

Date of Approval: ~~OCT 28 2001~~

**FREEDOM OF INFORMATION SUMMARY**

Supplemental NADA 141-219

**METACAM**

Meloxicam 5 mg/mL Solution for Injection

METACAM (meloxicam) 5 mg/mL Solution for Injection is indicated for the control of postoperative pain and inflammation associated with orthopedic surgery, ovariohysterectomy and castration in cats, when administered prior to surgery.

Sponsored by:

Boehringer Ingelheim Vetmedica, Inc.

141-219

FOIS 1

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**FREEDOM OF INFORMATION SUMMARY**

**1. GENERAL INFORMATION:**

- a. File Number: NADA 141-219
- b. Sponsor: Boehringer Ingelheim Vetmedica, Inc.  
2621 North Belt Highway  
St. Joseph, MO 64506-2002  
  
Drug Labeler Code: 000010
- c. Established Name: meloxicam
- d. Proprietary Name: METACAM 5 mg/mL Solution for Injection
- e. Dosage Form: injectable
- f. How Supplied: 10 mL bottle
- g. How Dispensed: Rx
- h. Amount of Active Ingredients: 5 mg meloxicam/mL
- i. Route of Administration: subcutaneous injection
- j. Species/Class: feline
- k. Recommended Dosage: **Administer a single, one-time subcutaneous dose of METACAM 5 mg/mL Solution for Injection to cats at a dose of 0.14 mg/lb (0.3 mg/kg) body weight.**  
  
**Use of additional meloxicam or other NSAIDs is contraindicated. (See Contraindications). To ensure accuracy of dosing, the use of a 1 mL graduated syringe is recommended.**
- l. Pharmacological Category: Non steroidal anti-inflammatory (NSAID)

- m. **Indications:** METACAM (meloxicam) 5 mg/mL Solution for Injection is indicated in dogs for the control of pain and inflammation associated with osteoarthritis and in cats for the control of postoperative pain and inflammation associated with orthopedic surgery, ovariohysterectomy and castration when administered prior to surgery.
- n. **Effect of Supplement:** This supplement to NADA 141-219 provides revisions to 21 CFR 522.1367 (2) *Indications for Use*. To add a claim for the control of postoperative pain and inflammation associated with orthopedic surgery, ovariohysterectomy and castration when administered prior to surgery in cats.

## 2. **EFFECTIVENESS:**

### a. **Dosage Characterization:**

1. **Title:** Pharmacokinetics and Bioavailability of Meloxicam in Cats Following a Single Intravenous, Subcutaneous and Oral Administration.  
**Study Number:** 6820 UHA 9204
  - a. **Investigators:** Catherine Caulfield, BSc, HDE, C. Biol., F.I. Biol.  
H. Franke, MD.  
Biological Laboratories (Ballina) Ltd.  
Carrentrila  
Ballina  
County Mayo  
Ireland
  - b. **Test Animals:** Eight mature cats (4 males and 4 females), weighing between 2.3 - 4.16 kg (5.06 – 9.15 lb).
  - c. **Study Design:** This investigation was divided into two study phases, each phase designed as a 2-period, 2-treatment, 2-sequence crossover. Each phase employed 4 cats (2 males, 2 females), and all meloxicam treatments were administered as a 0.3 mg/kg dose. The treatments were either oral suspension and intravenous solution (phase 1) or subcutaneous solution and intravenous solution (phase 2). Subcutaneous doses were injected under the skin above the right scapula. Oral doses were administered directly into the mouth. Intravenous doses were administered into the cephalic or saphenous veins on the side contralateral to blood collection. Cats were fasted 12 hours prior to administration of the test articles, and water was available ad libitum. This study included an *in vitro* examination of the extent of drug plasma protein binding, using

ultrafiltration methods, radiolabelled meloxicam, and drug concentrations ranging from 0.2 mcg/mL to 10 mcg/mL.

d. *Variables:* Total meloxicam levels in plasma (free plus bound) were measured using a validated HPLC analytical method. Blood samples were collected from the left or right antebrachial vein into potassium EDTA-coated tubes prior to drug administration and at 0.5, 1, 3, 6, 10, 24, 48, 72 and 120 hrs post-dose. An additional 5 minute blood sample was included following intravenous administration.

e. *Results:*

*In vitro:* Approximately 97% of the total drug concentrations of meloxicam measured in plasma represent drug that is bound to plasma proteins. The percent protein binding does not vary across plasma meloxicam concentrations ranging from 0.2 – 10 mcg/mL.

*In vivo:* The pharmacokinetic variables and bioavailability of meloxicam following intravenous, oral and subcutaneous administrations are presented in Table 1.

TABLE 1: Pharmacokinetic variables (mean and relative standard deviation) obtained by non-compartmental analysis after administration of a single dose of 0.3 mg meloxicam/kg body weight

Parameter	Units	Phase 1		Phase 2	
		Intravenous	Oral	Intravenous	Subcutaneous
CL total	mL/min/kg	0.21 (36)	---	0.22 (26)	---
VD area	L/kg	0.28 (7)	---	0.27 (5)	---
VDss	L/kg	0.28 (7)	---	0.25 (1)	---
AUCinf	mcg x hr/mL	26.1 (35)	21.0 (44)	24.0 (28)	24.9 (5)
AUClast	mcg x hr/mL	23.8 (33)	18.8 (46)	21.9 (25)	23.1 (67)
T <sub>1/2</sub>	hr	14.5 (31)	15.6 (37)	14.6 (31)	14.5 (36)
C <sub>max</sub>	mcg x hr/mL	---	0.9 (22)	---	1.1 (34)
T <sub>max</sub>		---	1.5 (67)	---	1.5 (28)
F		---	0.83 (49)	---	1.06 (29)

Notes:

where VD = volume of distribution estimated either on the basis of terminal elimination half life (= VD area) or mean residence time (=VDss), CL total = total (free plus bound) systemic clearance, AUClast = the area under the concentration versus time curve measured from time zero to the last concentration exceeding the limit of quantification of the analytical method, AUCinf = AUC extrapolated to time infinity (= AUClast + last measurable concentration divided by the terminal elimination rate constant), T<sub>1/2</sub> = the terminal elimination half life, estimated as 0.693/the terminal elimination rate constant, C<sub>max</sub> = the observed maximum concentration, T<sub>max</sub> = the time to

$C_{max}$ , and  $F = AUC_{inf}$  after oral or subcutaneous administration divided by  $AUC_{inf}$  following intravenous injection.

These data confirm that meloxicam is completely absorbed following subcutaneous injection, and is nearly completely absorbed following oral administration. The values for VD are consistent with drug distribution being limited to the extracellular fluids (where reported values for extracellular fluid volume are approximately 0.2-3 L/kg<sup>1</sup>). The relatively slow total body clearance results in a 15 hr terminal elimination half-life.

- f. *Conclusion:* This study demonstrates that meloxicam sterile solution is completely bioavailable (> 100%) following subcutaneous administration in cats. Therefore, the administration of meloxicam as a single dose by the subcutaneous route is a viable therapeutic option.

**b. Substantial Evidence:**

Title: The Control of Postoperative Pain with Meloxicam Compared to Butorphanol in Cats Undergoing Onychectomy.  
Study Number: 635-0986-98F-164

A. *Type of Study:* Field Study

B. *Investigators:*

TABLE 2: List of Investigators

Investigator	Clinic Name	City	State
Dr. Gwendolyn Carroll	College of Veterinary Medicine	College Station	TX
Dr. Barbara Teter	The Pet Clinic	Omaha	NE
Dr. Mette Tomkins	Timberlyne Animal Clinic	Chapel Hill	NC
Dr. Nigel Gumley	Alta Vista Animal Clinic	Ottawa	ON

C. *General Design:*

- 1) Purpose: The objectives of this study were to determine the effectiveness and safety of meloxicam for the control of postoperative pain and inflammation associated with onychectomy only, or onychectomy and surgical neutering in cats, compared to butorphanol as an active control.
- 2) Test Animals: One hundred thirty-nine client-owned cats enrolled in the study. All cats were pre-medicated with acepromazine, induced with propofol and maintained on isoflurane. One cat that was enrolled in the butorphanol treatment group died under anesthesia. Therefore, in the butorphanol treatment group, 67 cats were enrolled, but 66 cats completed the study. Seventy-two cats received meloxicam. The cats ranged in age

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<sup>1</sup> Davies B, Morris T: Physiological parameters in laboratory animals and humans. *Pharm Res*, 10: 1093-1095, 1993.

from 4 months to 16 years of age and ranged in weight from 2.4 to 15.5 pounds.

- 3) Control: Active control, butorphanol
- 4) Enrollment: Cats that required onychectomy or onychectomy plus neutering elective surgeries were eligible for enrollment.

Inclusion criteria:

- Greater than 4 months old
- Score of 1 or 2 for the American Society of Anesthesiologists (ASA) system.
- No medical abnormalities on physical examination.
- Owners signed the Owner Consent Form
- Not pregnant

Exclusion criteria:

- Cats with a history of blood dyscrasia, hepatic, renal or cardiac disease.
- Cats that received an NSAID or steroid in the previous 14 days.
- Cats that received glycosaminoglycans in the previous 30 days.

