Date of Approval: August 16, 2010

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-267

DEXDOMITOR

Dexmedetomidine Hydrochloride

sterile injectable solution

cats

This supplement provides for a new indication for use as a preanesthetic to general anesthesia in cats.

Sponsored by:

Orion Corporation

Table of Contents

I. GENERAL INFORMATION 3
II. EFFECTIVENESS 4
A. Dosage Characterization 4
B. Substantial Evidence 5
III. TARGET ANIMAL SAFETY 16
IV. HUMAN FOOD SAFETY 16
V. USER SAFETY 16
VI. AGENCY CONCLUSIONS 17
A. Marketing Status 17
B. Exclusivity 17
C. Supplemental Applications 17
D. Patent Information: 17

I. GENERAL INFORMATION

A. File Number

NADA 141-267

B. Sponsor

Orion Corp.
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02200 Espoo
Finland

Drug Labeler Code: 052483

U.S. Agent: James H. Schafer, DVM
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C. Proprietary Name

DEXDOMITOR

D. Product Established Name

Dexmedetomidine hydrochloride

E. Pharmacological Category

Alpha$_2$-adrenoceptor agonist

F. Dosage Form

Sterile injectable solution

G. Amount of Active Ingredient

Each mL contains 0.5 mg dexmedetomidine hydrochloride.

H. How Supplied

10 mL, multidose vials

I. Dispensing Status

Rx

J. Dosage Regimen

40 mcg/kg

K. Route of Administration

IM

L. Species/Class

Cat

M. Indication

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 and cats.

N. Effect of Supplement

This supplement provides for a new indication for use as a preanesthetic to general anesthesia in cats.

II. EFFECTIVENESS

This supplemental approval does not change the previously approved canine/feline product. The Freedom of Information (FOI) Summary for the original approval of NADA 141-267 (December 1, 2006) contains information used for the approval of DEXDOMITOR for dogs. The FOI Summary for the supplemental approval of NADA 141-267 (September 7, 2007) contains information for the approval of DEXDOMITOR in cats. This FOI Summary contains information for the approval of DEXDOMITOR when used as a preanesthetic to general anesthesia in cats.

A. Dosage Characterization

A total of 36 clinically healthy cats received a single intramuscular (IM) dose of 40 mcg/kg dexmedetomidine 10 minutes prior to 5 mg/kg IM ketamine for induction of general anesthesia in a masked, multicenter field study (MPV00.05). Additional injections of ketamine were permitted at the professional discretion of the veterinarian. Cats were not included in the study if the veterinarian felt that the procedure could not be completed within 15 to 45 minutes. The following assessments were made prior to, and at 5, 15, 30, 60, 90, 120 and 180 minutes after administration of dexmedetomidine (given at 0 min): subjective sedation, analgesia and anesthesia scores; heart rate (HR); heart rhythm by electrocardiography (ECG); respiratory rate (RR); rectal temperature (RT); hemoglobin oxygen saturation (pulse oximetry; SpO2); and mucous membrane appearance.

Mean procedure duration was 23 minutes (range 15 to 47) and the most frequently performed procedures were ovariectomy and castration. Clinically relevant sedation and analgesia were observed within 5 minutes after dexmedetomidine administration. After administration of ketamine, sedation and analgesia scores increased significantly, lasting approximately 45 minutes. The procedure was successfully performed in all but one cat (fracture reduction); this cat however responded favorably to additional doses of ketamine. No treatment failures were observed. Anesthesia was graded as sufficient in all 36 cats and recovery from anesthesia was graded as moderate or smooth in 33 (of 36) cats.

Compared to baseline values (approximately 166 beats/minute), HR decreased following dexmedetomidine injection and remained low (on average 105 beats/minute). Sinus bradycardia was observed in all cats. The incidence of all other ECG findings was low (< 20%) and included atrioventricular dissociation (mainly second degree atrioventricular block) and extrasystole. Compared to baseline values (approximately 55 breaths/minute), RR decreased following dexmedetomidine injection to approximately 25 breaths/minute and then gradually increased over time after ketamine injection. RT decreased over time. Mean SpO2 ranged between 89 and 98 percent.

