension (MVO2), rate pressure product (RPP), cardiac index (CI), and systemic and pulmonary vascular resistance (SVR and PVR, respectively)

Categorical: spontaneous posture (SP), response to noise (RN), relaxation of the jaw and tongue (RJT), summed sedation score (SED), and pedal withdrawal reflex (PWR). Mucous membrane color was not evaluated during the study.

Hematology and clinical chemistry variables: white blood cell count (WBC), band neutrophils (Band), segmented neutrophils (Seg), lymphocytes (Lymph), monocytes (Mono), eosinophils (Eosin), red blood cell morphology (RBCmorph), red blood cell count (RBC), hemoglobin (Hb), packed cell volume (PCV), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular hemoglobin (MCH), red cell distribution width (RDW), platelets, mean platelet volume (MPV), alanine aminotransferase (ALT), alkaline phosphatase (AP), cholesterol, blood urea nitrogen (BUN), creatinine, glucose, total protein (TPROTEIN), albumin, globulin, calcium, phosphorus, sodium, potassium, chloride, carbon dioxide (CO2), and anion gap

Cardiac rhythm variables: The following categories were recorded: 2^{nd} and 3^{rd} degree atrioventricular (AV) block, ventricular escape beat (VE), ventricular premature contraction (VPC), supraventricular tachycardia (SVT), other arrhythmias. A continuous ECG recording was made using a battery operated solid state Holter recorder designed for ambulatory ECG data.

Other observation variables: incidence of vomiting, diarrhea, apnea, muscle tremor and/or twitching, muscle rigidity and/or extension of the limbs, and any other comments

(i) *Primary endpoint:* The primary endpoint in this safety study was the determination of differences in HR and/or the association of adverse events (including arrhythmias) following atropine administration (none, T –10, T 0, or T 15 minutes).

(j) *Statistical methods:* Repeated measures analysis of variance was used to analyze the continuous outcome variables for significance of effects of dose, atropine administration time, observation time and their interactions. Pair-wise comparisons were used to test for significant differences between responses at different observation times within a group and between groups at the same observation time. Significance was noted for p-values of 0.10 or less.

4. Results:

Clinical observations: All dogs became sedated; no severe clinical abnormalities were associated with the administration of dexmedetomidine or atropine during the 60 minute study period.

Clinical pathology: Once-weekly administration of 0.01, 0.02, or 0.04 mg/kg atropine and IM dexmedetomidine (500 mcg/m^2) did not reveal any clinically relevant effects on hematology and clinical chemistry variables.

Cardiac arrhythmias:

Second degree AV block: Dexmedetomidine alone tended to temporarily increase the frequency of second degree AV block (and the associated ventricular escape beats) in all eighteen dogs.

When dexmedetomidine was administered *with* atropine, a marked *increase* in the frequency (numbers/minute) of second degree AV block was temporarily observed. This effect was greatest for the 0.01 mg/kg atropine dose, regardless of atropine administration time, and was the least for 0.02 or 0.04 mg/kg atropine when administered at T –10 minutes.

Third degree AV block: Six dogs experienced transient third degree AV block. The frequency of third degree AV block (as well as the associated ventricular escape beats) increased when dexmedetomidine was given, but the relationship to the administration of atropine was not determined.

VPCs: Transient VPCs (and one occurrence of ventricular bigeminy) occurred in 14 (of 18) dogs during the study. Their relationship to the administration of atropine was not determined.

SVT and SVPCs: Transient SVTs or SVPCs occurred in 16 (of 18) dogs during the study. Their relationship to the administration of atropine was not determined.

Occurrence of various arrhythmias:

Arrhythmias recorded during laboratory safety study*	
Type of arrhythmia	*Number of dogs (of 18)*
Second degree AV block	18
Third degree AV block	6
Ventricular escape beats	16
VPCs	14
Supraventricular tachycardia (SVT) or SVPCs	16
Idioventricular rhythm	1
paroxysmal VT	1
ventricular bigeminy; SVPCs; pulse alternans	1
junctional escape beat	1

*Table does not relate arrhythmias to the presence or absence of atropine

Discussion of cardiac arrhythmias: Second degree AV block, third degree AV block, and their associated escape rhythms are directly related to the bradycardia that occurs after administration of the alpha$_2$-agonist. As the effects of dexmedetomidine wane and the HR begins to rise, the occurrence of these arrhythmias ceases. These occurrences were transient (although frequent over time in some dogs) and returned toward baseline within the 55 minute period after receiving dexmedetomidine. The occurrence of arrhythmias was not related to the presence or absence of the anticholinergic drug.

Paroxysmal ventricular tachycardia (VT) and ventricular bigeminy could both present with the appearance of pulse alternans. None of these arrhythmias were persistent or affected the clinical status of any dog in the study.

