Date of Approval: September 7, 2007

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-267

DEXDOMITOR

Dexmedetomidine Hydrochloride
sterile injectable solution
cats

The effect of the supplement is to add an indication for its use as a sedative and analgesic to facilitate clinical examinations, clinical procedures, minor surgical procedures, and minor dental procedures in cats.

Sponsored by:

Orion Corporation

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I. GENERAL INFORMATION:

A. File Number:	NADA 141-267
B. Sponsor:	Orion Corp. Orionintie 1, 02200 Espoo, Finland Drug Labeler Code: 052483
C. Proprietary Name(s):	DEXDOMITOR
D. Established Name(s):	dexmedetomidine hydrochloride
E. Pharmacological Category:	alpha$_2$-adrenoceptor agonist
F. Dosage Form(s):	sterile injectable solution
G. Amount of Active Ingredient(s):	Each mL contains 0.5 mg dexmedetomidine hydrochloride
H. How Supplied:	10 mL, multidose vials
I. How Dispensed:	Rx
J. Dosage(s):	40 mcg/kg
K. Route(s) of Administration:	IM
L. Species/Class(es):	Cat
M. Indication(s):	DEXDOMITOR is indicated for use as a sedative and analgesic in dogs and cats 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 in dogs.
N. Effect(s) of Supplement:	The effect of the supplement is to add an indication for its use as a sedative and analgesic to facilitate clinical examinations, clinical procedures, minor surgical procedures, and minor dental procedures in cats.

II. EFFECTIVENESS:

This supplemental approval does not change the previously approved canine product. The FOI Summary for the original approval of NADA 141-267 (December 1, 2006) contains information used for the approval of DEXDOMITOR for dogs. This FOI Summary contains information for the approval of DEXDOMITOR when used for sedation and analgesia in cats.

A. Dosage Characterization:

A single, intramuscular dose of 40 mcg/kg of dexmedetomidine was evaluated in a masked, multicenter field study. A total of thirty-one clinically healthy cats received 40 mcg/kg dexmedetomidine by the intramuscular (IM) route of administration, for procedures requiring sedation, restraint and analgesia.

Assessments of sedation, analgesia, ability to perform the procedure, and clinical status were made prior to and at 5, 15, 30, 60, 90, 120 and 180 minutes after administration of dexmedetomidine. The evaluations were based on variables for sedation (body posture, response to noise, muscle tone of jaw) and analgesia (pedal reflex response). The ability to perform the procedure was evaluated. The clinical status of the cat was monitored (heart rate and rhythm, respiratory rate, rectal body temperature). Adverse events were recorded.

Intramuscular administration of 40 mcg/kg dexmedetomidine resulted in moderate to deep sedation and analgesia. Sedative or analgesic effects were observed within five minutes after administration, as reflected in body posture, response to noise, muscle tone of jaw, and pedal reflex (response to toe pinch). The deepest effects were observed between 15 and 60 minutes after administration (cats were recumbent or could rise with difficulty, showed a weak response or a lack of response to noise, had weakened jaw muscle tone, and showed a slight or very weak pedal reflex).

The majority of cats returned to pre-drug behavioral status within 180 minutes after administration.

Table 1: Sedation and analgesia variables in cats receiving 40 mcg/kg dexmedetomidine:

Variable	**Number of cats Normal by 180 Minutes**
Body posture	12* (of 30)
Response to noise	22 (of 30)
Muscle tone of jaw	20 (of 29)
Pedal reflex response	28 (of 29)

*sixteen additional cats were standing but were still slightly lethargic

During the study, five cats showed tachycardia, ten cats showed bradycardia, and three cats showed other uncharacterized arrhythmias during at least one time point after dexmedetomidine administration. All of these cats completed the study.

Following the administration of dexmedetomidine, mucous membranes were frequently reported as pale or slightly blue. At time point 60 minutes, twenty cats were reported

with pale mucous membranes. At time point 15 minutes, six cats were reported with pale/slightly bluish mucous membranes. One cat was reported with cyanotic mucous membranes at 15, 30 and 60 minutes (this cat's mucous membranes were reported as normal at all other time points).

Mean respiratory rates were still decreased by the end of the study (baseline mean value of 54 breaths/minute decreased to 39 breaths/minute at 180 minutes), with the maximum decrease in rate occurring at 90 minutes after dexmedetomidine (39 breaths/minute).