No deaths occurred during the study. Adverse reactions recorded during the study included: 3 (of 36) cats were hypothermic, 8 vomited, 5 were observed with arrhythmia and/or cardiorespiratory disorder, 1 had apnea, and 1 showed nervousness/agitation. All of these cats completed the study. One serious adverse reaction was observed in a 9-year-old female cat characterized by severe bradycardia, apnea, and cardiovascular depression after the 30 minute time point. That cat was withdrawn from the study and recovered uneventfully after treatment with the alpha2-adrenoceptor antagonist, atipamezole, and manual ventilation.

Conclusion: This study demonstrated that an IM dose of 40 mcg/kg dexmedetomidine is an appropriate preanesthetic dose prior to general anesthesia for common feline procedures such as ovariohysterectomy and castration.

B. Substantial Evidence

1. Type of Study: field study titled, Field Efficacy and Safety of Dexmedetomidine as a Preanesthetic Prior to General Anesthesia in Cats (#1987C-60-07-319)

2. Investigators:

Dr. Jason St. Romain Zachary, LA	Dr. Patrick McSweeney Metairie, LA
Dr. Philip VanVranken Battle Creek, MI	Dr. Samuel Geller Quakertown, PA
Dr. Randall Carpenter Grand Rapids, MI	n/a

3. General Design:

   a. Purpose: The objective of this study was to demonstrate the dose-sparing effect of dexmedetomidine on the amount of propofol or ketamine needed for successful induction of anesthesia; and to confirm that the use of dexmedetomidine as a preanesthetic is safe under field conditions. Secondary objectives included demonstrating the dose-sparing effect of dexmedetomidine on the concentration of isoflurane required for maintenance anesthesia during longer procedures; and demonstrating an improvement in perioperative analgesia when dexmedetomidine is administered preemptively as a preanesthetic prior to procedures requiring general anesthesia.

   b. Test animals: One hundred eighty four client-owned cats were enrolled with 116 receiving dexmedetomidine and 68 receiving saline. The majority of cats (73.4%) were of the domestic shorthair breed ranging in age from 0.2 – 16 years. Female cats represented 38.6% of the cats followed by males (31.5%), female spayed cats (16.8%) and male neutered cats (13.0%) respectively. Cats weighed from 2.1 – 18.8 pounds. Participating cats 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).

      Two dexmedetomidine-treated cats were excluded from the effectiveness analysis due to protocol deviations.

      Cats that were enrolled for short (<15 minutes) or long (>15 minutes) procedures were randomly assigned to 4 preanesthetic by induction drug treatment groups, each group divided into short and long procedures:

Table 1. Treatment groups

Treatment Group	**Procedure Length**	**Dexmedetomidine Preanesthetic**	**Induction Anesthetic**	**Dosage**	**n**
T01	Short	0 mcg/kg IM	Ketamine	5 mg/kg IM	18
T02	Short	40 mcg/kg IM	Ketamine	5 mg/kg IM	30
T03	Short	0 mcg/kg IM	Propofol	8.0-13.2 mg/kg IV over 60-90 sec	15
T04	Short	40 mcg/kg IM	Propofol	8.0-13.2 mg/kg IV over 60-90 sec	27
T01	Long	0 mcg/kg IM	Ketamine	5 mg/kg IM	19
T02	Long	40 mcg/kg IM	Ketamine	5 mg/kg IM	34
T03	Long	0 mcg/kg IM	Propofol	8.0-13.2 mg/kg IV over 60-90 sec	16
T04	Long	40 mcg/kg IM	Propofol	8.0-13.2 mg/kg IV over 60-90 sec	25

c. Control drug: The negative control treatment was saline.

d. Reason for treatment: Cats were enrolled in the study for a single procedure requiring general anesthesia including (but not limited to) ovariohysterectomy, onychectomy, orchiectomy, dental cleaning and mass removal.

e. Dosage forms:

- Injectable solution, DEXDOMITOR 0.5 mg dexmedetomidine/mL
- Injectable solution, 0.9% sterile saline for negative control
- Injectable solution, propofol 10 mg propofol/mL
- Injectable solution, ketamine, 100 mg ketamine/mL

f. Route of administration:

DEXDOMITOR and ketamine: intramuscular (IM)
Propofol: Intravenous (IV)

g. Dosage:

DEXDOMITOR: 40 mcg/kg
Saline: same dose volume as DEXDOMITOR

Propofol: 8.0-13.2 mg/kg to effect
Ketamine: 5 mg/kg

h. Test duration: May 9, 2008 to August 15, 2008

i. Variables:

Induction drug (ketamine and propofol) dose sparing:
The primary variable for determination of effectiveness was an assessment of the successful intubation of the cat following administration of the preanesthetic - induction drug combination.

