

Date of Approval: **AUG 15 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

2007-141-267

FOIS 2

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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:** alpha₂-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:

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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	XYL	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).

Score	DEX (N = 120*)		XYL (N = 120)	
	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 (SpO₂, %), and rectal temperature (TEMP, °F) for cats treated at 0 minutes with dexmedetomidine (DEX, n = 122 cats) or xylazine (XYL, n = 120 cats).

variable	treatment	Time point (minutes)							
		-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

*SpO₂ 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).

treatment	category	Time point (minutes)							
		-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)									
	P	P	0.25	0.5	1	2	4	8	12	24	36	48
	r	r										
	e	e										
	s	s										
	t	t										
	u	u										
	d	d										
	y	y										
	*	*										
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, vomiting, 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)							
	P	P	0.25	0.5	1	1.5	2	4	8	24 [@]
	r	r								
	e	e								
	s	s								
	t	t								
	u	u								
	d	d								
	y	y								
	*	*								
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 °F to 102.4 °F. 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 °F.

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

VII. ATTACHMENTS:

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

PACKAGE INSERT

NADA 141-267, Approved by FDA.

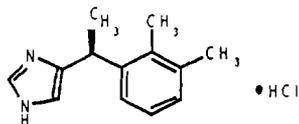
DEXDOMITOR®

(dexmedetomidine hydrochloride)
Sterile Injectable Solution – 0.5 mg/mL

For intramuscular and intravenous use in dogs and for intramuscular use in cats

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: DEXDOMITOR (dexmedetomidine hydrochloride) is a synthetic α_2 -adrenoreceptor agonist with sedative and analgesic properties. The chemical name is (+)-4-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole monohydrochloride. It is a white, or almost white, crystalline, water soluble substance having a molecular weight of 236.7. The molecular formula is $C_{13}H_{16}N_2 \cdot HCl$ and the structural formula is:



Each mL of DEXDOMITOR contains 0.5 mg dexmedetomidine hydrochloride, 1.6 mg methylparaben (NF), 0.2 mg propylparaben (NF), 9.0 mg sodium chloride (USP), and water for injection (USP), q.s.

INDICATIONS: 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.

DOSAGE AND ADMINISTRATION:

Dogs: DEXDOMITOR produces sedation and analgesia when administered intramuscularly (IM) at a dose of 500 mcg/m², or intravenously (IV) at a dose of 375 mcg/m². Doses for preanesthesia are 125 or 375 mcg/m² IM. The choice of preanesthetic dose depends on the duration and severity of the procedure, as well as the anesthetic regime. The following two tables may be used to determine the correct dexmedetomidine dosage. **Note that the mcg/kg dosage decreases as body weight increases.** For example, dogs weighing 2 kg are dosed at 28 mcg/kg dexmedetomidine IV, compared to dogs weighing 80 kg that are dosed at 9 mcg/kg. Due to the small volume of administration, accurate dosing is not possible in dogs weighing less than 2 kg.

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

Sedation/analgesia in dogs					
Dog Weight lbs	kg	Dexmedetomidine 375 mcg/m ² IV		Dexmedetomidine 500 mcg/m ² IM	
		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
73-81	33-37	11.6	0.81	15.0	1.10
81-99	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 in dogs					
Dog Weight lbs	kg	Dexmedetomidine 125 mcg/m ² IM		Dexmedetomidine 375 mcg/m ² IM	
		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
73-81	33-37	3.9	0.27	11.6	0.81
81-99	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

The use of dexmedetomidine as a preanesthetic markedly reduces anesthetic requirements. Injectable induction drug requirements for intubation will be reduced between 30% and 60%, depending on the choice of anesthetic and the dexmedetomidine preanesthetic dose. The concentration of inhalation maintenance anesthetic will be reduced between

PRECAUTIONS:

For cats, the concurrent use of DEXDOMITOR prior to or with an anesthetic has not been evaluated. Dexmedetomidine in cats has not been evaluated in the presence of other sedatives. Dexmedetomidine sedation is not recommended for cats with respiratory disease. Adverse reaction reports for dexmedetomidine include a cat with severe dyspnea and respiratory crackles diagnosed as acute pulmonary edema. The cat's health history was not known and the cat recovered with treatment.