Body temperatures decreased following the administration of dexmedetomidine. Mean body temperature at baseline was 101.5°F (98.2-105.1 °F); mean body temperature at 180 minutes was 99.0 °F (92.5-103.8 °F).

Clinical examinations, dental procedures, radiography, lancing abscesses, grooming, removal of sutures, and blood sampling were successfully performed. Decreases in heart and respiratory rates were noted in all cats. Two cats were withdrawn from the study due to ineffectiveness (the intended procedures could not be performed). In one case, a dental procedure could not be performed due to excitation, possibly a paradoxical reaction to dexmedetomidine. In the other case, laryngoscopy/bronchoscopy could not be performed due to persistent laryngospasm.

Vomiting was reported as an adverse reaction in 5 (of 62) cats after administration of dexmedetomidine.

Conclusion: An IM dose of 40 mcg/kg dexmedetomidine induced moderate to deep sedation, and provided restraint and analgesia that were sufficient for conducting a variety of clinical procedures.

B. Substantial Evidence:

1. Type of study: field study titled, Clinical Evaluation of the Effectiveness and Safety of a Single Intramuscular (IM) Injection of 40 mcg/kg Dexmedetomidine Hydrochloride as a Sedative and Analgesic Agent in Cats (MPV 03 02)

2. Investigators:

Mikael Granholm, DVM Raisio, Finland	Arne Adolfsson, DVM Norsholm, Sweden
Jouni Niemi, DVM Halikko, Finland	Gry Øye, DVM Sandviken, Sweden
Beatrice Cleve, DVM Helsinki, Finland	Odd Höglund, DVM Täby, Sweden
Iris Rastas, DVM Kaarina, Finland	Anna Kangasnevalainen, DVM Rauma, Finland
Eva Lundell, DVM Uppsala, Sweden	Serban Ursachi, DVM Hämeenlinna, Finland

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, xylazine. The study also recorded adverse events due to the administration of either product.

b. *Test Animals:* A total of 242 cats were enrolled, ranging in age between 0.5 and 17 years, and in size between 2.3 and 9.6 kg (5 and 21 lbs). Cats of any breed were allowed to enroll in the study; of the 19 breeds, Domestic Shorthair or Longhair were the most common. Participating cats were classified as American Society of Anesthesiologists Class I (normal healthy patient with no detectable disease) or Class II (slight or moderate systemic disease causing no obvious incapacity).

The cats were randomly assigned to two treatment groups and were studied using a masked double-dummy administration technique. Cats in the dexmedetomidine group (n = 122) received an intramuscular injection of dexmedetomidine and an intramuscular injection of a placebo. Cats in the xylazine group (n = 120) received an intramuscular injection of xylazine and an intramuscular injection of a placebo.

c. *Control Drug:* The active control was xylazine in the approved formulation of ANASED 20 mg/mL solution for injection.

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

Table 1: Procedure types and number for cats treated with dexmedetomidine (DEX) or xylazine (XYL):

Procedure	DEX (number of cats)	XYL (number of cats)	TOTAL (number of cats)
Ear examination and treatment of otitis	6	7	13
Eye examination	2	4	6
Grooming and bathing	16	22	38
Abscess treatment, suture removal, or skin biopsy	11	7	18
Oral examination, treatment, and dentistry	57	44	101
Other diagnostic procedures or treatment (for example, blood and urine sampling)	20	21	41
Radiography and ultrasound	10	15	25
Total	122	120	242

e. *Dosage forms:*

-Injectable solution, DEXDOMITOR 0.5 mg dexmedetomidine/mL, final market formulation.
-Injectable solution, DEXDOMITOR vehicle for placebo.

-Injectable solution, ANASED 20 mg xylazine/mL, market formulation.
-Injectable solution, ANASED vehicle for placebo.