- 5) Dosage Form: Final formulation of METACAM (meloxicam) 5 mg/mL Solution for Injection. Commercial TORBUGESIC-SA / TORBUGESIC (butorphanol tartrate).
- 6) Route of Administration: Single subcutaneous injection
- 7) Dosages Used: Meloxicam at 0.3 mg/kg body weight and butorphanol at 0.4 mg/kg body weight.
- 8) Treatment Duration: Meloxicam or butorphanol treatment was administered once prior to surgery. Pain intervention therapy (butorphanol at 0.4 mg/kg body weight) was allowed for either treatment group after extubation as needed.
- 9) Variables Measured:

Pain Assessment Variables:

The cats were given a physical examination prior to enrollment. At multiple time points throughout the study, various assessments of pain were evaluated, as described below.

a. Pain Intervention:

At each time point, the investigator evaluated the cat for adequacy of pain control. The criteria for butorphanol intervention were a recovery score of 5, an analgesia score of 3 or 4 at any time, or a Cumulative Pain Score greater than or equal to 8 at any time. The number of cats requiring intervention and the time to intervention were analyzed.

b. Gait/Lameness Score:

1 = Sound

2 = Barely noticeable. May shift weight. Not lame if running.

3 = Noticeable, but weight bearing. Places foot down when standing.

4 = Bears weight occasionally, especially if needed for balance.

5 = Non-weight bearing

c. Analgesia Score:

1 = No pain. Relaxed, freely moving. Does not resent surgical site palpation. Normal attention to environment. Playfully interactive

2 = Faintly painful. Barely noticeable alteration from normal. May have slightly abnormal stance or gait. Orients to palpation site, but does not resent it. Observant, but restricted interaction. May sit with one paw raised, but stands on all paws.

3 = Mildly painful. Slightly restricted movement. Holds one paw raised. May stand slightly arched or tucked, with toes just touching ground. Orients and withdraws from palpation site. Licks paws

4 = Moderately painful. Noticeably arched, abnormal posture. Non-weight bearing. Tries to escape palpation. May bite. Marked guarding. May chew, bite or shake foot. May cry, growl. Limited interest in surroundings. Will move around, but may be restless

5 = Very painful. Pain could not be worse. Tense, writhing, shivering, shuddering. May not move at all. May be rigid. Non-weight bearing. May refuse to walk or stand. May be self-mutilating. May have fixed stare. Unsolicited crying, growling.

If at any time point, the analgesia score was 3 or 4, the cat qualified for additional pain intervention.

d. Visual Analog Scale (VAS):<sup>2</sup>

This score was accomplished by marking on a 10 centimeter line, labeled “no pain” at one end and “worst pain possible” at the opposite end, the assessment of the animal’s pain. The numerical score was obtained by measuring the distance in centimeters from the “no pain” end to the observer’s mark.

e. General Impression Score:

Excellent (4) = The animal exhibited a comfortable postoperative recovery without need of medical intervention.

Good (3) = The animal was generally comfortable, with occasional periods of discomfort.

Fair (2) = The animal was mildly uncomfortable postoperatively and required additional medical intervention.

Poor (1) = The animal was generally uncomfortable postoperatively and required medical intervention.

f. Cumulative Pain Score (CPS):<sup>3</sup>

The Cumulative Pain Score is the sum of the scores for analgesia, heart rate, sedation and respiratory pattern.

g. Recovery Score:

The recovery score was evaluated within 5 minutes of the endotracheal tube removal. Any cat that scored a 5 qualified for additional pain intervention.

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<sup>2</sup> Lascelles BDX, Cripps P, Mirchandani S, Waterman AE: Carprofen an analgesic for postoperative pain in cats: dose titration and assessment of efficacy in comparison to pethidine hydrochloride. *J Sm Anim Prac* 36:535-541, 1995.

<sup>3</sup> Pibarot P, Dupis J, Grisneaux E, Cuvelliez S, Plante J, Beauregard G, Bonneau NH, Bouffard J, Blais D: Comparison of ketoprofen, oxymorphone hydrochloride, and butorphanol in the treatment of postoperative pain in dogs. *J Am Vet Med Assoc* 211:438-444, 1997.

1 = Extubated with easy transition to alertness. Swallowing, lifting head with control. No outward signs of incoordination/disorientation. Lies quietly until able to move in coordinated purposeful fashion. Return to alertness is quick. May stretch, roll sternal or stand.

2 = Relatively easy transition to alertness. Holds head up. Follows movement and looks around, even though may not have perfect head control. Does not attempt to move until purposeful coordinated movement is possible. Duration of recovery is not extended. Cats which have a few seconds of disorientation on extubation before calming may be included in this category.

3 = May raise or lower head without obvious stimuli. Startles when reached for. Undirected focus. Lies quietly, but whole body movement may be precipitated by sound, touch or reach. May cry or growl.

4 = Has some whole body stereotypical behavior (for example, crawling in circles, attempting to stand prematurely). Startles, cries or growls. Can be controlled by either restraining or leaving alone. Measurements such as rectal temperature can be obtained with patience.

5 = Extreme emergence delirium. Violent thrashing, flipping over. Entire body in non-purposeful, non-directed movement. Unable to focus. Basically uncontrollable. May inflict damage to self or observers. May defecate. Measurements out of the question.

h. Sedation Score:<sup>4</sup>

1 = Asleep or calm

2 = Mild agitation

3 = Moderate agitation

4 = Severe agitation (hysterical).

i. Tenderness Score:<sup>5</sup>

The investigators obtained the Tenderness Score by quantifying the pain threshold with a palpometer (or dolorimeter). [A palpometer is a device that measures the amount of pressure that can be borne without causing pain].

Injection Site Reaction:

Immediately following test article administration, the cat's reaction to the injection was evaluated as:

1 = no pain apparent (other than routine reaction to needle)

2 = mild pain (turned head in recognition)

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<sup>4</sup> Carroll GL, Howe LB, Slater MS, Haughn L, Martinez EA, Hartsfield SM, Matthews NS: Evaluation of analgesia provided by postoperative administration of butorphanol to cats undergoing onychectomy. *J Am Vet Med Assoc* 213:246-250, 1998.

<sup>5</sup> Sammarco JL, Conzemius MG, Perkowski SZ, Weinstein MJ, Gregor TP, Smith GK: Postoperative analgesia for stifle surgery: A comparison of intra-articular bupivacaine, morphine, or saline. *Vet Surg* 25:59-69, 1996.

3 = moderate pain (tried to move away)

4 = severe pain (vocalized or became aggressive)

Twenty-four hours following test article administration, the injection site was evaluated for signs of swelling, pain or redness.

The following clinical pathology variables were evaluated pre- and post-treatment.

- a. Buccal Mucosal Bleeding Time
- b. Complete Blood Count (platelet count, hematocrit and hemoglobin)
- c. Serum Chemistry (blood urea nitrogen, creatinine, sodium, potassium, chloride)

D. *Results:*

1) Pain Intervention:

About two-thirds of the cats in the study received one or more butorphanol interventions in the 0-24 hour post-surgical period. The majority of these interventions took place within the first hour. Therefore, the occurrence of pain intervention was designated as the primary assessment variable.

The statistical evaluation supports the conclusion that meloxicam is non-inferior to butorphanol (Table 3). Forty-eight of the 72 cats in the meloxicam group received one or more interventions (66.7%), and 47 of the 66 cats in the butorphanol group received one or more interventions (71.2%). Based on the non-inferiority evaluation, the percentage of cats in the target population that receive intervention is likely to be no more than 8.7% greater with meloxicam than with butorphanol (Table 3). The median number of interventions was 1 per cat in the meloxicam group and 2 per cat in the butorphanol group. Based on the non-inferiority evaluation, cats in the target population treated with meloxicam are not likely to need any more interventions than cats treated with butorphanol (Table 3).

TABLE 3. Number of cats / percent of total in each treatment group that received one or more interventions with butorphanol

	<b>Meloxicam</b> n = 72	<b>Butorphanol</b> n = 66
	Number / percentage of cases that received one or more interventions <sup>1</sup>	
	48 / 66.7%	47 / 71.2%
Evaluation period	Number / percentage of interventions at each evaluation period <sup>2</sup>	
0 minutes	39 / 54.2%	34 / 51.5%
30 minutes	15 / 20.8%	15 / 22.7%
1 hour	4 / 5.6%	10 / 15.2%
3 hours	3 / 4.2%	22 / 33.3%
5 hours	2 / 2.8%	15 / 22.7%
8 hours	1 / 1.4%	5 / 7.6%
12 hours	1 / 1.4%	10 / 15.2%
24 hours	0 / 0.0%	4 / 6.1%
Number of butorphanol interventions	Number / percentage of cases with this number of butorphanol interventions <sup>3</sup>	
0	24 / 33.3%	19 / 27.8%
1	36 / 50.0%	13 / 19.7%
2	8 / 11.1%	16 / 24.2%
3	3 / 4.2%	9 / 13.6%
4	1 / 1.4%	4 / 6.1%
5	0 / 0.0%	3 / 4.5%
6	0 / 0.0%	2 / 3.0%

## Notes:

<sup>1</sup> The non-inferiority analysis is based on the difference "Meloxicam – Butorphanol" in the occurrence of intervention for pain. The one-sided upper 95% confidence bound of this difference is examined for non-inferiority.

<sup>2</sup> For the percentage of cases with one or more interventions, the upper confidence bound of the difference between meloxicam and butorphanol is 8.7%. Based on this result, the percentage of cats in the target population that receive intervention may be no more than 8.7% greater with meloxicam than with butorphanol.

<sup>3</sup> The median number of interventions per cat is 1 in the meloxicam group and 2 in the butorphanol group. The upper confidence bound of the difference between medians is 0. Based on this result, cats in the target population treated with meloxicam are not likely to need any more interventions than cats treated with butorphanol.