Although not observed in the feline field study with dexmedetomidine, rare cases of delayed pulmonary edema, some resulting in death, have been reported in cats that received medetomidine (another α_2 -agonist), usually in conjunction with anesthesia. In these cases, dyspnea due to the delayed onset of pulmonary edema developed up to three days after medetomidine administration.

Dexmedetomidine should not be administered in the presence of preexisting hypotension, hypoxia, or bradycardia. Due to the pronounced cardiovascular effects of dexmedetomidine, only clinically healthy dogs and cats should be treated. Animals should be frequently monitored for cardiovascular function and body temperature during sedation or anesthesia.

Intramuscular ANTISEDAN (atipamezole) may be routinely used to rapidly reverse the effects of dexmedetomidine in dogs. Since analgesic as well as sedative effects will be reversed, pain management may need to be addressed.

In the event of apnea, accompanied by bradycardia and cyanotic mucous membranes, additional oxygen should be supplied. Administration of ANTISEDAN (atipamezole) to dogs exhibiting these signs is warranted.

Atipamezole has not been evaluated as a routine dexmedetomidine reversal agent in cats.

A decrease in body temperature is likely to occur during sedation with dexmedetomidine unless externally maintained. Once established, hypothermia may persist longer than sedation and analgesia. To prevent hypothermia, treated animals should be kept warm and at a constant temperature during the procedure, and until full recovery.

Nervous or excited animals with high levels of endogenous catecholamines may exhibit a reduced pharmacological response to α_2 -adrenoreceptor agonists like dexmedetomidine. In agitated animals, the onset of sedative/analgesic effects could be slowed, or the depth and duration of effects could be diminished or nonexistent. Therefore, allow dogs and cats to rest quietly for 10 to 15 minutes after injection. Repeat dosing has not been evaluated.

Reversible corneal opacity may occur during sedation in cats. An eye lubricant should be applied to prevent corneal desiccation that may result from a reduction in the blink reflex during sedation.

Spontaneous muscle contractions (twitching) can be expected in some dogs sedated with dexmedetomidine.

The use of dexmedetomidine as a preanesthetic in dogs significantly reduces the amount of induction and maintenance anesthetic requirements. Careful patient monitoring during anesthetic induction and maintenance is necessary to avoid anesthetic overdose.

Analgesia resulting from preanesthetic dexmedetomidine in dogs is dose-dependent, and may not provide adequate pain control during the postoperative or postprocedural period. Additional pain management should be addressed as needed.

Administration of anticholinergic agents in dogs at the same time or after dexmedetomidine could lead to adverse cardiovascular effects (secondary tachycardia, prolonged hypertension, and cardiac arrhythmias^{1,2}). However, an anticholinergic drug may be administered at least 10 minutes before dexmedetomidine for the prevention of the dexmedetomidine-induced reduction in heart rate. Therefore, the routine use of anticholinergics simultaneously with, or after dexmedetomidine in dogs, is not recommended (see ANIMAL SAFETY).

The use of anticholinergics in the presence of dexmedetomidine has not been evaluated in cats.

Dexmedetomidine has been evaluated only in fasted dogs; therefore, its effects on fed dogs (for example, the occurrence of vomiting) have not been characterized. In cats, there is a high frequency of vomiting whether fed or fasted; therefore, fasting is recommended to reduce stomach contents.

Dexmedetomidine has not been evaluated in dogs younger than 16 weeks of age, in cats younger than 12 weeks of age, or in geriatric dogs and cats.

Dexmedetomidine has not been evaluated for use in breeding, pregnant, or lactating dogs or cats.

ADVERSE REACTIONS:

Canine sedation/analgesia field study: In the field study safety analysis, 106 dogs received dexmedetomidine and 107 received medetomidine. Dogs ranged from 16 weeks to 16 years of age, representing 49 breeds. The following table shows the number of dogs displaying each clinical observation (some dogs experienced more than one adverse reaction).

Table 4: Adverse reactions during the canine sedation/analgesia field study

	Dexmedetomidine Total n=106	Medetomidine Total n=107
Auscultated unidentified arrhythmias	19	20
Severe bradycardia requiring treatment	1	1
Apnea requiring treatment	1	0
Slow onset of sedation (exceeding 30 minutes)	1	1
Ineffectiveness (dog standing throughout the study)	3	2
Severe hypothermia requiring treatment	2	0
Prolonged recovery	1	4

The occurrence of auscultated unidentified arrhythmias (some at multiple time points) decreased following the administration of atipamezole.