Ventricular premature complexes (VPCs), supraventricular tachycardia (SVT), and supraventricular premature complexes (SVPCs) can be expected to occur after periods of bradycardia, hypotension, and/or hypoxia. Therefore, although associated with the administration of dexmedetomidine, they also occur when animals are hypotensive or hypoxic for other reasons. Therefore, labeling contains a precautionary statement concerning the administration of dexmedetomidine in the presence of preexisting hypotension, hypoxia, or bradycardia.

Dexmedetomidine without atropine: Without the anticholinergic drug, dexmedetomidine produced clinically relevant sedation accompanied by a statistically significant reduction in heart rate, respiratory rate, cardiac output, pulmonary arterial temperature, mixed venous oxygen tension, cardiac index and rate pressure product. A statistically significant increase in arterial blood pressure, pulmonary capillary wedge pressure, central venous pressure, and systemic vascular resistance was noted. No dogs experienced hypotension. Dexmedetomidine tended to increase pulmonary vascular resistance. However, dexmedetomidine alone had no statistically significant effect on mean pulmonary arterial pressure, arterial pH, arterial carbon dioxide tension, and arterial oxygen tension.

Dexmedetomidine plus anticholinergic: The lowest atropine dose (0.01 mg/kg IM), regardless of time of administration, was not effective in preventing or treating low heart rate in dogs administered dexmedetomidine. Either of the two higher anticholinergic doses (0.02 or 0.04 mg/kg IM) was effective in the prevention or treatment of the dexmedetomidine-induced reduction in heart rate.

When either 0.02 or 0.04 mg/kg atropine was administered *15 minutes after* dexmedetomidine, marked dose dependent increases in the occurrence of various cardiac arrhythmias occurred compared to the saline group. In particular, the occurrence of second degree AV block was transiently but significantly ($p<0.01$) increased 15 minutes after administration of atropine.

When the higher doses of anticholinergic drug were given *at the same time or 15 minutes after* dexmedetomidine, large increases in heart rate ($p<0.01$) and blood pressure ($p<0.05$) were seen. These increases were also dose related; the 0.04 mg/kg dose elicited larger increases in heart rate and blood pressure.

When the higher doses of atropine were given *10 minutes before* dexmedetomidine, mean heart rate, arterial blood pressure, mean pulmonary arterial pressure, or pulmonary capillary wedge pressure increased in a dose dependent manner (only the 0.04 mg/kg atropine dose showed statistical significance).

5. Adverse reactions: Vomiting was recorded for 3 (of 18) fasted dogs. Other adverse reactions during the study included tremors and/or twitching (11 dogs), muscle rigidity (1), paddling (1), and whining (1).

6. Conclusions: An IM atropine dose of 0.02 mg/kg, given *ten minutes before* dexmedetomidine, performed best for the prevention of dexmedetomidine-induced reduction of heart rate in dogs because:

   a. The IM 0.02 mg/kg atropine dose was as successful as the higher dose in partially preventing the dexmedetomidine-induced reduction in cardiac output, and

   b. Administration prior to dexmedetomidine did not result in as large an increase in cardiac arrhythmias (compared to atropine administered at the same time or after dexmedetomidine). Therefore, the routine use of anticholinergics given simultaneously with, or after dexmedetomidine, is not recommended.

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.

Dexmedetomidine hydrochloride can be absorbed following direct exposure to skin, eyes, or mouth, and may cause irritation. 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.

Appropriate precautions should be taken while handling and using filled syringes. Accidental topical (including ocular) exposure, oral exposure, or exposure by injection could cause adverse reactions, including sedation, hypotension, and bradycardia. Seek medical attention immediately.

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

Caution should be exercised when handling sedated animals. Handling or any other sudden stimuli, including noise, may cause a defense reaction in an animal that appears to be heavily sedated.

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 agonist.

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 DEXDOMITOR when used under the labeled conditions of use is safe and effective for use as a sedative and analgesic in dogs, to facilitate clinical examinations, clinical procedures, minor surgical procedures, and minor dental procedures. DEXDOMITOR is also indicated for use as a preanesthetic to general anesthesia.

The drug is restricted to use by or on the order of a licensed veterinarian because professional veterinary expertise is needed to determine and monitor the level of sedation and analgesia required for various veterinary procedures, and to initiate and maintain balanced anesthesia.

Under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval because dexmedetomidine is the dextrorotary enantiomer of the approved racemic compound medetomidine.

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

U.S. Patent Number	Date of Expiration
US 4,910,214	July 15, 2008

6. ATTACHMENTS:

Facsimile labeling is attached as indicated below:

package insert
vial label
carton label
shipping label