2) Pain Assessment Variables (overall):

The pain assessment variables were used to characterize the response to the meloxicam test article in comparison with the butorphanol active control. They are presented without further statistical analysis because of the potential for the pain intervention to influence the evaluation of these variables.

a. Gait/Lameness (G/L) Score:

As shown in Table 4, the meloxicam-treated cats returned to preoperative soundness (Gait/Lameness score of 1) at 3 hours post-treatment. This return to soundness was quicker than the butorphanol-treated cats, which had only one cat with a Gait/Lameness score of "1" at 5 and 8 hours post-treatment. Similarly, after hour 1, no cats in the meloxicam-treated group were non-weight bearing (Gait/Lameness score of 5), while at least a minimum of two cats remained non-weight bearing throughout the 24-hour observation period.

TABLE 4: Gait/Lameness Score  
(number of cats/percent of total cats in the treatment group)

Time	G/L score 1		G/L score 2		G/L score 3		G/L score 4		G/L score 5	
	M <sup>1</sup>	B <sup>2</sup>	M	B	M	B	M	B	M	B
30 min	0 0.0%	0 0.0%	14 20.9%	5 7.9%	22 32.8%	21 33.3%	18 26.9%	25 39.7%	13 19.4%	12 19.0%
1 hr	0 0.0%	0 0.0%	24 34.3%	12 18.2%	31 44.3%	19 28.8%	13 18.6%	26 39.4%	2 2.9%	9 13.6%
3 hr	5 6.9%	0 0.0%	31 43.1%	13 19.7%	30 41.7%	27 40.9%	6 8.3%	21 31.8%	0 0.0%	5 7.6%
5 hr	9 12.5%	1 1.5%	34 47.2%	23 34.8%	25 34.7%	19 28.8%	4 5.6%	19 28.8%	0 0.0%	4 6.1%
8 hr	13 18.1%	1 1.5%	31 43.1%	21 31.8%	26 36.1%	27 40.9%	2 2.8%	14 21.2%	0 0.0%	3 4.5%
12 hr	19 26.4%	4 6.2%	31 43.1%	20 30.8%	19 26.4%	28 43.1%	3 4.2%	9 13.8%	0 0.0%	4 6.2%
24 hr	33 45.8%	18 27.3%	32 44.4%	34 51.5%	6 8.3%	9 13.6%	1 1.4%	3 4.5%	0 0.0%	2 3.0%

Notes:

<sup>1</sup> The meloxicam treatment group

<sup>2</sup> The butorphanol treatment group

The totals varied because of occasional missed observations. The percentages are based on the total number of cases with recorded observations for that time period.

## b. Analgesia Score:

Only one meloxicam-treated cat was very painful (analgesia score of 5), while seven butorphanol-treated cats scored the highest analgesia score. Furthermore, by the end of the 24-hour observation period, all of the meloxicam-treated cats attained an analgesia score of either 1 (non-painful) or 2 (faintly painful), while seven butorphanol cats were still scoring either 3 (mildly painful) or 4 (moderately painful). Refer to Table 5.

TABLE 5: Analgesia Score  
(number of cats/percent of total cats in the treatment group)

Time	Analgesia score 1		Analgesia score 2		Analgesia score 3		Analgesia score 4		Analgesia score 5	
	M <sup>1</sup>	B <sup>2</sup>	M	B	M	B	M	B	M	B
0 min	13 18.1%	20 30.3%	20 27.8%	11 16.7%	16 22.2%	13 19.7%	22 30.6%	16 24.2%	1 1.4%	6 9.1%
30 min	8 11.1%	4 6.1%	38 52.8%	29 43.9%	15 20.8%	20 30.3%	11 15.3%	12 18.2%	0 0.0%	1 1.5%
1 hr	7 9.7%	5 7.6%	47 65.3%	32 48.5%	15 20.8%	23 34.8%	3 4.2%	6 9.1%	0 0.0%	0 0.0%
3 hr	9 12.7%	5 7.6%	49 69.0%	30 45.5%	11 15.5%	19 28.8%	2 2.8%	12 18.2%	0 0.0%	0 0.0%
5 hr	17 24.3%	5 7.7%	46 65.7%	33 50.8%	6 8.6%	19 29.2%	1 1.4%	8 12.3%	0 0.0%	0 0.0%
8 hr	22 31.4%	7 10.8%	46 65.7%	40 61.5%	1 1.4%	14 21.5%	1 1.4%	4 6.2%	0 0.0%	0 0.0%
12 hr	26 37.1%	12 18.5%	40 57.1%	29 44.6%	3 4.3%	21 32.3%	1 1.4%	3 4.6%	0 0.0%	0 0.0%
24 hr	39 54.2%	25 37.9%	33 45.8%	34 51.5%	0 0.0%	6 9.1%	0 0.0%	1 1.5%	0 0.0%	0 0.0%

## Notes:

<sup>1</sup> The meloxicam treatment group

<sup>2</sup> The butorphanol treatment group

The totals varied because of occasional missed observations. The percentages are based on the total number of cases with recorded observations for that time period.

c. VAS Score:

By hour 1, the highest VAS score in the meloxicam group was consistently lower than the highest VAS score in the butorphanol group. The highest VAS scores over time continue to diverge so that by hour 24, the highest VAS scores in the butorphanol group is twice as high as the highest VAS score in the meloxicam group (6.1 vs. 3.1). See Table 6.

TABLE 6: Summary Statistics for VAS score in Each Treatment Group

Time	Number		Mean		Standard Dev.		Minimum VAS		Maximum VAS	
	M <sup>1</sup>	B <sup>2</sup>	M	B	M	B	M	B	M	B
0 min	72	66	3.1	3.4	2.3	2.6	0	0	9.6	10
30 min	72	66	2.6	3.1	1.5	1.9	0.1	0.2	7.0	7.8
1 hr	72	66	2.2	2.8	1.3	1.6	0	0	5.1	6.9
3 hr	71	66	2.6	1.8	1.1	1.8	0	0	4.1	9.2
5 hr	70	65	1.5	2.4	1.1	1.6	0	0	3.9	6.9
8 hr	70	65	1.3	2.0	1.1	1.6	0	0	4.5	6.4
12 hr	70	65	1.2	1.8	1.0056	1.7517	0	0	3.6	6.7
24 hr	72	66	0.8	1.3	0.8689	1.4095	0	0	3.1	6.1

Notes:

<sup>1</sup> The meloxicam treatment group

<sup>2</sup> The butorphanol treatment group

The totals varied because of occasional missed observations. The percentages are based on the total number of cases with recorded observations for that time period.

## d. General Impression Score:

Table 7 shows the percentages of cats evaluated as excellent, good, fair or poor by treatment group. The meloxicam group contained more cats with an "Excellent" or "Good" score than the butorphanol treatment group. Similarly, the meloxicam group contained fewer cats with a "Fair" or "Poor" score than the butorphanol group.

TABLE 7: General Impression Scores by Treatment Group  
(number of cats/percent of total cats in the treatment group)

<b>General Impression Score</b>	<b>Meloxicam n = 72</b>	<b>Butorphanol n = 66</b>
Excellent	13 / 18.1 %	7 / 10.6 %
Good	41 / 56.9 %	22 / 33.3 %
Fair	17 / 23.6 %	23 / 34.8 %
Poor	1 / 1.4 %	14 / 21.2 %

## e. Cumulative Pain Score (CPS):

The cumulative pain score (CPS) was obtained by summing the scores for analgesia, heart rate, sedation and respiratory pattern. Table 8 summarizes the CPS results within the framework of rescue pain therapy intervention. Part of the criteria to determine if a cat qualifies for rescue pain therapy was a CPS of "8" or greater. As shown in Table 8, after extubation, fewer cats in the meloxicam group qualified for rescue pain therapy than in the butorphanol group. Furthermore, the disparity between the numbers of cats qualifying for rescue pain therapy in the meloxicam group compared to the butorphanol group becomes less ambiguous after the 1 hour observation.

TABLE 8: Summary Cumulative Pain Score Results

Time	CPS < 8 (Intervention is not indicated)		CPS ≥8 (Intervention is indicated)	
	Meloxicam	Butorphanol	Meloxicam	Butorphanol
0 min	35 49.3%	34 53.1%	36 50.7%	30 46.9%
30 min	51 70.8%	39 59.1%	21 29.2%	27 40.9%
1 hr	63 87.5%	49 74.2%	9 12.5%	17 25.8%
3 hr	67 94.4%	50 75.8%	4 5.6%	16 24.2%
5 hr	69 98.6%	51 78.5%	1 1.4%	14 21.5%
8 hr	68 97.1%	60 92.3%	2 2.9%	5 7.7%
12 hr	69 98.6%	55 84.6%	1 1.4%	10 15.4%
24 hr	72 100.0%	64 97.0%	0 0.0%	2 3.0%

Notes:  
The totals varied because of occasional missed observations. The percentages are based on the total number of cases with recorded observations for that time period.

## f. Recovery Score:

To aid in evaluating the cat's recovery from anesthesia, a recovery score was determined at removal of the endotracheal tube (time 0). If cats obtained a score of "5", then additional pain intervention was warranted. Three butorphanol and two meloxicam animals had a recovery score of "5", requiring additional pain relief. See Table 9.

**TABLE 9: Recovery Score**  
(number of cats/percent of total cats in the treatment group)

	Recovery score 1		Recovery score 2		Recovery score 3		Recovery score 4		Recovery score 5*	
	M <sup>1</sup>	B <sup>2</sup>	M	B	M	B	M	B	M	B
# of cats	6	11	17	19	32	20	15	13	2	3
Percent	8.3%	16.7%	23.6%	28.8%	44.4%	30.3%	20.8%	19.7%	2.8%	4.5%

## Notes:

<sup>1</sup> The meloxicam treatment group<sup>2</sup> The butorphanol treatment group

\*A recovery score of "5" was an indication for intervention with butorphanol.