Canine preanesthesia field study: The preanesthesia field study safety analysis included 192 dogs, between 5 months and 15 years of age, representing 43 breeds enrolled for

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

The use of dexmedetomidine as a preanesthetic markedly reduces anesthetic requirements. Injectable induction drug requirements for intubation will be reduced between 30% and 60%, depending on the choice of anesthetic and the dexmedetomidine preanesthetic dose. The concentration of inhalation maintenance anesthetic will be reduced between 40% and 60%, depending on the dose of dexmedetomidine. The anesthetic dose should always be titrated against the response of the patient. The choice of anesthetic is left to the discretion of the veterinarian.

Cats: DEXDOMITOR produces sedation and analgesia when administered IM at a dose of 40 mcg/kg. The following table may be used to determine the correct dexmedetomidine dosage for cats based on body weight.

Table 3: SEDATION/ANALGESIA DOSE TABLE: Intramuscular (IM) dosing on the basis of body weight in cats.

Cat Weight		Sedation/analgesia in cats Dexmedetomidine 40 mcg/kg IM	
lbs	kg	mcg/kg	DEXDOMITOR, mL
4-7	2-3	40	0.2
7-9	3-4	40	0.3
9-13	4-6	40	0.4
13-15	6-7	40	0.5
15-18	7-8	40	0.6
18-22	8-10	40	0.7

It is recommended that dogs and cats be fasted for 12 hours before treatment with DEXDOMITOR. An eye lubricant should be applied to cats to prevent corneal desiccation that may result from a reduction in the blink reflex during sedation. Following injection of DEXDOMITOR, the animal should be allowed to rest quietly for 15 minutes; sedation and analgesia occur within 5 to 15 minutes, with peak effects at 30 minutes after dexmedetomidine.

CONTRAINDICATIONS: Do not use DEXDOMITOR in dogs or cats with cardiovascular disease, respiratory disorders, liver or kidney diseases, or in conditions of shock, severe debilitation, or stress due to extreme heat, cold or fatigue.

As with all alpha₂-adrenoceptor agonists, the potential for isolated cases of hypersensitivity, including paradoxical response (excitation), exists.

HUMAN WARNINGS: 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.

Ineffectiveness (dog standing throughout the study)	3	2
Severe hypothermia requiring treatment	2	0
Prolonged recovery	1	4

The occurrence of auscultated unidentified arrhythmias (some at multiple time points) decreased following the administration of atipamezole.

Canine preanesthesia field study: The preanesthesia field study safety analysis included 192 dogs, between 5 months and 15 years of age, representing 43 breeds enrolled for elective procedures conducted under general anesthesia. The following table shows the number of dogs within a treatment group that showed each clinical sign (some dogs experienced more than one adverse reaction).

Table 5: Adverse reactions during the canine preanesthesia field study

Induction Anesthetic:	Treatment Groups					
	Propofol			Barbiturate		
Preanesthetic Dose:	0 mcg/m ² n=32	125 mcg/m ² n=32	375 mcg/m ² n=32	0 mcg/m ² n=32	125 mcg/m ² n=32	375 mcg/m ² n=32
Ventricular premature contractions	0	2	0	4	1	0
Severe bradycardia	0	0	1	0	0	1
Tachycardia	0	0	0	1	1	0
Diarrhea	1	0	0	3	1	1
Emesis	4	7	4	2	3	6
Urinary incontinence	0	0	0	0	0	1
Self trauma	0	2	1	2	1	0

Other clinical signs observed in dogs treated with dexmedetomidine include decreased respiratory rate and hypothermia.

Feline sedation/analgesia field study: The field study safety analysis included 242 cats (122 received dexmedetomidine; 120 received xylazine), 0.5 to 17 years of age, and representing 19 breeds. The following table shows the number of cats reported with an adverse reaction (some cats experienced more than one adverse reaction).

