Date of Approval: March 8, 2011

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-320

ONSIOR

Robenacoxib
tablets
Cats

ONSIOR tablets are indicated for the control of postoperative pain and inflammation associated with orthopedic surgery, ovariohysterectomy and castration in cats $\geq$ 5.5 lbs (2.5 kg) and $\geq$ 6 months of age; for up to a maximum of 3 days.

Sponsored by:

Novartis Animal Health US, Inc.

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I. GENERAL INFORMATION:

A. File Number: NADA 141-320

B. Sponsor: Novartis Animal Health US, Inc.
3200 Northline Ave., suite 300
Greensboro, NC 27408

Drug Labeler Code: 058198

C. Proprietary Name(s): ONSIOR

D. Established Name(s): Robenacoxib

E. Pharmacological Category: Non-steroidal anti-inflammatory drug (NSAID)

F. Dosage Form(s): Non-scored tablet

G. Amount of Active Ingredient(s): Each tablet contains 6 mg robenacoxib

H. How Supplied: ONSIOR tablets are available as 6 mg round, flavored tablets in blisters. Each individual blister card contains 3 tablets. Ten blister cards are supplied in a carton. Each blister card should be dispensed in an ONSIOR dispensing envelope containing the product insert/information for owner sheet, supplied with the product.

I. How Dispensed: Rx

J. Dosage(s): The dose of ONSIOR (robenacoxib) tablets is 0.45 mg/lb (1 mg/kg) orally once daily, for a maximum of three days.
Preoperatively: Administer dose approximately 30 minutes prior to surgery.
Postoperatively: Tablets may be given with or without food. See dosing chart for dosage directions.
Dosing Directions: to be used in cats ≥ 6 months of age and ≥ 5.5 lbs. Tablets are not scored and should not be broken.

Body weight	6 mg ONSIOR (robenacoxib) Tablet
5.5 to 13.2 lbs (2.5 to 6 kg)	1 whole tablet once daily
13.3 to 26.4 lbs (6.1 to 12 kg)	2 whole tablets once daily

K. Route(s) of Administration:	Oral
L. Species/Class(es):	Cats
M. Indication(s):	ONSIOR tablets are indicated for the control of postoperative pain and inflammation associated with orthopedic surgery, ovariohysterectomy and castration in cats $\geq$ 5.5 lbs (2.5 kg) and $\geq$ 6 months of age; for up to a maximum of 3 days.

II. EFFECTIVENESS:

A. Dosage Characterization:

A dose of 0.45 mg/lb (1 mg/kg) administered orally once daily for up to three treatments was selected based on the results of the following experimental studies.

A kaolin-induced acute pain and inflammation model study was performed in 10 European short-haired cats of both sexes in a single dose pharmacokinetic/pharmacodynamic (PK/PD) experiment for which robenacoxib was administered at 2 mg/kg subcutaneously (SC). The objective of the study was to assess robenacoxib pharmacodynamic parameters by correlating concentration-effect relationships with analgesic, anti-inflammatory and antipyretic activity. Blood samples were collected and clinical endpoints (body temperature, locomotion score, locomotion test, local skin temperature and paw withdrawal time) were assessed at multiple times from Day 0 to Day 4 after kaolin injection. The effective dose for lameness and locomotion were determined to be 1.5 and 3 mg/kg respectively, after SC administration of robenacoxib in the cat. Using a PK/PD simulation approach with the pharmacodynamic parameters obtained in this study and PK parameters calculated from oral pharmacokinetic data from two other studies, it was predicted that robenacoxib would provide good anti-inflammatory, antipyretic and analgesic activity after oral administration of 1 mg/kg in the cat.

The above studies indicated that a dose of 1 mg/kg administered orally once daily was an appropriate dose for further investigation. To confirm these results, a pilot study was conducted in client-owned animals to evaluate the effectiveness of robenacoxib tablets (final formulation) at a dose of 1 mg/kg administered once daily for the control of postoperative pain and inflammation associated with an onychectomy (forelimbs only) and ovariohysterectomy (OVH) or castration. The study was a masked, negative controlled, multi-center field study in which 24 cats were enrolled in the two groups (12 cats per treatment group). Each cat received either robenacoxib or the negative control approximately 30 minutes prior to surgery or at the same time the pre-anesthetic agents were administered and then daily for two days post-surgery.

Animals were evaluated post-surgically at predetermined times to assess the overall response to treatment and to monitor their condition. Effectiveness variables included rescue therapy due to pain, overall pain, pain on palpation (orthopedic pain and OVH or castration incision site), posture, behavior and sedation. There were fewer cases needing rescue therapy in the robenacoxib group (3/12) compared to the negative control group (7/12). The difference was not statistically significant, presumably due to the low number of cats enrolled in the study. Overall pain, pain on palpation (orthopedic pain, and OVH or castration incision site), posture and behavior showed a reduction in mean overall values in favor of the robenacoxib group when compared to the negative control group. In this study, robenacoxib was well tolerated when used to control postoperative pain and inflammation associated with ovariohysterectomy or castration, and onychectomy. The results from this study indicated that the dose of 1 mg/kg should be effective for controlling postoperative pain and inflammation associated with an onychectomy and ovariohysterectomy or castration.