## g. Sedation Score:

Table 10 illustrates the sedation trend over the 24-hour observation period. At time 0, both groups had approximately the same percentage of cats in each category, with the exception of the highest score of "4", which contains 6% of the butorphanol-treated cats. After time 0, however, the sedation scores between groups diverge with more meloxicam-treated cats achieving the lower sedation scores than the butorphanol-treated cats. Also, throughout the entire observation period, no cat in the meloxicam group ever scored the lowest possible score of "4" (severe agitation), while at least one cat in the butorphanol group was scoring a "4" until hour 3.

**TABLE 10: Sedation Score**  
(number of cats/percent of total cats in the treatment group)

Time	Sedation score 1		Sedation score 2		Sedation score 3		Sedation score 4	
	M <sup>1</sup>	B <sup>2</sup>	M	B	M	B	M	B
0 min	32 45.1%	30 45.5%	15 21.1%	12 18.2%	24 33.8%	20 30.3%	0 0.0%	4 6.1%
30 min	49 68.1%	43 65.2%	18 25.0%	15 22.7%	5 6.9%	5 7.6%	0 0.0%	3 4.5%
1 hr	62 86.1%	50 75.8%	8 11.1%	12 18.2%	2 2.8%	3 4.5%	0 0.0%	1 1.5%
3 hr	67 94.4%	50 75.8%	3 4.2%	11 16.7%	1 1.4%	5 7.6%	0 0.0%	0 0.0%
5 hr	66 94.3%	52 80.0%	4 5.7%	12 18.5%	0 0.0%	1 1.5%	0 0.0%	0 0.0%
8 hr	67 95.7%	60 92.3%	2 2.9%	5 7.7%	1 1.4%	0 0.0%	0 0.0%	0 0.0%
12 hr	67 95.7%	58 89.2%	3 4.3%	6 9.2%	0 0.0%	1 1.5%	0 0.0%	0 0.0%
24 hr	70 97.2%	59 89.4%	2 2.8%	7 10.6%	0 0.0%	0 0.0%	0 0.0%	0 0.0%

## Notes:

<sup>1</sup> The meloxicam treatment group<sup>2</sup> The butorphanol treatment group

The totals varied because of occasional missed observations. The percentages are based on the total number of cases with recorded observations for that time period.

## h. Tenderness Score:

Table 11 presents a summary of the palpometer results. The mean tenderness score is higher (not as tender) for the meloxicam group at all time points. However, at all time points, both groups had cats with equivalent minimum and maximum palpometer results.

TABLE 11: Summary Statistics for the Tenderness Score

Time	Number of cats		Mean		Standard Deviation		Minimum Tenderness Score		Maximum Tenderness Score	
	M <sup>1</sup>	B <sup>2</sup>	M	B	M	B	M	B	M	B
Base	72	64	3.2	3.2	2.5	2.5	0	0	9	9
30 min	72	64	2.8	2.2	2.4	2.1	0	0	9	9
1 hr	72	63	2.7	2.4	2.5	2.0	0	0	9	9
3 hr	71	64	3.2	2.9	2.3	2.8	0	0	9	9
5 hr	70	64	3.2	2.4	2.4	2.3	0	0	9	9
8 hr	70	64	2.8	1.8	2.3	1.9	0	0	9	9
12 hr	69	63	2.9	2.2	2.2	2.3	0	0	9	9
24 hr	72	64	2.5	2.3	2.5	2.6	0	0	9	9

Notes:

<sup>1</sup> The meloxicam treatment group

<sup>2</sup> The butorphanol treatment group

The totals varied because of occasional missed observations. The percentages are based on the total number of cases with recorded observations for that time period.

### 3) Injection Site Reaction:

The individual administering the test article evaluated pain at the injection site immediately following administration. Cats in the meloxicam group tended to have lower injection site reaction scores, resulting in less pain at the injection site compared to cats in the butorphanol group. The following table (Table 12) shows the distribution of pain on injection between the two treatment groups. Fewer cats in the meloxicam group experienced pain (83.3% of meloxicam cats had an injection score of "1" [no apparent pain]) compared to the cats in the butorphanol group (48.5%). Additionally, more cats in the butorphanol group experienced severe pain (injection score of "4") than in the meloxicam group (22.7% in the butorphanol group compared with 2.8% in the meloxicam group). See Table 12.

**TABLE 12: Pain on Injection Score**  
 (number of cats/percent of total cats in the treatment group)

	Injection Site Reaction score 1		Injection Site Reaction score 2		Injection Site Reaction score 3		Injection Site Reaction score 4	
	M <sup>1</sup>	B <sup>2</sup>	M	B	M	B	M	B
# of cats	60	32	7	9	3	10	2	15
% of cats	83.3%	48.5%	9.7%	13.6%	4.2%	15.2%	2.8%	22.7%
Notes:								
<sup>1</sup> The meloxicam treatment group								
<sup>2</sup> The butorphanol treatment group								

Twenty-four hours after administration of the test material, the injection site was evaluated for signs of pain, swelling or redness. One cat in the meloxicam group exhibited pain upon palpation of the injection site. No cats in the butorphanol group exhibited swelling or redness 24 hours post-injection.

- 4) Clinical Pathology Variables:  
 Table 13 provides a summary of the clinical pathology results.

TABLE 13: Clinical Pathology Results Summary Table

Clinical Pathology Parameter	Mean ± Standard Deviation (min, max)			
	Pre-Surgery		Post-Surgery	
	Meloxicam	Butorphanol	Meloxicam	Butorphanol
BMBT <sup>1</sup> (seconds)	67.7 ± 28.4 (16, 174)	65.2 ± 30.5 (10, 217)	78.4 ± 34.2 (35, 196)	75.8 ± 34.4 (31, 265)
Platelet counts (thous/cmm)	277.9 ± 172.4 (14, 999)	244.5 ± 127.2 (22, 591)	249.0 ± 128.5 (50, 701)	218.5 ± 123.6 (25, 537)
Hematocrit (%)	34.3 ± 6.2 (18, 53)	34.5 ± 5.6 (21, 49)	29.6 ± 6.3 (14, 43)	31.5 ± 6.1 (19, 46)
Blood urea nitrogen (mg/dL)	23.9 ± 4.5 (15, 35)	23.4 ± 4.0 (16, 40)	20.9 ± 9.4 (11, 73)	18.3 ± 3.5 (10, 26)
Creatinine (mg/dL)	1.2 ± 0.3 (0.6, 1.9)	1.2 ± 0.3 (0.5, 1.9)	1.1 ± 0.3 (0.4, 1.8)	1.1 ± 0.3 (0.3, 1.6)
Sodium (mmol/L)	149.4 ± 4.3 (137, 160)	149.2 ± 3.8 (137, 157)	149.4 ± 4.7 (128, 160)	148.8 ± 6.1 (128, 158)
Potassium (mmol/L)	4.3 ± 1.5 (2.7, 9.0)	4.3 ± 1.7 (2.7, 9.0)	4.0 ± 1.0 (2.1, 9.0)	3.8 ± 0.8 (2.1, 9.0)
Chloride (mmol/L)	121.6 ± 3.4 (116, 135)	122.3 ± 3.4 (115, 131)	122.8 ± 4.1 (116, 140)	122.0 ± 5.4 (99, 140)

<sup>1</sup> Buccal mucosal bleeding time.

a. Hematocrit:

The hematocrit (HCT) decreased in both treatment groups between pre- and post-surgery. Table 14 shows the occurrence of anemia post-treatment. All but one cat had normal pre-treatment hematocrit (HCT) and hemoglobin (Hg) values. The one cat with abnormal pre-treatment values was in the butorphanol group and had a pre-treatment hematocrit of 21% and hemoglobin of 7 g/dL. Table 14 shows that more cats in the meloxicam group experienced anemia than in the butorphanol group (12.5% compared to 6.1%).

TABLE 14: The Incidence of Anemia (HCT < 24% and/or Hg < 8.0 g/dL)  
 (number of cats/percent of total cats in the treatment group)

Meloxicam	Butorphanol
9/12.5% <sup>1</sup>	4/6.1%
Notes: <sup>1</sup> Post-treatment, one cat also had an elevation in BUN outside the normal range (41 mg/dL) and an increase in creatinine within the normal range.	

b. Serum Chemistry (blood urea nitrogen, creatinine, sodium, potassium, chloride):

Post-surgically, the average BUN in the meloxicam group was higher than the butorphanol group. Additionally, six cats (8.3%) in the meloxicam treatment group had an elevated BUN (outside the normal range) post-treatment, compared with no cats (0%) in the butorphanol treatment group. Of these six cats, the highest post-treatment BUN was 73 mg/dL. Additionally, three of these six cats with elevations of BUN outside the normal range also had an increase in creatinine (within the normal range) post-treatment when compared with the pre-treatment value.

No cat in either treatment group had a creatinine outside the normal range (either pre- or post-treatment).

There were no appreciable differences between the incidences of abnormal sodium, potassium or chloride values among treatment groups.

E. *Statistical Analysis:*

The experimental unit was the individual test animal. This study had 72 and 66 cats in the meloxicam and butorphanol groups, respectively.

The use of intervention for pain was designated as the primary effectiveness variable. A non-inferiority evaluation was used to compare meloxicam with butorphanol with respect to the occurrence of intervention. A one-sided upper 95% confidence bound for the difference “Meloxicam – Butorphanol” was evaluated for non-inferiority. Two forms of the intervention variable were evaluated: the percentage of cats that received one or more interventions, and the median number of interventions per cat. The confidence bound was calculated from an exact procedure for the difference of two percentages, and from a Mann-Whitney nonparametric procedure adjusted for ties for the difference of two medians.