Table 6: Adverse reactions during the feline field study

	Dexmedetomidine n = 122	Xylazine n = 120
Vomiting	70	82
Urinary incontinence	6	11
Hypersalivation	4	5
Involuntary defecation	4	1
Hypothermia	2	1
Diarrhea	2	0
Arrhythmia	1	2
Corneal ulcer	1	0
Cyanosis	1	0
Dyspnea	1	0

The most frequently observed adverse reaction was vomiting in both fasted and fed cats. Other infrequent clinical signs observed in cats treated with dexmedetomidine included fatigue, anorexia, cystitis, and peripheral vascular disorder. One incidence of dyspnea was reported, 43 minutes after dexmedetomidine administration during an oral examination/dental procedure. Prior to dexmedetomidine, the cat was free of clinical signs, but had a history of asthma and respiratory infection. The cat responded successfully to treatment.

INFORMATION FOR OWNERS: Due to the rare possibility of delayed onset of pulmonary edema which has been associated with administration of other alpha₂-adrenergic agonists in cats, animal owners should notify their veterinarian immediately if their cat experiences difficulty breathing.

CLINICAL PHARMACOLOGY: Dexmedetomidine is a potent non-narcotic alpha₂-adrenoceptor agonist which produces sedation and analgesia. These effects are dose dependent in depth and duration. Blood pressure is initially increased due to peripheral vasoconstriction, subsequently dropping to normal or slightly below normal levels. Vasoconstriction may cause mucous membranes to appear pale or mildly cyanotic. This initial vasopressor response is accompanied by a compensatory marked decrease in heart rate mediated by a vagal baroreceptor. The peripheral pulse may feel weak and a transient change in the conductivity of the cardiac muscle may occur, as evidenced by first and second degree atrioventricular blocks. Other arrhythmias may occur. Dexmedetomidine also decreases the respiratory rate and decreases body temperature. The magnitude and duration of the decrease in body temperature is dose dependent. Dexmedetomidine causes depression of gastrointestinal motility due to decrease in smooth muscle activity, increases blood glucose levels due to inhibition of insulin release, and increases production of urine. Spontaneous muscle contractions (twitching) can be expected in some dogs sedated with dexmedetomidine. Vomiting in cats has been associated with alpha₂-adrenergic agonist central stimulation of the brain⁴.

EFFECTIVENESS:

Canine sedation/analgesia field study: Dexmedetomidine was evaluated in a masked, controlled, multi-site field study, using parallel treatment groups. Effectiveness was evaluated in 200 (of 213) healthy client-owned dogs, ranging in age between 16 weeks and 16 years of age, and in size between 4.8 lbs and 141 lbs (2.2 kg and 64 kg). Dogs admitted to veterinary clinics for various procedures requiring sedation and/or analgesia received either dexmedetomidine or medetomidine once, by IV or IM injection. Procedures included dental care, radiography, minor skin tumor removal, and treatment of otitis. Sedation and analgesia occurred within 5 minutes after IV dexmedetomidine, and within 15 minutes after IM dexmedetomidine, with peak effects approximately at 15 or 30 minutes, respectively. Effects waned by approximately two hours after IV administration, and by three hours using the IM route. Dexmedetomidine and medetomidine showed comparable clinical effects.

Cardiac rhythms were evaluated by auscultation. Bradycardia occurred within 5 to 15 minutes after IV dexmedetomidine or medetomidine, and within 15 to 30 minutes after either drug given IM. Sixty-four dexmedetomidine-treated dogs and 50 medetomidine-treated dogs were observed with bradycardia.

Adverse reactions during the field study included ausculted unidentified arrhythmias, apnea, hypothermia, and ineffectiveness (see ADVERSE REACTIONS).

Eleven dogs received concomitant medication during the field study, including amoxicillin, cephalixin, triamcinolone, methyl-prednisolone acetate, neomycin, nystatin, thiostrepton, acepromazine, atropine, and atipamezole.

The results of this field study demonstrate that dexmedetomidine produces satisfactory levels of sedation and analgesia for clinical examinations and procedures, minor surgical procedures, and minor dental procedures.

Canine preanesthesia field study: The use of dexmedetomidine as a preanesthetic was evaluated in a controlled, multi-site field study, using parallel treatment groups. Effectiveness was evaluated in 192 healthy, client-owned dogs, between 5 months and 15 years of age, weighing 4 to 196 lbs (2 kg to 89 kg). Dogs received IM dexmedetomidine or saline as a preanesthetic to general anesthesia. All dogs were induced by an injectable anesthetic; half of the dogs were maintained with an inhalation anesthetic. Procedures included castration, ovariohysterectomy, skin surgery, radiography, physical examination, dental procedures, ear cleaning, anal sac treatment, and grooming.