Isoflurane required for maintenance anesthesia:
Isoflurane was administered at the discretion of study personnel based on the need for additional anesthesia and analgesia during a procedure. The vaporizer setting and oxygen flow rate were at the discretion of study personnel.

Post operative analgesia:
Subjective assessments of pain and analgesia were made at set times pre and post operatively using a visual analog scale (VAS). All VAS assessments for an individual cat were carried out by the same study participant. Animals assessed to be in pain could be treated with rescue analgesia.

Physiological parameters:
Heart rate (beats/min)
Heart rhythm
Electrocardiographic tracing
Respiratory rate
Rectal temperature (ºF)
Hemoglobin oxygen saturation (pulse oximetry,%)

Sedation scores
Spontaneous posture (0=normal; to 3=lying and unable to move)
Response to noise (0=sensitive/normal; to 3=no reaction)
Jaw tone (0=normal; to 3=jaw tone very weak)

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

Response to injection (none, slight, moderate, strong).

Adverse events: Abnormal clinical signs observed during the study and in the period 2-5 days after the procedure (including the side effects known to be associated with alpha2 agonists) were reported as adverse events.

4. Statistical methods: For all analyses, the individual cat was treated as the experimental unit. For cats receiving ketamine, a generalized linear mixed model was used to test the effect of treatment on the incidence of successful intubation at significance level 0.05. For cats receiving propofol, a linear mixed model was used to test the effect of treatment on the amount of propofol necessary to attempt intubation at significance level 0.05. For both ketamine and propofol, long and short procedures were analyzed separately.

5. Criteria for success/failure: For cats receiving ketamine, the primary variable for determination of effectiveness was the ability or inability to successfully intubate the cat following preanesthetic when administered ketamine at a dosage of 5 mg/kg instead of the currently recommended 22-33 mg/kg induction dose. For cats receiving propofol, the primary variable was the amount of propofol necessary to attempt intubation.

6. Results:

   a. Induction drug dose sparing – ketamine:
   Cats premedicated with saline had intubation success rates of 5.5% and 15.8% for the long and short procedures, respectively. Cats premedicated with dexmedetomidine had intubation success rates of 90.8% and 88.2% for the long and short procedures, respectively.

Table 2. Intubation success rate – ketamine

Procedure	**Preanesthetic**	**Percent success for intubation**	**Treatment P-value**
Short	Saline (T01)	15.8%	0.0110
Short	Dexmedetomidine (T02)	88.2%	0.0110
Long	Saline (T01)	5.5%	0.0201
Long	Dexmedetomidine (T02)	90.8%	0.0201

b. Induction drug dose sparing – propofol:
Cats premedicated with saline required mean doses of 10.56 mg/kg and 10.80 mg/kg of propofol for successful intubation prior to long and short procedures, respectively. Cats premedicated with dexmedetomidine required mean doses of 5.16 mg/kg and 5.65 mg/kg, 51.1% and 47.7% (respectively) less propofol, for successful intubation prior to long and short procedures.

Table 3. Mean propofol dose (mg/kg) required for successful intubation with and without dexmedetomidine preanesthesia for short and long procedures

Procedure	**Preanesthetic**	**Mean Propofol dose (mg/kg)**	**Range**
Short	Saline (T03)	10.80	5.81-13.78
Short	Dexmedetomidine (T04)	5.65	1.79-10.25
Long	Saline (T03)	10.56	5.55-14.7
Long	Dexmedetomidine (T04)	5.16	2.28-10.47

c. Isoflurane required for maintenance anesthesia: The mean isoflurane concentration in cats receiving ketamine and isoflurane was 2.97% when cats were premedicated with saline versus 1.94%, a 35% reduction, when the premedication was dexmedetomidine. The mean isoflurane concentration in cats receiving propofol and isoflurane was 3.01% when cats were premedicated with saline versus 1.67%, a 44.4% reduction, when the premedication was dexmedetomidine.