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

g. *Dosages:*

DEXDOMITOR: 40 mcg/kg
Placebo for ANASED: same dose volume as ANASED

ANASED: 2.2 mg/kg
Placebo for DEXDOMITOR: same dose volume as DEXDOMITOR

h. *Test duration*: March 15, 2004 to February 3, 2005

i. *Variables:*

(1) ***Ability to perform the procedure***:
Numerical rating score (1=cannot be performed; to 4=performed with no resistance)

(2) ***Quality of sedation:***
Posture score (1=normal; to 4=lying and unable to move)

Response to noise score (1=sensitive/normal; to 4=no reaction)
Muscle tone of jaw score (1=normal; to 4=no resistance to opening)

(3) ***Quality of analgesia:***
Evaluation of pain score (1=no pain; to 4=severe pain)
Pedal reflex response score induced by toe pinching
(1=sensitive/normal; to 4=no response)

(4) ***Physiological parameters:***
heart rate (beats/min)
heart rhythm (ECG)
pulse character (increased, normal, weak, not detectable)
respiratory rate (breaths/min)
respiratory pattern (regular, irregular)
respiratory depth (normal, deeper than when awake)
vasoconstriction of mucous membranes (normal, pale, white)
capillary refill time (seconds)
oxygenation of mucous membranes (normal, gray, blue)
hemoglobin oxygen saturation (pulse oximetry, %)
rectal temperature (°F)

(5) ***Response to injection (none, slight, marked).***

(6) ***Adverse events were monitored throughout the study.***

4. Statistical methods: The primary endpoint of the study was to demonstrate that dexmedetomidine was not inferior to xylazine with respect to the success rate (success = scores of 3 or 4; failure = scores of 1 or 2) for the ability to perform the procedure, 30 minutes after treatment administration. Confidence intervals and cumulative log odds ratios were used to determine non-inferiority. A claim of non-inferiority of dexmedetomidine was made if the lower bound of the confidence interval of the estimated treatment difference did not exceed -13%. Secondary analyses were made with generalized estimating equations (stratified by study site) to estimate treatment effects over time for the categorical variables: quality of sedation and quality of analgesia. All other variables were not subject to statistical analyses but were tabulated by treatment over time with descriptive statistics.

5. Criteria for Success/Failure: The investigator subjectively scored the ability to perform the procedure 30 minutes after administration of IM dexmedetomidine or IM xylazine. This endpoint was satisfied if the cat was clinically sedated, the procedure was satisfactorily completed, recovery was satisfactory, and adverse reactions were minimal.

6. Results:

a. Ability to perform the procedure: The success rate at 30 minutes was 91.7% for dexmedetomidine and 87.5% for xylazine (Table 1). Because the lower bound of the confidence interval of the estimated treatment difference (-4%) is greater than the pre-established limit (-13%), dexmedetomidine is considered non-inferior to xylazine.

Table 2. Ability to perform the procedure score, 30 minutes after treatment with dexmedetomidine (DEX) or xylazine (XYL).

	DEX (N = 120*)		XYL (N = 120)	
Score	n	%	n	%
1 = Cannot be performed	2	1.7	4	3.3
2 = Performed with much resistance	8	6.7	11	9.2
3 = Performed with some resistance	39	32.5	56	46.7
4 = Performed with no resistance	71	59.2	49	40.8
Success rate (3 or 4)	110	91.7	105	87.5

*Data from site 2 (2 cats) were not included in the statistical analysis because of small sample size.

b. Quality of sedation: The success rates for posture, response to noise, and muscle tone of jaw were consistently higher for dexmedetomidine compared to xylazine at the majority of time points. Intramuscular administration of 40 mcg/kg dexmedetomidine resulted in moderate to deep sedation. Sedative effects were observed within five minutes after administration with the deepest effects observed at 30 minutes, remaining deep through 60 minutes. The majority of cats had returned to pre-drug behavioral status within 180 minutes after administration

c. Quality of analgesia: The success rates for evaluation of pain were similar for dexmedetomidine and xylazine. The success rates for pedal reflex response were consistently higher for dexmedetomidine compared to xylazine at all time points. Intramuscular administration of 40 mcg/kg dexmedetomidine resulted in moderate to deep analgesia. Analgesic effects were observed within five minutes after administration with the deepest effects observed between 15 and 60 minutes. Pedal reflex response scores had returned to pretreatment values by 180 minutes in the large majority of cats.

d. Physiologic parameters: No clinically relevant differences were observed between dexmedetomidine and xylazine for any physiological variable. Compared to baseline values, heart rate, respiratory rate, and rectal temperature decreased following dexmedetomidine and xylazine and remained low throughout the observational period. Hemoglobin oxygen saturation did not change over time following treatment (Table 2).

Table 3. Mean heart rate (HR, beats/min), respiratory rate (RR, breaths/min), hemoglobin oxygen saturation (SpO_2, %), and rectal temperature (TEMP, °F) for cats treated at 0 minutes with dexmedetomidine (DEX, n = 122 cats) or xylazine (XYL, n = 120 cats).