Compared to saline controls, dexmedetomidine IM reduced induction drug requirements by 30-36% (at 125 mcg/m²) and by 38-61% (at 375 mcg/m²). Inhalation anesthetic requirements were 40-60% less for dexmedetomidine-preanesthetized dogs. The number of dogs with clinical signs of pain was less for at least 30 minutes after the procedure in dogs treated with 375 mcg/m² dexmedetomidine, compared to saline controls.

Recovery times were dose dependent, averaging 15-32 minutes to extubation and 71-131 minutes to standing recovery (longer times correspond to higher dexmedetomidine dose). Recovery times also depended on the induction anesthetic. Recovery times following barbiturate induction were longer (30 minutes to extubation and 118 minutes to standing), compared to dogs induced with propofol (23 minutes to extubation and 84 minutes to standing).

Cardiac arrhythmias were monitored by ECG. Dexmedetomidine-treated dogs were more frequently observed with at least one incidence of arrhythmia compared to saline controls. The most commonly observed arrhythmias were bradycardia, 1st and 2nd degree AV block, and sinus arrest. Other less frequently observed arrhythmias included ventricular premature complexes, supraventricular premature complexes, 3rd degree AV block, and sinus pause.

Adverse events included bradycardia, tachycardia, VPCs, vomiting, diarrhea, urinary incontinence, and self trauma (see ADVERSE REACTIONS).

The results of the preanesthesia field study demonstrate that dexmedetomidine provided anesthetic dose-sparing, sedation, and analgesia during procedures conducted under general anesthesia.

Feline sedation/analgesia field study: DEXDOMITOR was evaluated in a masked, controlled, multiple site field study, using parallel treatment groups. Effectiveness was evaluated in 242 client-owned cats, ranging in age between 0.5 and 17 years, and in size between 2.3 and 9.6 kg (5 and 21 lbs). Cats admitted to veterinary clinics for various procedures requiring restraint, sedation, and/or analgesia were randomized to treatment group and given dexmedetomidine (400 mcg/kg)

of twelve dogs (IV) for up to 1.5 hours; decreased transient pupillary light reflex was seen for up to 60 minutes in two of twelve dogs (IM). Vomiting was seen in one of twelve dogs. First and second degree AV blocks were observed in one of twelve dogs. Elevated concentrations of ALT were observed in 3 of 12 dogs, without histological changes to the liver.

Dexmedetomidine demonstrated dose dependent effects related to its pharmacology when administered IV or IM to healthy dogs at doses up to five times the recommended dose.

Canine safety study with an anticholinergic: In another laboratory safety study, one of three doses of an IM anticholinergic drug or saline was administered 10 minutes before, at the same time, or 15 minutes after 500 mcg/m² IM dexmedetomidine. The anticholinergic drug was given for the prevention or treatment of dexmedetomidine-induced reduction in heart rate. In a crossover design, 18 dogs were used in a total of 72 trials, to evaluate the safety of dexmedetomidine used with an anticholinergic drug.

Dogs were instrumented for the accumulation of continuous ECG data. The following arrhythmias were recorded during the study (some dogs experienced more than one arrhythmia).

Table 7: Arrhythmias recorded during the canine laboratory safety study⁴

Type of arrhythmia	Number of dogs (of 18)
Second degree AV block	18
Third degree AV block	6
Ventricular escape beats	16
Ventricular premature contractions	14
Idioventricular rhythm	1
Supraventricular tachycardia (SVT) or SVPCs	16
Paroxysmal VT	1
Ventricular bigeminy; SVPCs; pulse alternans	1
Junctional escape beat	1

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

The occurrence of arrhythmias was not related to the presence or absence of the anticholinergic drug. Arrhythmias were transient (although frequent over time in some dogs), returning toward baseline levels within 55 minutes after dexmedetomidine. No dogs required treatment related to these arrhythmias, and none of these arrhythmias persisted or adversely affected the overall clinical status of any dog in the study.