Descriptive summaries of the clinical assessment variables are presented, as well as summaries of clinical pathology variables and other variables used to assess safety.

F. *Conclusions:*

METACAM (meloxicam) 5 mg/mL Solution for Injection was effective in controlling postoperative pain and inflammation for up to 24 hours from onychectomy and onychectomy in conjunction with surgical neutering when administered at 0.3 mg/kg body weight one-time subcutaneously prior to surgery.

G. *Adverse Reactions:*

Six cats (8.3%) in the meloxicam treatment group experienced post-treatment elevated serum blood urea nitrogen (BUN) levels. The pre-treatment values were in the normal range. Of the 66 cats in the butorphanol treatment group, no cats experienced post-treatment elevated serum blood urea nitrogen levels. The administration of subcutaneous or intravenous fluids during surgery was often employed and recommended to decrease potential renal complications when using NSAIDs.

Nine cats (12.5%) receiving meloxicam had post-treatment anemia. Pre-treatment, these cats all had hematocrit and hemoglobin values in the normal range. Four cats (6.1%) in the butorphanol treatment group had post-treatment anemia. All but one cat, who had a mild anemia pre-treatment (hematocrit = 21% and hemoglobin = 7.0 g/dL) had normal pre-treatment values.

Twenty-four hours after the injection with meloxicam, one cat experienced pain upon palpation of the injection site. No cats in the butorphanol treatment group experienced any pain on injection 24 hours after the injection.

In studies used for the foreign approval of meloxicam, lethargy, vomiting, and inappetance were noted. Additionally, transient pain immediately after injection was reported.

3. **TARGET ANIMAL SAFETY:**

Title: METACAM 0.5% Solution for Injection Target Animal Safety Study in Cats Following Subcutaneous Administration over Three Days.  
Study Number: P98-BIVI008 (BOI/200)

A. *Type of Study:* Safety Study

B. *Study Director:* Vanessa A. Redgrave  
Huntingdon Life Sciences Ltd.  
Wooley Road, Alconbury  
Huntingdon, Cambridgeshire, England

C. *General Design:*

- 1) Purpose: The objectives of this study were to determine the toxicological effects of increasing doses of METACAM (meloxicam) 5 mg/mL Solution for Injection administered to cats.
- 2) Test Animals: Twenty-four crossbred cats, 12 males and 12 females were used in this study. At commencement of treatment, the cats were between 7 and 36 months of age and weighed between 1.92 and 3.71 kg.
- 3) Control: Vehicle
- 4) Dosage Form: Injectable solution containing 5 mg meloxicam per mL. The final market formulation was used.
- 5) Route of Administration: Subcutaneous injection
- 6) Dosages Used:

TABLE 15: Dosage groups

Dose (mg/kg/day)	Relative Dose
0	0X
0.3	1X
0.9	3X
1.5	5X

- 7) Treatment Duration: 3 days
- 8) Variables Measured: Clinical signs, body weight, food consumption, water consumption, rectal temperature, hematology, serum chemistry, urinalysis, fecal occult blood, and gross pathology

D. *Results:*

- 1) Clinical Signs:  
Loose stools were observed in four cats (2/6 controls and 2/6 5X cats). Vomiting was detected in three cats (1/6 controls and 2/6 5X cats). Fecal occult blood was noted in ten of the 24 cats, including two cats in the control group. Inappetance was observed in 1/6 5X cats. Licking and scratching after dosing was observed in 1/6 controls.
- 2) Hematology/Serum Chemistry/Urinalysis:  
Clinically significant hematological changes seen included increased PT and APTT in two cats (1/6 controls and 1/6 5X cats), and elevated white blood cell counts in cats having renal or GI tract lesions. Serum chemistry changes observed included decreased total protein in four of 24 cats (1/6 1X, 2/6 3X, and 1/6 5X cats) and concomitant increases in BUN and creatinine values in 2/6 5X cats.
- 3) Gross Necropsy Observations:  
Macroscopic changes noted included depressions of the jejunum in 1/6 3X and 2/6 5X cats. One of 6 controls demonstrated congestion of the colon.
- 4) Histologic Observations:  
Microscopic examination of the heart revealed minimal subendocardial inflammatory cell infiltration in 1/6 5X cats. Slight myxoid degeneration

of wall for intramural coronary arteries was also detected in 1/6 5X cats. Subendocardial fibrosis with mineralization was detected in 2/6 controls. Minimal focal vacuolations of gray matter of the brain were reported in all three 5X female cats. Slight vacuolation in white matter of the brain was detected in 1/6 5X cats.

Histopathology of the injection sites revealed hemorrhage and inflammation, myofiber atrophy, panniculitis, fibrin deposition, and fibroblast proliferation. These findings were present in the control (vehicle) and all treated groups, with the 3X group having the greatest incidence.

Mucosal inflammatory cell infiltration was observed throughout the intestinal tract. It was detected in the stomach body (3/6 controls, 1/6 1X, and 1/6 5X cats), the stomach antrum (1/6 1X, 2/6 3X, and 1/6 5X cats), the duodenum (1/6 controls), the duodenal papilla (1/6 5X cats), the jejunum (1/6 controls and 1/6 1X cats), the ileum (1/6 controls, 1/6 1X, and 2/6 3X cats), the cecum (1/6 controls, 3/6 1X, 3/6 3X, and 3/6 5X cats), and the colon (1/6 controls, 2/6 1X, 1/6 3X, and 3/6 5X cats). Diffuse inflammation lesions in the large intestine were seen in 1/6 controls and 1/6 5X cats.

Mucosal erosions of the jejunum were noted in 2/6 5X cats, and slight mucosal erosions of GALT tissue of the jejunum in 1/6 3X cats. Slight mucosal erosions of GALT tissue of the cecum was also observed in 1/6 cats in the 3X group. Moderate mucosal erosions of the colon was recorded for 1/6 controls. Mesenteric lymphadenopathy was noted in 1/6 1X cats.

Renal changes included fibrosis of Bowman's capsule, which was noted in 2/6 controls, 1/6 1X, 3/6 3X, and 1/6 5X animals. Dilated cortical tubules were identified in 3/6 1X, 1/6 3X, and 3/6 5X cats. Minimal necrosis of the cortical tubules was detected in 1/6 5X cats. Dilated medullary tubes were observed in 1/6 controls, 2/6 1X, 1/6 3X, and 1/6 5X cats. Interstitial inflammatory cell infiltration was recorded for 2/6 1X, 2/6 3X, and 2/6 5X cats. Interstitial fibrosis was detected in 1/6 controls, 2/6 3X, and 2/6 5X cats. Microscopic renal pathology revealed minimal to slight renal papillary necrosis (tip of the papilla) in 5/6 5X cats.

#### E. *Statistical Analysis:*

For all parameters, males and females were analyzed separately and combined.

Levene's test for homogeneity was applied. If the test was significant at the 1% level, then a logarithmic transformation was applied and the test was repeated. If Levene's test was still significant, than a square root transformation was tried.

Except for organ weights, if no significant heterogeneity of variance was detected (with or without transformation), a one-way analysis of variance was carried out, using treatment as a factor. If the analysis of variance showed evidence (at the 10% level) of differences between the groups, then a two-sided Dunnett's test was used to compare the treated groups with the controls group. Significance testing was carried out at the 5% and 1% levels. If heterogeneity of variance was significant and could not be stabilized by transformation, then the Kruskal-Wallis test on ranks was performed on the untransformed data. If the Kruskal-Wallis test showed evidence (at the 10% level) of differences between the groups, then for the combined sexes, the Wilcoxon Rank Sum test was used to test for differences between the treated groups and the control, whilst for the separate sexes, Steel's test (a non-parametric analogue of Dunnett's test) was used.

For absolute organ weights, an analysis of covariance was performed, adjusting for the final bodyweight where the regression coefficient describing the linear relationship between organ weight and the covariate was significantly different from zero at the 10% level. Where there was no such relationship, analysis of variance was performed on the unadjusted values as described above. If the analysis of covariance was applied, and if a significant difference (at the 10% level) was found between the groups, the groups were compared using Dunnett's test.

F. *Conclusions:*

The subcutaneous administration of METACAM (meloxicam) 5 mg/mL Solution for Injection to cats for three days at 0.3 mg/kg (1X) was tolerated clinically. Cats receiving five times the proposed dose demonstrated signs typical of non-steroidal anti-inflammatory compounds. These signs included loose feces and vomiting. Cats receiving doses of 0.9 (3X) and 1.5 (5X) mg/kg/day showed histological changes of the gastrointestinal tract and kidneys.

G. *Adverse Reactions:*

The following adverse reactions were seen during the study: vomiting, diarrhea, anorexia, and scratching/licking the injection site.

Title: Tolerance Study in Cats on Meloxicam (METACAM) at a Dose Level of 0.3 and 0.6 mg/kg Bodyweight Given as Single Subcutaneous Injections Followed by Oral Treatment at the Same Dose for 9 Consecutive Days.