		Time point (minutes)							
variable	treatment	-10	5	15	30	60	90	120	180
HR	DEX	179	117	102	94	90	91	92	109
	XYL	176	121	105	98	93	95	97	105
RR	DEX	62	48	43	42	38	36	35	36
	XYL	62	49	44	40	37	36	36	37
SpO_2	DEX	-*	96	95	94	95	96	95	-
	XYL	-	94	96	95	96	96	96	-
TEMP	DEX	101.2	101.6	101.4	100.9	99.9	98.9	98.1	97.2
	XYL	101.5	101.8	101.6	101.2	100.1	99.2	98.5	97.7

*SpO_2 was not evaluated at T -10 or T 180 minutes.

Electrocardiogram findings revealed bradycardia in most cats at all time points after treatment (Table 3). Atrioventricular dissociation, ventricular escape rhythm, and junctional escape rhythms were observed in as many as 40% of dexmedetomidine-treated cats; the incidence of these arrhythmias was ≤ 10% by 180 minutes. Premature complexes and atrioventricular block were observed in ≤ 6% of dexmedetomidine-treated cats. The incidence and type of arrhythmias did not consistently correlate with any abnormal physiological findings.

Table 4. Percentage of cats for each cardiac arrhythmia category** following treatment at 0 minutes with dexmedetomidine (DEX) or xylazine (XYL).

		Time point (minutes)							
treatment	category	-10	5	15	30	60	90	120	180
DEX	n* =	14	55	91	109	114	100	80	30
	AVB	0	0	1	0	0	0	0	0
	AVD	0	33	40	36	25	22	15	10
	BRDY	0	66	80	85	92	96	96	73
	PC	0	4	6	2	2	0	1	0
	TCHY	14	0	0	0	0	0	0	0
XYL	n =	11	40	79	109	107	97	63	33
	AVB	0	0	0	0	0	0	0	0
	AVD	0	35	24	29	18	11	13	6
	BRDY	0	68	80	81	87	87	92	76
	PC	0	0	1	1	2	0	2	3
	TCHY	9	0	1	0	0	0	0	0

*n = number of cats with available ECG recordings.
**AVB = atrioventricular block; AVD = atrioventricular dissociation or ventricular or junctional escape rhythm; BRDY = bradycardia; PC = supraventricular or ventricular premature complexes; TCHY = tachycardia.

Respiratory pattern was described as normal in 91% of dexmedetomidine-treated cats, and respiratory depth was described as deeper than awake in 36% of dexmedetomidine-treated cats. Vasoconstriction and oxygenation were described as normal in 99% of dexmedetomidine-treated cats. Capillary refill time increased within 5 minutes following treatment and then decreased to pretreatment values by 180 minutes in both treatment groups.

e. Response to injection: The response of the cat to injection was described as no reaction or slight reaction in 85% of dexmedetomidine-treated cats.

7. Conclusions:

The study showed that DEXDOMITOR administered at 40 mcg/kg by the intramuscular (IM) route of administration was effective for sedation and analgesia in cats.

8. Adverse reactions: A total of 242 cats from 19 breeds between 0.5 and 17 years of age were included in the field safety analysis. The following table (Table 4) shows the number of cats displaying each adverse reaction. These observations reflect the pharmacological effects of dexmedetomidine and xylazine.

Table 5. Summary of the number and percentage of cats with adverse reactions after dexmedetomidine (DEX) or xylazine (XYL).

Adverse event	DEX (N = 122)		XYL (N = 120)	
	n	%	n	%
Vomiting	70	57	82	68
Urinary incontinence	6	5	11	9
Hypersalivation	4	3	5	4
Fatigue	1	≤ 1	5	4
Involuntary defecation	4	3	1	≤ 1
Arrhythmia	1	≤ 1	2	2
Hypothermia	2	2	1	≤ 1
Sedation	0	≤ 1	3	3
Diarrhea	2	2	0	≤ 1
Hypotension	0	≤ 1	2	2
Anorexia	0	≤ 1	1	≤ 1
Bradycardia	0	≤ 1	1	≤ 1
Corneal ulcer	1	≤ 1	0	≤ 1
Cyanosis	1	≤ 1	0	≤ 1
Cystitis	1	≤ 1	0	≤ 1
Dyspnea	1	≤ 1	0	≤ 1
Hemorrhagic diarrhea	0	≤ 1	1	≤ 1
Hyperactivity	0	≤ 1	1	≤ 1
Lethargy	0	≤ 1	1	≤ 1
Nausea	1	≤ 1	0	≤ 1
Peripheral vascular disorder	1	≤ 1	0	≤ 1
Total	97	100	119	100

The most frequently observed adverse event was vomiting. Vomiting was reported as an adverse event most frequently during the first 5 minutes after dexmedetomidine administration, and did not appear to be influenced by the fasting status of the cat.