Dexmedetomidine without anticholinergic: Without the anticholinergic drug, and in addition to arrhythmias, dexmedetomidine produced clinically relevant sedation accompanied by a statistically significant reduction in heart rate, respiratory rate, cardiac output, pulmonary arterial temperature, and mixed venous oxygen tension. 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. 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: Either of the two higher anticholinergic doses was effective in the prevention or treatment of the dexmedetomidine-induced reduction in heart rate. Anticholinergic (higher doses) given after dexmedetomidine caused marked increases in the occurrence of various cardiac arrhythmias, especially second degree AV block. 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. Increases were dose related; the highest anticholinergic dose elicited more frequent arrhythmias and larger increases in heart rate and blood pressure.

In conclusion, moderate doses of anticholinergic drug given prior to dexmedetomidine performed best for the prevention of dexmedetomidine-induced reduction of heart rate in dogs. The routine use of anticholinergics given simultaneously with, or after dexmedetomidine, is not recommended.

Feline safety study: In a multiple dose safety study, DEXDOMITOR was administered intramuscularly (IM) at 1X, 3X, and 5X (40, 120, and 200 mcg/kg) the recommended dose of 40 mcg/kg on 3 consecutive days to healthy cats 6 to 8 months old. A control group received the product vehicle as a placebo (0X). No mortality was observed. The depth and duration of sedation was dose dependent, lasting approximately 2 hours in the 1X group, 2 to 4 hours in the 3X group, and greater than 8 hours in the 5X group. The lowest recorded individual heart rate was 60 beats/minute and occurred in the 5X dose group (2 cats). Cardiac arrhythmias characterized by isolated junctional escape complexes with episodes of junctional escape rhythm were observed during periods of low heart rate or following sinus pauses in all dexmedetomidine dose groups. In most cases the arrhythmia was no longer observed after 1 to 2 hours. Atrioventricular block was not observed. Incidences of arrhythmias were not related to dose; however, more cats were affected by cardiac arrhythmias on the third day of treatment, compared to the first two days of the study. The decrease in respiratory rate, but not the duration, was dose dependent. The rectal temperature decreased in all dexmedetomidine-treated groups, with the lowest temperatures in the 5X group at 8 hours on all three days. Two cats vomited (40 and 120 mcg/kg). Corneal opacity was noted in all dexmedetomidine-dose groups, was transient, related to dose and duration of sedation, and was attributed to lack of lubrication with decreased blinking during sedation. Hematology and blood chemistry were unaffected by treatment. Injection site tolerance was good, with mild inflammatory lesions representative of the IM injection procedure. Gross and histological examination of all other tissues did not reveal any abnormalities related to DEXDOMITOR administration.

Feline sedation/analgesia field study: DEXDOMITOR was evaluated in a masked, controlled, multiple site field study, using parallel treatment groups. Effectiveness was evaluated in 242 client-owned cats, ranging in age between 0.5 and 17 years, and in size between 2.3 and 9.6 kg (5 and 21 lbs). Cats admitted to veterinary clinics for various procedures requiring restraint, sedation, and/or analgesia were randomized to treatment group and given dexmedetomidine (122 cats) or xylazine (120 cats) once by IM injection. Procedures performed using dexmedetomidine included dental care, radiography, minor superficial surgery, otitis treatment, blood or urine sample collection, tattooing, microchip placement, and grooming.

Sedation and analgesia occurred within 5 to 15 minutes and peak effects were observed 30 minutes after dexmedetomidine. The procedure was easily performed in 91% of cats beginning 30 minutes after dexmedetomidine. Sedative and analgesic effects waned by three hours after dexmedetomidine.

Signs of sedation were deeper for cats receiving dexmedetomidine compared to those receiving xylazine. No clinically relevant differences were observed between dexmedetomidine and xylazine with respect to analgesia or physiological variables. Heart rate, respiratory rate, and rectal temperature decreased. Bradycardia was observed within 5 to 15 minutes and heart rates of ≤ 70 beats/minute were seen in 18% of cats. The most commonly observed arrhythmias assessed with ECG were atrioventricular dissociation and escape rhythms, followed by a few incidences of premature complexes and one incidence of atrioventricular block. Oxygen saturation, mucous membrane color, capillary refill time, pulse character, respiratory depth and pattern, and response of the animal to injection were clinically satisfactory. All cats recovered from changes induced by dexmedetomidine.

Ninety-seven adverse events were reported after dexmedetomidine. The most frequently reported adverse reactions included vomiting (70), urinary incontinence (6), hypersalivation (4), involuntary defecation (4), hypothermia (2), and diarrhea (2) (see ADVERSE REACTIONS).