Study Number: 6821 UHA 9210

A. *Type of Study:* GLP Safety Study

B. *Study Director:* Catherine Caulfield  
Biological Laboratories (Ballina) Ltd.  
Carrentilla

Ballina  
County Mayo  
Ireland

C. *General Design:*

- 1) Purpose: The purpose of this study was to assess the tolerance in cats following multiple administrations of METACAM (meloxicam) over a period of 10 days.
- 2) Test Animals: Twelve cats, 6 males and 6 females, were used in this study. At commencement of treatment, the cats were between 18 months and 4 years of age.
- 3) Control: Saline
- 4) Dosage Form: Injectable solution containing 5 mg meloxicam per mL  
Oral suspension containing 1.5 mg/mL
- 5) Route of Administration: The initial dose was administered by subcutaneous injection. The subsequent oral doses were administered into the mouth via a syringe.
- 6) Dosages Used:

TABLE 16: Dosage Groups

Treatment Group	Injectable Dose (mg/kg)	Oral Dose (mg/kg)
1	0	0
2	0.3 (1X)	0.3
3	0.6 (2X)	0.6

- 7) Treatment Duration: 10 days
- 8) Variables Measured: Clinical signs, hematology, serum chemistry, fecal occult blood, food consumption and gross pathology

D. *Results:*

- 1) Clinical Signs:  
By Day 9, one cat in the placebo group had intermittent diarrhea and poor appetite of one day's duration. One cat in the 0.3 mg/kg group was found dead on Day 8. By Day 9, three out of the four cats in the 0.3 mg/kg group were lethargic and tachycardic. One cat was vomiting, had enlarged kidneys and was moribund. One cat in the 0.6 mg/kg group was found dead on Day 8. By Day 9, three out of the four cats in the 0.6 mg/kg group were lethargic and tachycardic. One cat had an irregular heart beat and one cat had enlarged and painful kidneys.
- 2) Hematology/Serum Chemistry:

Clinically significant hematology results were observed for the moribund cat in the 0.3 mg/kg group. On Day 9, his white blood cell count was 1800 compared with 16,500 on Day 4. No drug-related changes were noted in the serum chemistry results.

3) Fecal Occult Blood:

Fecal occult blood was identified in all treatment groups.

4) Food Consumption:

The cats in both of the meloxicam groups showed an obvious decrease in food consumption by Day 6. The cats in the placebo group ate consistently during the entire study.

5) Gross Pathology:

Two of the four cats in the 0.3 mg/kg group and all of the four cats in the 0.6 mg/kg group had pyloric/duodenal ulceration with secondary lesions of peritonitis. Two of the four cats in each of the meloxicam-treated groups had basophilic renal tubules and interstitial lymphocytosis. None of the cats in the placebo group had any gastrointestinal or renal abnormalities.

*E. Conclusions:*

Meloxicam, when initially dosed as a subcutaneous injection followed by oral dosing for nine days at  $\geq 0.3$  mg/kg was associated with severe adverse effects, including death.

**4. HUMAN SAFETY:**

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

Human Warnings are provided on the product label as follows: Not for use in humans. Keep this and all medications out of reach of children. Consult a physician in case of accidental ingestion by humans.

**5. AGENCY CONCLUSIONS:**

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that METACAM (meloxicam) 5 mg/mL Solution for Injection when used under the labeled conditions of use is safe and effective for the control of postoperative pain and inflammation associated with orthopedic surgery, ovariohysterectomy and castration in cats when administered prior to surgery.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is needed to diagnose and provide guidance in the control of postoperative pain associated with orthopedic surgery, ovariohysterectomy

and castration in cats. Furthermore, the veterinarian monitors cats due to their unique drug metabolism and for possible adverse effects of the drug.

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of approval. The three years of marketing exclusivity applies only to the new indication for the control of postoperative pain and inflammation associated with orthopedic, ovariohysterectomy and castration in cats, for which this supplement is approved.

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

**6. ATTACHMENTS:**

Facsimile Labeling is attached as indicated below:

- a. Package insert
- b. Box
- c. Bottle
- d. Shipper label

601307L-XX-XXXX

Package Insert for Dogs

NADA 141-219, Approved by FDA

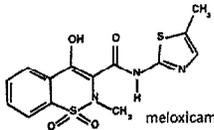
Metacam®  
(meloxicam)

5 mg/mL Solution for Injection

Non-steroidal anti-inflammatory drug for use in dogs and cats only

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

Description: Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam class. Each mL of this sterile product for injection contains meloxicam 5.0 mg, alcohol 15%, glycolufol 10%, poloxamer 188 5%, sodium chloride 0.6%, glycine 0.5% and meglumine 0.3%, in water for injection, pH adjusted with sodium hydroxide and hydrochloric acid.



Indications:

Dogs: Metacam (meloxicam) 5 mg/mL Solution for Injection is indicated in dogs for the control of pain and inflammation associated with osteoarthritis.

Dosage and Administration: Dogs: Metacam 5 mg/mL Solution for Injection should be administered initially as a single dose at 0.09 mg/lb (0.2 mg/kg) body weight intravenously (IV) or subcutaneously (SQ), followed, after 24 hours, by Metacam Oral Suspension at the daily dose of 0.045 mg/lb (0.1 mg/kg) body weight, either mixed with food or placed directly in the mouth.

Contraindications: Dogs with known hypersensitivity to meloxicam and other NSAIDs should not receive Metacam 5 mg/mL Solution for Injection.

Warnings: Not for use in humans. Keep this and all medications out of reach of children. Consult a physician in case of accidental ingestion by humans. For IV or SQ Injectable use in dogs. All dogs should undergo a thorough history and physical examination before administering any NSAID. Appropriate laboratory testing to establish hematological and serum biochemical baseline data is recommended prior to, and periodically during use of any NSAID in dogs.

Owner should be advised to observe their dogs for signs of potential drug toxicity.

Precautions:

The safe use of Metacam 5 mg/mL Solution for Injection in dogs younger than 6 months of age, dogs used for breeding, or in pregnant or lactating bitches has not been evaluated. Meloxicam is not recommended for use in dogs with bleeding disorders, as safety has not been established in dogs with these disorders. Safety has not been established for intramuscular (IM) administration in dogs. When administering Metacam 5 mg/mL Solution for Injection, use a syringe of appropriate size to ensure precise dosing. As a class, cyclo-oxygenase inhibitory NSAIDs may be associated with gastrointestinal, renal and hepatic toxicity. Sensitivity to drug-associated adverse events varies with the individual patient. Patients at greatest risk for renal toxicity are those that are dehydrated, on concomitant diuretic therapy, or those with existing renal, cardiovascular, and/or hepatic dysfunction. Concurrent administration of potentially nephrotoxic drugs should be carefully approached. NSAIDs may inhibit the prostaglandins that maintain normal homeostatic function. Such anti-prostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease that has not been previously diagnosed.

Since many NSAIDs possess the potential to produce gastrointestinal ulceration, concomitant use of Metacam 5 mg/mL Solution for Injection with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided or closely monitored in dogs. Consider appropriate washout times when switching from corticosteroid use or from one NSAID to another in dogs. The use of concomitantly protein-bound drugs with Metacam 5 mg/mL Solution for Injection has not been studied in dogs. Commonly used protein-bound drugs include cardiac, anticonvulsant and behavioral medications. The influence of concomitant drugs that may inhibit metabolism of Metacam 5 mg/mL Solution for Injection has not been evaluated. Drug compatibility should be monitored in patients requiring adjunctive therapy. The effect of cyclo-oxygenase inhibition and the potential for thromboembolic occurrence or a hypercoagulable state has not been studied.

Adverse Reactions:

Dogs: A field study involving 224 dogs was conducted. Based on the results of this study, GI abnormalities (vomiting, soft stools, diarrhea, and inappetence) were the most common adverse reactions associated with the administration of meloxicam. The following table lists adverse reactions and the numbers of dogs that experienced them during the study. Dogs may have experienced more than one episode of the adverse reaction during the study.

Adverse Reactions Observed During Field Study		
Clinical Observation	Meloxicam (n=109)	Placebo (n=115)
Vomiting	31	15
Diarrhea/Soft Stool	15	11
Inappetence	3	0
Bloody Stool	1	0

In foreign suspected adverse drug reaction (SADR) reporting, adverse reactions related to meloxicam administration included: auto-immune hemolytic anemia (1 dog), thrombocytopenia (1 dog), polyarthritis (1 dog), nursing puppy lethargy (1 dog), and pyoderma (1 dog).

Information for Dog Owners: Meloxicam, like other NSAIDs, is not free from adverse reactions. Owners should be advised of the potential for adverse reactions and be informed of the clinical signs associated with NSAID intolerance. Adverse reactions may include vomiting, diarrhea, lethargy, decreased appetite and behavioral changes. Dog owners should be advised when their pet has received a meloxicam injection. Dog owners should contact their veterinarian immediately if possible adverse reactions are observed, and dog owners should be advised to discontinue Metacam therapy.



Post-Approval Experience: The following adverse reactions are based on voluntary post-approval reporting. The categories are listed in decreasing order of frequency by body system.

Gastrointestinal: vomiting, anorexia, diarrhea, melena, gastrointestinal ulceration  
Urinary: azotemia, elevated creatinine, renal failure

Neurological/Behavioral/Special Sense: lethargy, depression

Dermatological/Immunological: pruritus

In rare situations, death has been reported as an outcome of the adverse events listed above. Renal failure has been reported as an outcome of repeated oral dosing of cats. To report suspected adverse reactions, to obtain a Material Safety Data Sheet, or for technical assistance, call 1-866-METACAM (1-866-638-2226).

Clinical Pharmacology: Meloxicam has nearly 100% bioavailability when administered orally or after subcutaneous injection in dogs. The terminal elimination half life after a single dose is estimated to be approximately 24 hrs (+/-30%) in dogs regardless of route of administration. Drug bioavailability, volume of distribution, and total systemic clearance remain constant up to 5 times the recommended dose for use in dogs. However, there is some evidence of enhanced drug accumulation and terminal elimination half-life prolongation when dogs are dosed for 45 days or longer.

Peak drug concentrations of 0.734 mcg/mL can be expected to occur within 2.5 hours following a 0.2 mg/kg subcutaneous injection in dogs. Based upon intravenous administration in Beagle dogs, the meloxicam volume of distribution in dogs (VdL) is approximately 0.32 L/kg and the total systemic clearance is 0.01 L/hr/kg. The drug is 97% bound to canine plasma proteins.