One incidence of dyspnea was reported during the study. When the cat was enrolled (for a dental procedure), it had a history of asthma and respiratory infection, but was free of adverse clinical signs when it received dexmedetomidine. When dyspnea occurred (43 minutes after dexmedetomidine administration), the cat was treated successfully with hydrocortisone and furosemide.

III. TARGET ANIMAL SAFETY:

A. Acute Tolerance Safety Study:

1. Study Title: Acute Tolerance Study: Single Dose Intramuscular Injection of DEXDOMITOR in Adult Cats (NOTOX Project 439649)

2. Type of Study: GLP acute tolerance safety study

3. Test Site: NOTOX B.V.
Hambakenwetering 7
5231 DD 's-Hertogenbosch
The Netherlands

4. General Design:

a. *Purpose*: The objective of the study was to assess the tolerance of DEXDOMITOR when administered as a single intramuscular dose to cats at 10X the recommended clinical dose of 40 mcg/kg.

b. *Test Animals*: Six (three male; three female), seven-month-old, healthy, Domestic Shorthair cats.

c. *Control Drug*: none

d. *Dosage Form*: Injectable solution containing 0.5 mg/mL dexmedetomidine hydrochloride (final market formulation)

e. *Route of Administration*: IM

f. *Dosage Used*: 400 mcg/kg

Six cats were studied as follows:

Table 1: Dosages and animal numbers

Treatment group	Dose level	Dose volume	Dose concentration	Number of dosing days	Number of animals		Day of Necropsy
	(mcg/kg/day)	(ml/kg/day)	(mg/mL)		male	female	
1	400	0.8	0.5	1	3	3	3

g. *Test Duration*: 2 days

h. *Relationship to feeding:* Food was withheld from all cats on the evening prior to treatment; cats were treated the following morning. Food was then provided once daily in the early morning and water was provided without restriction.

i. *Variables Measured*:

Table 2: Variables and time points

Variables	Timepoints before and after administration											
	Before		After (Observation period, hours)									
	Prestudy*	Predose*	0.25	0.5	1	2	4	8	12	24	36	48
Physical examination:	x											x
Clinical observations:	x	x	x	x	x	x	x	x	x	x	x	x
Body weight:	x	x								x		x
Food consumption:	Daily											
Heart rate (ECG):	x	x	x	x	x	x	x	x	x	x	x	x
Respiratory rate:	x		x	x	x	x	x	x	x	x	x	x
Rectal temperature:	x		x	x	x	x	x	x	x	x	x	x
Cardiac rhythm (ECG):	x	x	x	x	x	x	x	x	x	x	x	x
Hematology:	x	x								x		x
Blood chemistry:	x	x								x		x
Gross necropsy:	Performed on each animal after observation period											
Histopathology:	Performed on each animal											

* prestudy = prior to day 1; predose = immediately prior to dose on each dosing day

Special attention was paid to sedation related changes, corneal opacities, pupil changes, vomiting, and irritation at the injection site.

5. Statistical Methods: Individual animal data were tabulated and group mean, standard deviation, minimum, and maximum values were calculated.

6. Results:

***a. Clinical observations and physical examinations*:**

No mortalities occurred during the study. No relevant physical examination abnormalities were observed before or after treatment. Clinical abnormalities were related to the pharmacological action and duration of drug effects, and included corneal

opacity, miosis, vomition, changes in heart and respiratory rates, hypothermia, sedation, and injection site inflammation.