The results of this field study demonstrate that dexmedetomidine produces satisfactory levels of sedation and analgesia for clinical examinations and procedures, minor surgical procedures, and minor dental procedures.

ANIMAL SAFETY:

Canine safety study: In the multiple dose safety study, dexmedetomidine was administered at 0, 1, 3 or 5 times (X) the recommended IV and IM doses on 3 consecutive days to a total of 36 healthy, young beagles. Two additional groups were given a 3X dose of dexmedetomidine (IV or IM) followed by three 1X doses of the reversal agent, atipamezole (ANTISEDAN), every 30 minutes. This was repeated for a total of 3 days. No deaths occurred during the study.

1X dose group: At the recommended dose, sedation lasted less than 3 hours. During sedation, muscle twitches occurred intermittently, and decreases in temperature, respiratory rate and heart rate were observed in all animals. A slow pupil response to light was seen transiently about 15 minutes after dosing in one of twelve dogs. Second degree atrioventricular (AV) blocks were observed in one of twelve dogs.

3X dose group: At 3 times the recommended dose, the duration of sedation was between two and eight hours. During sedation, muscle twitches occurred, and temperature, respiratory rate, and heart rate decreased in all dogs. The pupillary light reflex was transiently decreased for up to 90 minutes in four of twelve dogs. Vomiting was seen in two of twelve dogs. One dog experienced first and second degree AV blocks; second degree AV block was observed in three of twelve dogs. Elevated concentrations of alanine aminotransferase (ALT) were observed in one dog, without histological changes to the liver.

5X dose group: At 5 times the recommended dose, the duration of sedation was between four and eight hours. Muscle twitches, decreases in temperature, respiratory rates, and heart rates were seen in all dogs. No pupil response was noted in six

and was attributed to lack of lubrication with decreased blinking during sedation. Hematology and blood chemistry were unaffected by treatment. Injection site tolerance was good, with mild inflammatory lesions representative of the IM injection procedure. Gross and histological examination of all other tissues did not reveal any abnormalities related to DEXDOMITOR administration.

Dexmedetomidine demonstrated dose dependent effects related to its pharmacology when administered IM to healthy cats at doses up to five times the recommended dose.

Feline acute tolerance study: IM DEXDOMITOR was administered once at 10X (400 mcg/kg) the recommended dose of 40 mcg/kg to 3 female and 3 male 7 month old cats. No mortality was observed. Sedation was observed within 15 minutes of dosing and lasted for at least 4 hours with full recovery noted between 8 and 24 hours after dosing. Transient observations of corneal dehydration and opacity, miosis, pale skin and gingiva, salivation, and watery ocular discharge were observed in some animals. Vomiting was observed 7 to 11 hours after dosing in all but one animal. Decreases in heart rate accompanied by prolonged PQ and QT intervals were most pronounced 2 to 4 hours after dosing. 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 which were considered secondary to bradycardia. Slightly lower respiratory rate and reduced rectal temperature were observed 4 to 8 hours after dosing. Observations had returned to normal by 24 hours after dosing. Mild inflammatory lesions observed histologically at the injection site were representative of the IM injection procedure. No treatment related changes were observed in hematology. Mild elevations in some clinical ALT, AST, and CK, were observed 24 hours after dosing, with a trend towards recovery by 48 hours. Total protein, albumin and globulin levels were slightly lowered in one cat 48 hours after dosing.

STORAGE INFORMATION: Store at controlled room temperature 15-30°C (59-86°F). Protect from freezing.

HOW SUPPLIED: DEXDOMITOR is supplied in 10-mL, multidose vials containing 0.5 mg of dexmedetomidine hydrochloride per mL.

REFERENCES:

- (1) Ko JCH, Fox SMF, Mandsager RE. Effects of preemptive atropine administration on incidence of medetomidine-induced bradycardia in dogs. J Am Vet Med Assoc 2001; 218:52-58.
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U.S. Patent No. 4,910,214

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TAKE TIME



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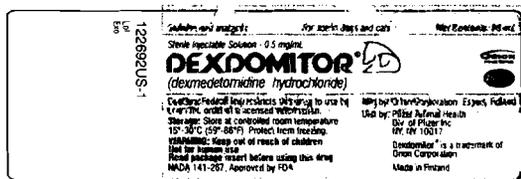


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DEXDOMITOR[®]

(dexmedetomidine hydrochloride)

Sterile Injectable Solution
0.5 mg/mL

Storage: Store at controlled room temperature 15°-30°C (59°-86°F). Protect from freezing.