Effectiveness:

Dogs: The effectiveness of Metacam 5 mg/mL Solution for Injection was demonstrated in a field study involving a total of 224 dogs representing various breeds, all diagnosed with osteoarthritis. This placebo-controlled, masked study was conducted for 14 days. Dogs received a subcutaneous injection of 0.2 mg/kg Metacam 5 mg/mL Solution for Injection on day 1. The dogs were maintained on 0.1 mg/kg oral meloxicam from days 2 through 14. Variables evaluated by veterinarians included lameness, weight-bearing, pain on palpation, and overall improvement. Variables assessed by owners included mobility, ability to rise, limping, and overall improvement. In this field study, dogs showed clinical improvement with statistical significance after 14 days of meloxicam treatment for all variables.

Animal Safety:

Dogs: 3 Day Target Animal Safety Study - In a three day safety study, Metacam 5 mg/mL Solution for Injection was administered intravenously to Beagle dogs at 1, 3, and 5 times the recommended dose (0.2, 0.6 and 1.0 mg/kg) for three consecutive days. Vomiting occurred in 1 of 6 dogs in the 5X group. Fecal occult blood was detected in 3 of 6 dogs in the 5X group. No clinically significant hematologic changes were seen, but serum chemistry changes were observed. Serum alkaline phosphatase (ALP) was significantly increased in one 1X dog and two of the 5X dogs. One dog in the 5X group had a steadily increasing GGT over 4 days, although the values remained within the reference range. Decreases in total protein and albumin occurred in 2 of 6 dogs in the 3X group and 3 of 6 dogs in the 5X group. Increases in blood urea nitrogen (BUN) occurred in 3 of 6 dogs in the 1X group, 2 of 6 dogs in the 3X group and 2 of 6 dogs in the 5X group. Increased creatinine occurred in 2 dogs in the 5X group. Increased urine protein excretion was noted in 2 of 6 dogs in the control group, 2 of 6 dogs in the 1X group, 2 of 6 dogs in the 3X group, and 5 of 6 dogs in the 5X group. Two dogs in the 5X group developed acute renal failure by Day 4. Bicarbonate levels were at or above normal levels in 1 of the 3X dogs and 2 of the 5X dogs.

Histological examination revealed gastrointestinal lesions ranging from superficial mucosal hemorrhages and congestion to erosions. Mesenteric lymphadenopathy was identified in 2 of 6 dogs in the 1X group, 4 of 6 dogs in the 3X group, and 5 of 6 dogs in the 5X group. Renal changes ranged from dilated medullary and cortical tubules and inflammation of the interstitium, to necrosis of the tip of the papilla in 2 of 6 dogs in the 1X group, 2 of 6 dogs in the 3X group, and 4 of 6 dogs in the 5X group.

Injection Site Tolerance - Metacam 5 mg/mL Solution for Injection was administered once subcutaneously to Beagle dogs at the recommended dose of 0.2 mg/kg and was well-tolerated by the dogs. Pain upon injection was observed in one of eight dogs treated with meloxicam. No pain or inflammation was observed post-injection. Long term use of Metacam 5 mg/mL Solution for Injection in dogs has not been evaluated.

Effect on Buccal Mucosal Bleeding Time (BMBT) - Metacam 5 mg/mL Solution for Injection (0.2 mg/kg) and placebo (0.4 mL/kg) were administered as single intravenous injections to 8 female and 16 male Beagle dogs. There was no statistically significant difference (p>0.05) in the average BMBT between the two groups.

Storage Information: Store at controlled room temperature, 68-77°F (20-25°C).

How Supplied:

Metacam 5 mg/mL Solution for Injection: 10 mL vial

Manufactured by: Boehringer Ingelheim Vetmedica, Inc.

St. Joseph, MO 64506 U.S.A.

Distributed by:

Merial Limited  
Duluth, GA 30096-4640 U.S.A.

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601307L-XX-XXXX

Code 601311

Revised 09-2004

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# Metacam®

5 mg/mL Solution for Injection

(non-steroidal anti-inflammatory drug) in dogs and cats only

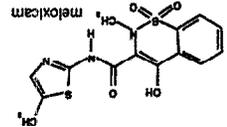
Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Description: Metacam is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam

class. Each mL of this sterile product for injection contains meloxicam 5.0 mg, alcohol

15% (v/v), polyoxamer 188 5% (w/v), sodium chloride 0.5%, glycine 0.5% and

hydrochloric acid. In water for injection, pH adjusted with sodium hydroxide and



### Indications:

Cats: For the control of postoperative pain and inflammation associated with orthopedic

surgery, ovariohysterectomy and castration when administered prior to surgery.

Dosage and Administration:

Cats: Administer a single, one-time subcutaneous dose of Metacam 5 mg/mL Solution

for injection to cats at a dose of 0.1 mg/kg (0.3 mg/kg) body weight. Use of additional

concomitant analgesics is not recommended. (See Contraindications). To ensure

accuracy of dosing, the use of a 1 mL graduated syringe is recommended.

Contraindications: Cats with known hypersensitivity to meloxicam and other NSAIDs

should not receive Metacam 5 mg/mL Solution for Injection. Additional doses of

metoxicam or other NSAIDs in cats are contraindicated, as no safe dosage for repeated

NSAID administration has been established. (See Animal Safety).

Warnings: Not for use in humans and all medications out of reach of children.

Control a pyrexia in cases of infectious origin by humane, for subcutaneous (SC)

injection use in cats. Do not use IV in cats.

Do not administer a second dose of metoxicam.

When administering any NSAID, appropriate laboratory testing to establish hematological

and serum biochemical baseline data is recommended prior to use in dogs and cats. All

cats should undergo a thorough history and physical examination before administering

metoxicam. Do not repeat dose in cats.

Owners should be advised to observe their cats for signs of potential drug toxicity.

Precautions:

The safe use of Metacam 5 mg/mL Solution for injection in cats younger than 4 months

of age is not recommended for use in cats with bleeding disorders, as safety has not

been established in cats with these disorders. Safety has not been established for

intravenous (IV) or intramuscular (IM) use in cats. When administering Metacam 5 mg/mL

Solution for injection, use a syringe to ensure precise dosing.

As a class, cyclo-oxygenase inhibitory NSAIDs may be associated with gastrointestinal,

renal and hepatic toxicity. Sensitivity to drug-associated adverse events varies with the

individual patient. Patients at greatest risk for renal toxicity are those that are dehydrated,

on concomitant diuretic therapy, or those with existing renal, cardiovascular, and/or

hepatic dysfunction. Concurrent administration of potentially nephrotoxic drugs should

be carefully approached. Assessing drugs may affect renal perfusion.

Concomitant use of NSAIDs and ACE inhibitors may increase the risk of renal toxicity.

NSAIDs may result in clinically significant disease in patients with underlying or pre-

existing diseases that has not been previously diagnosed.

In cats, appropriate monitoring procedures should be employed during all surgical

procedures. The use of parenteral fluids during surgery is recommended to decrease

potential renal complications when using NSAIDs. If additional pain medication is

needed after the single dose of metoxicam, a non-NSAID class of analgesic may be

intraparturative home care.

Concomitant use of Metacam 5 mg/mL Solution for injection with other non-steroidal

anti-inflammatory drugs is not recommended. NSAIDs should not be used to treat

inflammatory diseases. As a single use product in cats, meloxicam should not be followed by

additional NSAIDs or corticosteroids. The use of concomitantly administered drugs

with Metacam 5 mg/mL Solution for injection has not been studied in cats. Commonly

used pre-treatment drugs include analgesics and behavioral medications.

The influence of concomitant drugs on the pharmacokinetics and behavioral effects of

Metacam 5 mg/mL Solution for injection has not been studied in cats. Consider

appropriate use of NSAIDs. NSAIDs should be avoided or closely monitored in

inflammatory diseases. When used in cats, meloxicam should not be followed by

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with Metacam 5 mg/mL Solution for injection has not been studied in cats. Commonly

used pre-treatment drugs include analgesics and behavioral medications.

### Information for Cat Owners: Metacam. Like other NSAIDs, is not free from adverse

reactions. Owners should be advised of the potential for adverse reactions and be

informed of the clinical signs associated with NSAID intolerance. Adverse reactions may

include vomiting, diarrhea, lethargy, decreased appetite and behavioral changes.

Cat owners should be advised when their pet has received a meloxicam injection. Cat

owners should contact their veterinarian immediately if possible adverse reactions are

observed.

Clinical Pharmacology: Metacam has nearly 100% bioavailability after subcutaneous

injection in cats. The terminal elimination half-life after a single dose is estimated to be

approximately 15 hrs (~10%) in cats.

Peak drug concentrations of 1.1 mg/mL can be expected to occur within 1.5 hours

following a 0.3 mg/kg subcutaneous injection in cats. The volume of distribution (Vd) in

cats is approximately 0.27 L/kg with an estimated systemic clearance of 0.13

L/kg. The drug is 97% bound to feline plasma proteins.

Effectiveness: The effectiveness of Metacam 5 mg/mL Solution for injection was demonstrated in

a masked field study involving a total of 138 cats representing various breeds. This study

used butorphanol as an active control. Cats received either a single subcutaneous

injection of 0.3 mg/kg Metacam 5 mg/mL Solution for injection or 0.4 mg/kg butorphanol

prior to ovariohysterectomy, either alone or in conjunction with surgical neutering. All cats were

premedicated with acepromazine, induced with propofol and maintained on isoflurane.