All animals were sedated by 0.25 hours after dosing. Animals began to recover from sedation 4 hours after dosing, and full recovery was noted in 2 cats at 8 hours, in 2 cats at 12 hours, and 2 cats at 24 hours. Vomiting was observed in 5 (of 6) cats, and occurred between 7 and 11 hours after dosing. Corneal opacity and/or dehydration were observed in all cats (in 2 cats this was observed up to 24 hours after dosing). Miosis with an abnormal pupillary response to light was noted up to 8 hours after dosing. Corneal opacity was related to the duration of sedation and was due to an inadequate blink reflex and decreased lubrication. Other clinical signs such as pale skin and gingiva (1 cat), salivation (2 cats), blue discoloration of the ears (3 cats), and lacrimal discharge (2 cats) were observed. No clinical effects were visible at the injection site.

b. Body weight and food consumption:

Slightly lower body weights and a reduction in food consumption were observed after dosing.

c. Heart rate and cardiac rhythm*:*

Heart rate and cardiac rhythm were measured with electrocardiography (ECG). Heart rates were lower after dosing, compared to pre-dosing values. Heart rates were lowest 2 to 4 hours after dosing (minimum heart rate range of 52-112 beats/minute) and returned to pre-dosing values by 8 to 24 hours. Cardiac conduction times were generally prolonged, specifically PQ and QT intervals, and were associated with low heart rate. No atrioventricular (AV) blocks or escape rhythms were noted. In one cat, incidental and reversible premature junctional complexes were seen at 1 and 2 hours after dosing, and were considered secondary to bradycardia. Expected cardiac effects such as bradycardia and reduced cardiac conduction times are related to the pharmacology of DEXDOMITOR.

d. Respiratory rate and rectal temperature:

Slightly lower respiration rate and reduced rectal temperature were observed after dosing, compared to pre-dosing values. Respiratory rates were lowest 4-8 hours after dosing (minimum respiratory rate range of 20-40 breaths/minute) and returned to pre-dosing values by 8 to 24 hours after dosing. Rectal temperatures decreased shortly after dosing. In males, the lowest temperatures (93.0 to 94.3 °F) were measured 4-8 hours after dosing; in females, the lowest temperatures (86.0 to 89.2 °F) were measured 8 hours after dosing. Rectal temperature in all animals returned to pre-dosing values 12-24 hours post-dosing.

e. Hematology and clinical chemistry:

Hematological parameters were not clinically affected by treatment. A slightly lower hemoglobin and erythrocyte count was observed on day 3 in both sexes. A shift in the

leukocyte population characterized by a higher proportion of neutrophils with a lower proportion of lymphocytes was noted on day 2 for both sexes. These findings were not considered toxicologically relevant.

Some mild changes in clinical chemistry parameters were observed as a result of treatment. Liver-associated enzymes, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were slightly increased in 2 males 24 hours after dosing, with a tendency towards recovery 48 hours after dosing. Creatine kinase (CK) was slightly increased in all cats 24 hours after dosing, with a tendency towards recovery 48 hours after dosing. This increase is most likely due to prolonged recumbency. Glutamate dehydrogenase (GLDH) and lactate dehydrogenase (LDH) activity were increased in some cats; there is little significance associated with transient increases in these non-specific enzymes. Total protein, albumin and globulin levels were slightly lowered in one male 48 hours after dosing.

f. Pathology:

Gross pathology: Gross pathology and organ weights were unaffected by treatment.

Histopathology: Minor histological changes indicative of mild inflammation were seen in 2 males and 2 females at the injection sites.

Renal histological changes were observed in 2 male and 2 female cats, characterized by mild interstitial fibrosis, corticomedullary tubular basophilia, lymphoid inflammation, and/or tubular dilatation. In the two males there was also birefringent crystal deposition. These findings were related to pre-existing, low-grade, interstitial nephritis. The cats were necropsied 2 days after the single injection of drug; therefore, a relationship to treatment was considered improbable.

Other microscopic findings were sporadic and were not considered to be related to treatment.

7. Conclusions: Based on the administration of DEXDOMITOR to healthy young cats as a single IM injection at 400 mcg/kg, DEXDOMITOR is considered safe at the recommended dose of 40 mcg/kg.

B. Multiple Dosage Target Animal Safety Study:

1. Study Title:	Dexmedetomidine: Intramuscular (IM) Safety Study in the Cat (MDS 926/013).
2. Type of Study:	GLP target animal safety
3. Study Site:	MDS Pharma Services: Les Oncins

69210 Saint Germain sur L'Abresle
France
Study Director: S. Goubin, DVM

4. General Design:

a. *Purpose*: The objective of the study was to assess the safety of IM dexmedetomidine in Domestic Shorthair cats following three consecutive days of daily administration.

b. *Test Animals*: Thirty-six (18 male; 18 female), 6 to 8 months of age, healthy, Domestic Shorthair cats.