NET CONTENTS _____ x 10 mL

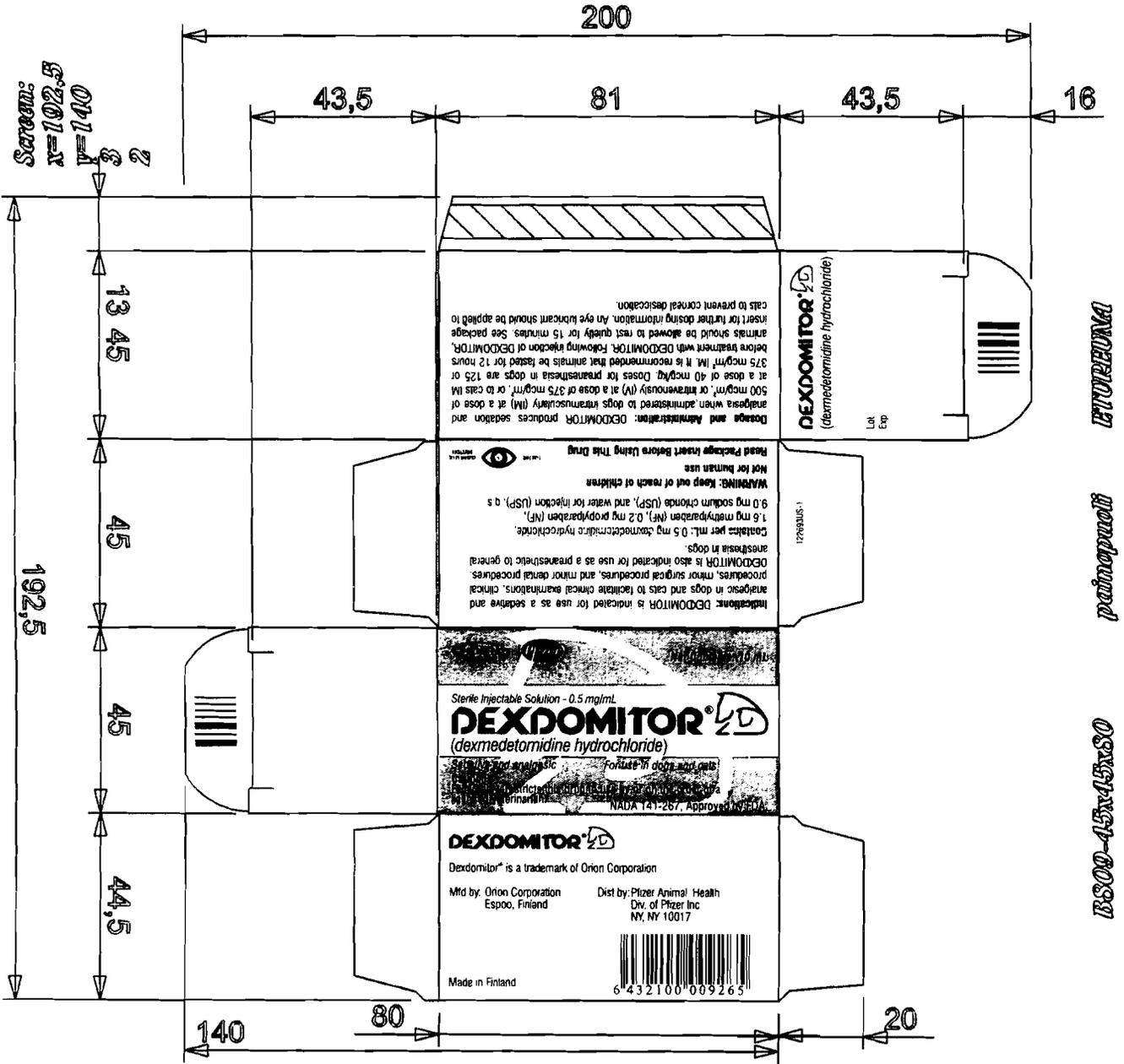
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