Table 4. Analysis of isoflurane concentration (%) required for maintenance anesthesia

Preanesthetic	**Induction agent**	**Means**	**Range**
Saline (T01)	Ketamine	2.97	1.50-4.74
Dexmedetomidine (T02)	Ketamine	1.94	0.50-3.70
Saline (T03)	Propofol	3.01	1.86-4.63
Dexmedetomidine (T04)	Propofol	1.67	0.74-5.00

d. Post operative analgesia: Compared to the saline control groups, mean post-operative visual analog scores (VAS) for pain were lower in the dexmedetomidine-treated groups. At 30 minutes into recovery, the mean VAS for dexmedetomidine-treated cats induced with ketamine and propofol were 1.7 and 3.1 respectively, compared to the saline control groups with mean VAS of 12.5 and 14.1, respectively. At 4 hours into recovery, the VAS pain scores in the dexmedetomidine-treated groups started to trend towards the saline control groups based on induction agent. At 24 hours into recovery, pain scores were similar between treatment groups.

   In the saline control groups, 42.4% of cats in the ketamine-induced cats and 46.7% of the propofol-induced cats received rescue analgesia, compared to 3.0% and 12.1%, respectively, in the dexmedetomidine-treated groups.

e. Physiological parameters:

   - Heart rate - Compared to the saline control groups, the mean heart rates of cats premedicated with dexmedetomidine remained lower during the procedural and recovery periods. The lower heart rates of the dexmedetomidine premedicated cats were not of clinical significance. At 24 hours into recovery, heart rates were similar between treatment groups and were similar to pretreatment values.

Table 5. Summary of mean heart rate (beats/minute) at selected timepoints

Preanesthetic Treatment	**Induction**	**Timepoint**										
		A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**
Saline (T01)	Ketamine	166.6	174.7	171.0	164.0	162.5	185.6	179.4	174.2	178.2	172.7	170.6
Dexmedetomidine (T02)	Ketamine	175.1	109.1	128.3	124.2	114.1	108.3	111.7	113.9	112.5	143.6	175.6
Saline (T03)	Propofol	172.8	179.3	158.6	127.2	146.5	181.5	185.6	176.1	173.1	176.7	166.7
Dexmedetomidine (T04)	Propofol	176.8	106.6	109.0	112.0	106.9	101.8	102.9	113.8	114.3	152.0	182.8

A=-4 days to -30 minutes. B=10-15 minutes post premedication. C=start procedure. D=15 minutes into procedure. E=end procedure. F=30 minutes into recovery. G=60 minutes into recovery. H=90 minutes into recovery. I=120 minutes into recovery. J=4 hours into recovery. K=24 hours into recovery.

   - Heart rhythm – Compared to the saline control groups, the number of irregular heart rhythms was greater in dexmedetomidine-treated cats. Irregular heart rhythms were reported in 10.3% of cats receiving dexmedetomidine prior to induction agent. After the cats were induced, in cats receiving isoflurane, irregular heart rhythms were reported in 26.3% and 40.0% of cats receiving ketamine and propofol, respectively. In cats that did not receive isoflurane, irregular heart rhythms were reported in 23.1% and 23.5% of cats receiving ketamine and propofol, respectively. No cats receiving saline controls were reported with irregular heart rhythms.

- Electrocardiographic tracing – Compared to the saline control groups, the number of cats observed with at least one arrhythmia after preanesthetic treatment administration but prior to induction was greater for dexmedetomidine-treated cats (Table 6). Additionally, the number of cats observed with at least 1 arrhythmia after induction and throughout the procedure was greater for dexmedetomidine-treated cats. The use of inhalant anesthesia altered the prevalence of certain arrhythmias (Tables 7 and 8).