Pain assessment variables evaluated by veterinarians included additional pain

intervention therapy, gait/limbness score, analgesia score, sedation score, general

appearance score, recovery score, and final analgesic score. Additionally, a

comparative pain score, which was the summation of the analgesic, sedation, and

respiratory rate scores was evaluated. A palpometer was used to quantify the pain

threshold.

A sustained number of cats required additional intervention in the 0-24 hour post-

surgical period, with the majority of these interventions taking place within the first hour.

Therefore, the percentage of cats in each group that received one or more interventions

was designated as the primary assessment variable. Approximately half of the cats in

each group received a pain intervention as a result of the first (time 0) post-surgical

evaluation, i.e., euthanasia. At this point, the need to provide a pain intervention was not

statistically significant between the two groups (p=0.723). However, the median number

of interventions was one per cat in the meloxicam group and two per cat in the

butorphanol group and this difference was statistically significant (p=0.0021). The

statistical evaluation supports the conclusion that the meloxicam test article is non-

inferior to the butorphanol active control. Forty-eight of the 72 cats in the meloxicam

group received one or more interventions (66.7%), and 47 of 66 cats in the butorphanol

group received one or more interventions (71.2%). The number of interventions

administered to the meloxicam group was less than the butorphanol group at 1, 3, 5, 8,

12, and 24 hours post-surgery.

Cats receiving Metacam 5 mg/mL Solution for injection showed improvement in the pain

assessment variable.

Animal Safety:

Cats 3 Day Target Animal Safety Study - In a three day safety study, subcutaneous

Metacam 5 mg/mL Solution for injection administration to healthy cats at up to 1.5

mg/kg (saline injection), 0.3 mg/kg and 0.6 mg/kg on Day 0, Metacam Oral Suspension,

1.5 mg/kg or saline was then administered orally once daily at the same respective dose

for eight consecutive days. Clinical adverse effects were observed in the treated groups and

adverse effects were observed in the control group. The gross necropsy report includes observation of

reduced GI masses in 3 of 4 cats in the 0.3 mg/kg group and 1 of 4 cats in the 0.6 mg/kg

group. All saline-treated cats were normal. By Day 9, one cat in both the 0.3 mg/kg group

and the 0.6 mg/kg group died and another cat in the 0.3 mg/kg group was moribund. The

cause of death for these cats could not be determined, although the pathologist reported

peritonitis/duodenal ulceration in the cats in 0.6 mg/kg group. The safety studies

demonstrated a narrow margin of safety.

Information on the Toxicology of the Injection sites revealed hemorrhage and

inflammation, myofibrillar atrophy, panniculitis, fibrin deposition, and fibroblast

proliferation. These findings were present in cats in all groups, with the 3X cats having the

most severe. No safe repeat dose has been established in cats.

Storage Information: Store at controlled room temperature, 68-77°F (20-25°C).

Metacam 5 mg/mL Solution for Injection: 10 mL vial

Manufactured by:

Boehringer Ingelheim Vetmedica, Inc.

51 Joseph, MO 64506 U.S.A.

Distributed by:

Merial Limited

Kenilworth, NJ 07033-4640 U.S.A.

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Code 601211

Revised 09-2004

Technical assistance, call 1-866-METACAM (1-866-638-2226).

To report suspected adverse reactions, to obtain a Material Safety Data Sheet, or for

Diarrhea and fecal occult blood have also been reported.

vomiting, inappetence, and transient pain immediately after injection were noted.

Repeated use in cats has been associated with acute renal failure and death. In studies

Foreign Experimentation: Twenty-four hours after the injection with Metacam 5 mg/mL

treatment values. Twenty-four hours after the injection with Metacam 5 mg/mL

butorphanol treatment group had post-treatment anemia. All but one cat, who had a mild

hematocrit and hemoglobin values in the normal range. Four cats (6.1%) in the

Solution for Injection had post-treatment anemia. Pre-treatment, these cats all had

elevated serum blood urea nitrogen levels. Nine cats (12.5%) receiving Metacam 5 mg/mL

blood urea nitrogen (BUN) levels. The pre-treatment values were in the normal range. Of

the 66 cats (injection) treatment group, no cats experienced post-treatment elevated serum

mg/mL Solution for Injection, six cats (8.3%) experienced post-treatment elevated serum

Adverse Reactions:

Cats: A field study involving 138 cats was conducted. Of the 72 cats receiving Metacam 5

mg/mL Solution for Injection, 10 mL vial

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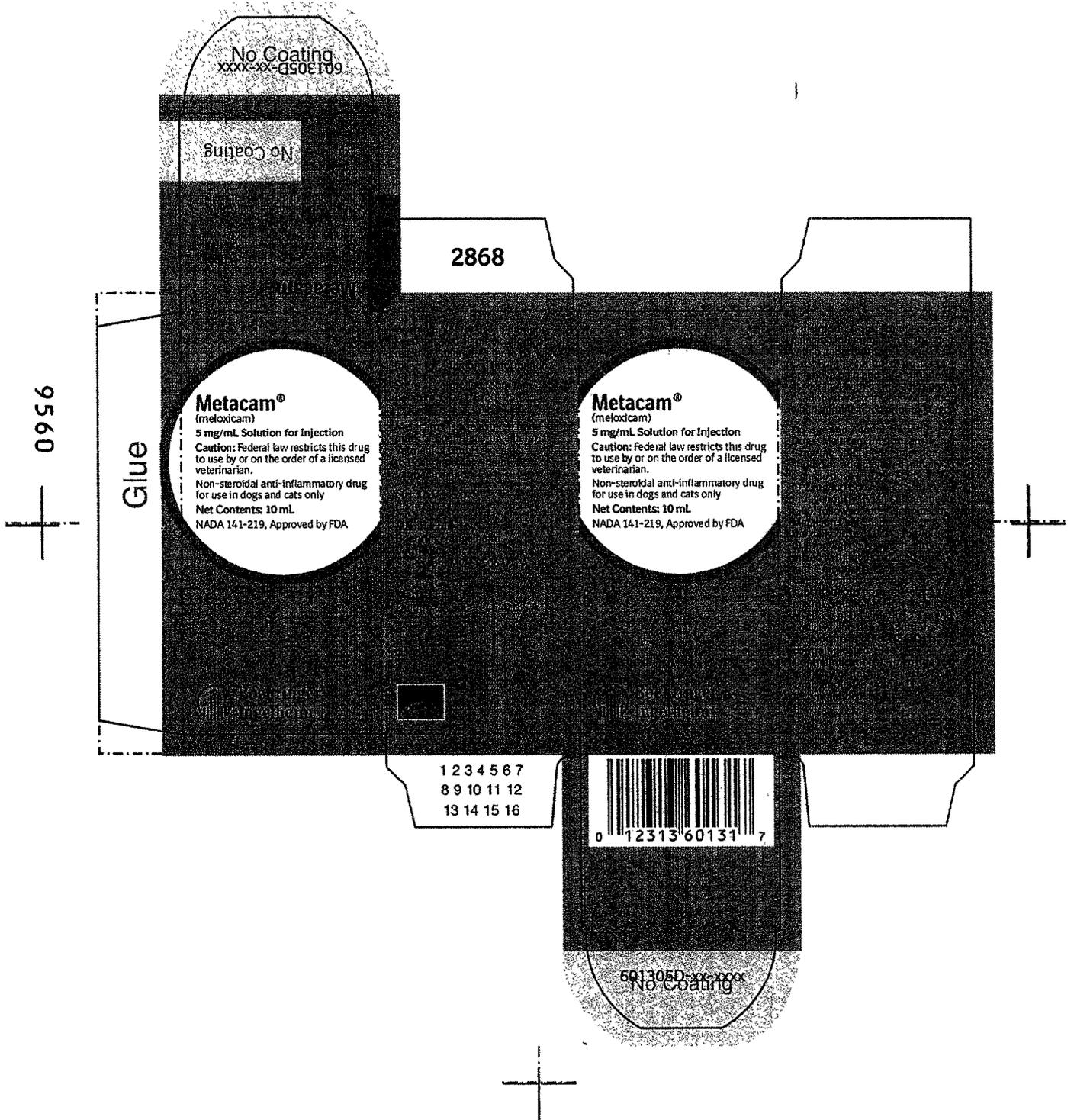
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Technical assistance, call 1-866-METACAM (1-866-638-2226).

To report suspected adverse reactions, to obtain a Material Safety Data Sheet, or for



Non-steroidal anti-inflammatory drug for use in dogs and cats only

**Warning:** Not for use in humans. Keep this and all medications out of reach of children. Refer to package insert for additional information.

Store at controlled room temperature, 68-77°F (20-25°C).

Manufactured by:  
**Boehringer Ingelheim Vetmedica, Inc.**  
St. Joseph, MO 64506 U.S.A.

Distributed by:  
**Merial Limited**  
Duluth, GA 30096-4640 U.S.A.



601304L-XX-XXXX  
Code 601311

**Metacam®**  
(meloxicam)  
**5 mg/mL Solution for Injection**

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

**Net Contents: 10 mL**

**Indications: Dogs:** For the control of pain and inflammation associated with osteoarthritis.  
**Cats:** For the control of postoperative pain and inflammation associated with orthopedic surgery, ovariohysterectomy and castration when administered prior to surgery.  
Refer to package insert for complete dosage and administration information.

Lot No.:

Exp. Date:



**Boehringer  
Ingelheim**

000013

000019

**Metacam 5 mg/mL Solution for Injection**  
**(meloxicam)**  
**For use in Dogs and Cats only**

QUANTITY	LOT NO.	EXP. DATE
 24x10mL		
ITEM NUMBER  601311000		 10012313601314

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Manufactured by:

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601306C-xx-0000