c. *Control Drug*: injectable vehicle

d. *Dosage Form*: Injectable solution containing 0.5 mg/mL dexmedetomidine hydrochloride (final market formulation)

e. *Route of Administration*: IM

f. *Dosage Used*: vehicle (0X), 40 mcg/kg (1X), 120 mcg /kg (3X), 200 mcg/kg (5X)

Twenty-four cats were randomized into treatment groups as follows:

Table 1: Treatment Groups

Treatment group	Dose level	Dose volume	Dose Concentration	Number of dosing days	Number of animals		Day of Necropsy
	(mcg/kg/day)	(mL/kg/day)	(mg/mL)		male	female	
vehicle control	0	0.40	0	3	3	3	4
1X dexmedetomidine	40	0.08	0.5	3	3	3	4
3X dexmedetomidine	120	0.24	0.5	3	3	3	4
5X dexmedetomidine	200	0.40	0.5	3	3	3	4

g. *Test Duration*: 3 days

h. *Relationship to feeding:* Food was withheld from all cats on the evening prior to treatment (given the following morning). Food and water were then provided four hours after treatment.

i. *Variables Measured*:

Table 2: Variables and time points

Variables	Timepoints before and after administration									
	Before		After (hours)							
	Prestudy*	Predose*	0.25	0.5	1	1.5	2	4	8	24@
Physical examination:	x									x
Clinical observations:		x	x	x	x	x	x	x	x	x
Respiratory rate:		x	x	x	x	x	x	x	x	x
Rectal temperature:		x	x	x	x	x	x	x	x	x
Body weight:		x	x	x	x	x	x	x	x	x
Food consumption:	Daily									
Heart rate:		x	x	x	x	x	x	x	x	x
Cardiac rhythm:		x	x	x	x	x	x	x	x	x
Hematology:	x									x
Blood coagulation:	x									x
Blood chemistry:	x									x
Gross Necropsy:	Performed on each animal on day after third dose									
Histopathology:	Performed on each animal. Gross lesions and the following known or suspected target organs were examined: eyes, heart, injection sites, liver and lung.									

* prestudy = prior to day 1; predose = immediately prior to dose on each dosing day
@ 24 h after third dose

Corneal opacity was recorded as present or absent; pupil diameter was recorded as normal, miosis, or mydriasis; and vomition as present or absent. Injection site phenomena were recorded as they occurred. Heart and respiratory rates, and temperature were also recorded on the same form.

5. Statistical Methods: For each of the variables heart rate, respiratory rate, and rectal temperature, a repeated measures analysis of variance was used to test the effects by group, group by sex, group by day, group by hour, and group by day by hour. The measurement at hour 0 on day 1 was included in the model as a covariate. For the hematology and chemistry variables, which were measured once post-treatment, an analysis of variance was used to test the effects of group and group by sex. Follow-up

pairwise mean comparisons between the control group and the treated groups were performed, as necessary, using linear contrasts with significance level 0.10.

6. Results:

***a. Clinical observations and physical examinations*:**

No mortalities occurred during the study. Clinical abnormalities were related to the pharmacological action and duration of the drug effects, and included corneal opacity, miosis, vomition, changes to heart and respiratory rates, temperature decrease, sedation, and injection site inflammation. Slight decreases in body weight were observed and were related to dose and duration of sedation.

b. Corneal opacity:

Corneal opacity was not observed in the control group (0X). The incidence of corneal opacity increased with increasing dose. Corneal opacity resolved by 4 hours in the 1X group but was still present at 8 hours in the 3X and 5X groups. Corneal opacity is due to drying of the cornea due to an inadequate blink reflex and sedation, and is easily prevented by eye lubrication.

c. Pupil diameter:

Abnormalities in pupil diameter were not observed in the control group (0X) or in the 1X and 3X groups. In the 5X group, miosis was observed in 2 (of 6) animals 4 hours after treatment on day 1, and in 3 (of 6) animals 8 hours after treatment on days 1 and 2.

d. Vomition:

Vomiting was observed in 2 animals: 1 (of 6) in the 1X group 15 minutes after treatment on day 1, and 1 (of 6) in the 3X group 4 hours after treatment on day 2. Food was withheld from the previous evening prior to drug administration.

e. Sedation:

Sedation was described as none, moderate, or severe. No sedation was noted in any animals in the control group 1 (0X). In the dexmedetomidine treated groups, the degree and duration of sedation were dose-related. For example, on day 1, one hour after receiving dexmedetomidine, 4 (of 6) were severely sedated in the 1X group, 2 (of 6) were severely sedated in the 3X group, and 6 (of 6) were severely sedated in the 5X group. In the 3X dose groups, cats recovered by 8 hours. No cats in any treatment groups were sedated at 24 hours after any dose.

f. Respiratory rate:

The mean respiratory rate, averaged across days, exhibited significantly greater decreases as dose increased ($p=0.0010$). However, the duration of the respiratory rate decrease was not affected by dose. The lowest mean values in all 3 treated groups occurred between 2 and 4 hours after drug administration, returning to normal by 24 hours.

g. Rectal temperature:

Mean temperatures ranged from less than 86 ºF to 102.4 ºF. Temperatures decreased during the first 4 to 8 hours after administration of dexmedetomidine on every dosing day. The most severe decreases occurred in the 3X group at hour 4, and in the 5X group at hour 8. At hour 8, hypothermic temperatures in 7 cats resulted in missing values that were known to be <86 ºF.

h. Heart rate (HR):

The mean heart rate showed significantly greater decreases as dose increased ($p<0.0001$), and relates to the pharmacology of the drug. The duration of decreases in HR is also dose dependent. By 24 hours, HR returned to baseline in all treated groups.

i. Cardiac rhythm:

An irregular cardiac rhythm (isolated junctional escape beats and occasional ventricular complexes and escape rhythms) was noted at all dexmedetomidine dose levels, without showing a dose related incidence. More cats were affected by cardiac arrhythmias on day 3 (9 cats) than on the first 2 days of the study (2 and 3 cats, respectively). These arrhythmias occurred either during the period of marked bradycardia, or more frequently following sinus pauses (abnormally long sinus cycle length). Four cats with arrhythmias showed an increase in the duration of bradycardia compared to cats without arrhythmias in the same dose groups. Irregular cardiac rhythm was not associated with other pharmacological findings. Dexmedetomidine did not induce atrioventricular block under these experimental conditions.

j. Hematology, coagulation parameters, and clinical chemistry:
No clinically abnormal changes in hematology, coagulation parameters, or serum biochemical parameters were noted in groups 2, 3, or 4 animals sedated at dexmedetomidine doses of 40, 120, or 200 mcg/kg/day for 3 days.

k. Pathology:

Gross pathology:

Macroscopically, dark areas were seen at the injection site in one female given 40 mcg/kg/day, in one female given 120 mcg/kg/day and two females given 200 mcg/kg/day.

Histopathology:

At the injection site, there was acute interstitial inflammatory infiltration in the muscle and muscle necrosis in all groups, including the control group. In the control and low dose groups, the severity (minimal to slight) and incidence of lesions were similar. In the intermediate and high dose groups, a slight exacerbation was seen in the severity (minimal to moderate) of the lesion. Other histological changes did not have clinical relevance or a relationship to treatment. No abnormal histological findings were seen in cornea.

7. Conclusions: Based on the administration of IM DEXDOMITOR to healthy young cats at 40, 120, and 200 mcg/kg/day on 3 consecutive days, the recommended dose of 40 mcg/kg is considered safe.

IV. HUMAN FOOD SAFETY:

This drug is intended for use in dogs and cats, which are non-food animals. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to DEXDOMITOR:

Human Warnings are provided on the product label as follows: “Not for human use. Keep this and all drugs out of the 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.

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.

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.

VI. 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. The data demonstrate that DEXDOMITOR, when used according to the label, is safe and effective for use as an intramuscular (IM) sedative and analgesic in cats to facilitate clinical examinations, clinical procedures, minor surgical procedures, and minor dental procedures.

A. Marketing Status:

The drug is restricted to use by or on the order of a licensed veterinarian because professional veterinary expertise is required to determine the level of sedation and analgesia required for the various veterinary procedures during which this drug may be used.

B. Exclusivity:

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 indication for the feline species for which this supplement is approved. Exclusivity is based on new safety data and a field study that demonstrates substantial evidence of effectiveness.

C. Supplemental Applications:

This supplemental NADA did not require a reevaluation of the safety or effectiveness data in the original NADA (21 CFR §514.106(b)(2)).

D. Patent Information:

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

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

VII. ATTACHMENTS:

Facsimile Labeling:
package insert
vial – 10 mL
carton – 10 mL
shipping label – 10 mL