Table 6. ECG abnormalities prior to induction agent

Abnormality	**Saline (T01, T03)**	**Dexmedetomidine (T02, T04)**
n (%)	60	114
Sinus pause	n/a	8 (7.0%)
Long QT	n/a	2 (1.8%)
Single ventricular escape beat	n/a	4 (3.5%)
Idioventricular rhythm	n/a	16 (14.0%)
atrial bigeminy	n/a	4 (3.5%)
Accelerated junctional rhythm	n/a	n/a
Delta wave	n/a	1 (0.9%)
SB (<120 bpm)		77 (67.5%)
ST (>240 bpm)	8 (13.3%)	n/a
1st DAVB	1 (1.7%)	30 (26.3%)
2nd DAVB	1 (1.7%)	2 (1.8%)
3rd DAVB	n/a	n/a
VPD	n/a	1 (0.9%)
SVPD	n/a	3 (2.6%)
Sinus Arrhythmia	3 (5.0%)	67 (58.8%)

SB=sinus bradycardia. ST=sinus tachycardia. DAVB=degree atrioventricular block. VPD=ventricular premature depolarizations. SVPD=supraventricular premature depolarizations.

Table 7. Cats that received isoflurane: ECG abnormalities at all timepoints after induction agent was given. Note: An arrhythmia is only counted 1 time for each cat even if it had multiple recordings of the same arrhythmia.

Induction	**Ketamine**		**Propofol**	
n/a	**Saline (T01)**	**Dexmedetomidine (T02)**	**Saline (T03)**	**Dexmedetomidine (T04)**
n (%)	37	38	28	34
Sinus pause		1 (2.6%)		2 (5.9%)
Long QT	1 (2.7%)	n/a	3 (11.5%) [n=26]	5 (14.7%)
Single ventricular escape beat	n/a	n/a	n/a	1 (2.9%)
Idioventricular rhythm	1 (2.7%)	1 (2.6%)	1 (3.6%)	1 (2.9%)
atrial bigeminy	n/a	n/a	n/a	n/a
Accelerated junctional rhythm	n/a	n/a	1 (3.6%)	n/a
Delta wave	n/a	n/a	n/a	n/a
SB	1 (2.7%)	15 (39.5%)	2 (7.1%)	22 (64.7%)
ST	n/a	n/a	n/a	n/a
1st DAVB	2 (5.4%)	6 (15.8%)	2 (7.1%)	17 (50.0%)
2nd DAVB	n/a	1 (2.6%)	n/a	1 (2.9%)
3rd DAVB	n/a	n/a	n/a	n/a
VPD	1 (2.7%)	2 (5.3%)	n/a	1 (2.9%)
SVPD	n/a	n/a	n/a	n/a
Sinus Arrhythmia	1 (2.7%)	15 (39.5%)	1 (3.6%)	20 (58.8%)

SB=sinus bradycardia. ST=sinus tachycardia. DAVB=degree atrioventricular block. VPD=ventricular premature depolarizations. SVPD=supraventricular premature depolarizations.

Table 8. Cats that did not receive isoflurane: ECG abnormalities at all timepoints after induction agent was given. Note: An arrhythmia is only counted 1 time for each cat even if it had multiple recordings of the same arrhythmia.

Induction	**Ketamine**		**Propofol**	
	Saline (T01)	**Dexmedetomidine (T02)**	**Saline (T03)**	**Dexmedetomidine (T04)**
n (%)	0	26	2	17
Sinus pause	n/a	n/a	n/a	n/a
Long QT	n/a	n/a	n/a	n/a
Single ventricular escape beat	n/a	n/a	n/a	1 (2.9%)
Idioventricular rhythm	n/a	n/a	n/a	n/a
atrial bigeminy	n/a	n/a	n/a	n/a
Accelerated junctional rhythm	n/a	n/a	n/a	n/a
Delta wave	n/a	1 (3.8%)	n/a	n/a
SB	n/a	16 (61.5%)	n/a	14 (82.4%)
ST	n/a	n/a	1 (50.0%)	n/a
1st DAVB	n/a	6 (23.1%)	n/a	6 (35.3%)
2nd DAVB	n/a	1 (3.8%)	n/a	n/a
3rd DAVB	n/a	n/a	n/a	n/a
VPD	n/a	n/a	n/a	n/a
SVPD	n/a	n/a	n/a	1 (5.9%)
Sinus Arrhythmia	n/a	17 (65.4%)	n/a	11 (64.7%)

SB=sinus bradycardia. ST=sinus tachycardia. DAVB=degree atrioventricular block. VPD=ventricular premature depolarizations. SVPD=supraventricular premature depolarizations.

- Respiratory rate – Compared to the saline control groups, the mean respiratory rates of cats premedicated with dexmedetomidine was mildly decreased following preanesthetic treatment. Throughout the procedural period, there was a reduction in respiratory rate for all treatment groups. Overall, during the procedural period cats receiving ketamine had lower respiratory rate than cats receiving propofol regardless of preanesthetic treatment. Cats in the dexmedetomidine-treated groups had lower respiratory rates in the postprocedural period, tending to increase slowly over time. At 24 hours into recovery, respiratory rates were similar between treatment groups and were slightly lower than pretreatment values.

Table 9. Summary of mean respiratory rate (breaths/minute) at selected timepoints

Preanesthetic Treatment	**Induction**	**Timepoint**										
		A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**
Saline (T01)	Ketamine	48.0	45.0	25.1	22.1	23.7	49.0	50.8	51.1	51.6	48.3	45.0
Dexmedetomidine (T02)	Ketamine	48.8	42.3	23.1	23.2	23.3	29.6	31.5	31.1	34.8	37.3	41.3
Saline (T03)	Propofol	51.8	55.2	28.0	23.2	29.4	40.5	42.1	40.3	43.4	44.6	49.4
Dexmedetomidine (T04)	Propofol	53.5	45.9	35.9	26.5	32.6	36.0	36.4	35.7	36.9	41.1	46.4

A=-4 days to -30 minutes. B=10-15 minutes post premedication. C=start procedure. D=15 minutes into procedure. E=end procedure. F=30 minutes into recovery. G=60 minutes into recovery. H=90 minutes into recovery. I=120 minutes into recovery. J=4 hours into recovery. K=24 hours into recovery.

- Rectal temperature - Following preanesthetic treatment prior to the start of the procedure, rectal temperature did not change appreciably compared to baseline. During the procedural period, rectal temperature tended to decrease for all of the groups. During the postprocedural period, the saline control groups had temperatures similar to baseline by 2 hours. In the dexmedetomidine-treated groups, rectal temperatures continued to decrease compared to the procedural period until 4 hours postprocedural when the rectal temperatures started to increase towards pretreatment values. At 24 hours into recovery, rectal temperatures were similar between treatment groups and were similar to pretreatment values.

Table 10. Summary of mean body temperature (ºF) at selected timepoints

Preanesthetic Treatment	**Induction**	**Timepoint**										
		A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**
	Ketamine	101.51	101.59	100.28	99.01	98.70	99.85	101.09	101.48	101.50	101.81	101.15
Dexmedetomidine (T02)	Ketamine	101.61	101.28	100.25	99.87	99.67	98.13	97.56	97.18	97.03	98.78	101.62
Saline (T03)	Propofol	101.62	101.68	100.24	98.73	98.71	99.15	100.00	100.95	101.36	101.53	101.40
Dexmedetomidine (T04)	Propofol	101.87	101.54	100.75	99.90	100.09	98.36	97.71	97.43	97.40	98.86	101.76

A=-4 days to -30 minutes. B=10-15 minutes post premedication. C=start procedure. D=15 minutes into procedure. E=end procedure. F=30 minutes into recovery. G=60 minutes into recovery. H=90 minutes into recovery. I=120 minutes into recovery. J=4 hours into recovery. K=24 hours into recovery.

- Hemoglobin oxygen saturation - Mean oxygen saturation for all treatment groups was at or above 95% at all timepoints. Compared to the saline control groups, mean values were slightly lower in the dexmedetomidine-treated groups at most timepoints. The lowest minimum oxygen saturation for the dexmedetomidine-treated groups was 82% and 84%, respectively, in the ketamine and propofol-induced cats. The lowest minimum oxygen saturation for the saline-control groups was 89% and 84%, respectively, in the ketamine and propofol-induced cats.

  Thirteen cats experienced oxygen saturations lower than 90%. Of these, 11 received dexmedetomidine (5 were induced with ketamine, 6 were induced with propofol).

f. Sedation scores: The sedation scores for posture, response to noise, and muscle tone of jaw were consistently higher for the dexmedetomidine-treated cats through 4 hours into the recovery period compared to the saline control groups.

g. Time to extubation, sternal recumbency, and standing (from the end of the procedure): Times from the end of procedure to extubation, sternal recumbency, and standing were longer for the dexmedetomidine-treated cats compared to the saline control groups.

   The mean time from end of procedure to extubation was 35.5 minutes and 38.4 minutes for the dexmedetomidine-treated groups induced with ketamine and propofol, respectively. The mean time from end of procedure to extubation was 5.5 minutes and 4.8 minutes for the saline control groups induced with ketamine and propofol, respectively.

   The mean time from end of procedure to sternal recumbency was 122.6 minutes and 103.0 minutes for the dexmedetomidine-treated groups induced with ketamine and propofol, respectively. The mean time from end of procedure to sternal recumbency was 15.2 minutes and 29.1 minutes for the saline control groups induced with ketamine and propofol, respectively.

   The mean time from end of procedure to standing was 160.9 minutes and 130.7 minutes for the dexmedetomidine-treated groups induced with ketamine and propofol, respectively. The mean time from end of procedure to standing was 31.8 minutes and 48.7 minutes for the saline control groups induced with ketamine and propofol, respectively.

h. Response to injection: Of 115 cats, 45 cats (39%) exhibited no reaction, 37 (32%) cats exhibited a slight reaction (nonspecific change in posture), 25 cats (22%) exhibited a moderate reaction (attention directed at injection site), and 8 cats (7%) exhibited a strong response (aggression).

7. Adverse reactions:

   The field study safety analysis included 184 cats (116 received dexmedetomidine; 68 received saline), 0.2 to 16 years of age, and representing 11 breeds. There were no serious adverse reactions reported during the study. The following table shows the number of cats reported with an adverse reaction (some cats experienced more than one adverse reaction).

Table 11. Adverse reactions during the feline preanesthesia field study

Induction Anesthetic	**Ketamine**		**Propofol**	
Preanesthetic	**Saline (T01) n=37**	**Dexmedetomidine (T02) n=64**	**Saline (T03) n=31**	**Dexmedetomidine (T04) n=52**
Apnea	n/a	1	n/a	n/a
Behavioral change	n/a	n/a	1	n/a
Corneal injury	1	n/a	n/a	n/a
Decreased body temperature	n/a	4	n/a	n/a
Emesis	2	20	1	12
Fluid in endotracheal tube	n/a	n/a	1	n/a
Heart murmur	n/a	n/a	n/a	2
Loose stool	n/a	2	n/a	n/a
Pale mucous membranes	n/a	11	n/a	9
Retching	n/a	1	1	3

One case of apnea was reported that received ketamine as the induction agent. This cat required artificial ventilation from the start of the procedure until 30 minutes into recovery when the cat began to breathe on its own and then recovered without further problems.

8. Conclusions:

   The study showed that DEXDOMITOR administered at 40 mcg/kg by the intramuscular (IM) route was effective as a preanesthetic for cats.

III. TARGET ANIMAL SAFETY

CVM did not require target animal safety studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-267 dated December 1, 2006, and supplemental approval dated September 7, 2007, contains a summary of target animal safety studies for cats.

IV. HUMAN FOOD SAFETY

This drug is intended for use in cats. 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 safety: 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 alpha2-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 (FD&C Act) and 21 CFR part 514. The data demonstrate that DEXDOMITOR, when used according to the label, is safe and effective for use as a preanesthetic to general anesthesia in cats.

A. Marketing Status

This product may be dispensed only by or on the lawful order of a licensed veterinarian. Adequate directions for lay use cannot be written because professional veterinary expertise is required to determine appropriate preanesthetic levels of sedation and analgesia that are required prior to anesthesia.

B. Exclusivity

This supplemental approval for DEXDOMITOR qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the FD&C Act because the supplemental application included safety and effectiveness studies. This exclusivity begins as of the date of our approval letter and only applies to the indication for the feline species.

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:

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.