B. Substantial Evidence:

The effectiveness of ONSIOR tablets for the control of postoperative pain and inflammation associated with orthopedic surgery, ovariohysterectomy (OVH) and castration was evaluated in cats presented for reproductive sterilization and forelimb onychectomy procedures. The study was conducted at twelve (12) veterinary clinics throughout various geographic regions within the U.S. Results of the study demonstrate that ONSIOR tablets are well-tolerated and effective when administered at a dose of 1 mg/kg of body weight once daily for a maximum of 3 days.

1. Field Study:

a. Title: Field effectiveness and safety of ONSIOR (tablet) for the control of postoperative pain and inflammation associated with ovariohysterectomy, castration and onychectomy in cats, (NAH-07-0001)

b. Investigators(s):

Dr. Deborah Edwards-Pettey Largo, FL	Dr. Sam Geller Quakertown, PA
Dr. Mary Gray Lafayette, IN	Dr. Amy Jessup Winston-Salem, NC
Dr. Joe Kinnarney Reidsville, NC	Dr. Kristi Rowland Lawrence, KS
Dr. Eddie Robinson Columbia, SC	Dr. Roger Sifferman Springfield, MO
Dr. Tammy Sadek Kentwood, MI	Dr. Phillip VanVranken Battle Creek, MI
Dr. Susan Streeter Oklahoma City, OK	Dr. Emily Walker Albuquerque, NM

c. Study Design: This was a masked, randomized, multi-center field study comparing ONSIOR tablets to a vehicle control (placebo).

1) Objective: The objective of the study was to demonstrate the effectiveness and field safety of ONSIOR tablets, at a dose of 1 mg/kg of body weight, for the control of postoperative pain and inflammation associated with reproductive sterilization performed in conjunction with an onychectomy (forelimbs only) in cats. As part of the pre-operative anesthetic protocol, all study participants received butorphanol tartrate and a forelimb metacarpal four-point ring block. In addition to the pre-operative therapy, treated animals received ONSIOR tablets as a pre-operative treatment and continued to receive it once daily for two additional treatments. Control animals received a placebo (vehicle control) at the same time points.

2) Study Animals: There were two hundred and forty-nine (110 males and 139 females) healthy, intact cats of various breeds, between 6 months and 13 years of age and weighing between 2.5 and 7.4 kg. The majority of cats were young. Of the 167 cats treated with robenacoxib, 161 (96%) were $\leq$ 4 years of age. Of the 167 cats treated with robenacoxib, 114 (68%) of these cats were 6 months to 1 year of age.

3) Treatment Groups: The animals were randomized into two treatment groups in a 2:1 ratio of ONSIOR tablet and vehicle control (placebo), respectively.

Table 1. Treatment Groups

Body weight (kg)	6 mg ONSIOR (robenacoxib) Tablet	Placebo (vehicle control)
2.5 to 6	1 whole tablet once daily	1 whole tablet once daily
6.1 to 12	2 whole tablets once daily	2 whole tablets once daily

All cats received butorphanol subcutaneously as a pre-anesthetic medication and a metacarpal four-point ring block. Robenacoxib or placebo was administered approximately 30 minutes prior to surgery at the time of administration of pre-anesthetic medication.

Surgical procedures – All cats were adequately hydrated prior to and during surgery. Ovariohysterectomy was performed by a midline incision. Castrations were performed via the standard scrotal approach.

Onychectomy: Three types of procedures could be used to declaw the front paws. These included surgical scalpel, laser, and guillotine nail trimmers.

4) Drug Administration: The robenacoxib group received the final market formulation of ONSIOR tablets as 6 mg, non-scored tablets. The control group received placebo tablets (vehicle) identical in appearance. Robenacoxib or placebo was administered approximately 30 minutes prior to surgery at the time of administration of pre-anesthetic medication.

5) Measurements and Observations:

A clinical examination was conducted prior to surgery and at study exit. Assessments for pain were performed prior to surgery (following a minimum two hour acclimation) and at various time points on Day 0 (day of surgery), Day 1 (day after surgery) and Day 2 (day of discharge from hospital). Assessments included the need for rescue pain medication, posture, behavior (viewed from a distance and following social interaction), pain elicited on palpation (paws and incision site) and overall pain control. Hematology, serum chemistry and urine samples were obtained prior to study and at exit. In addition, all owners received a follow-up phone call 3-7 days post-study.

Scheduled evaluations and determination of the need for rescue pain medication were conducted at 0 minutes (extubation), 30 min, 1 hr, 3 hrs, 5 hrs, 8 hrs, 24 hrs, 28 hrs, 32 hrs, 48 hrs, and 52 hrs following surgery. Although these were the scheduled evaluation timepoints, rescue pain medication could be given any time at the veterinarian's discretion.

Pain Assessments: Cats were evaluated at baseline and at the pre-determined intervals postoperatively to assess overall response to treatment and to monitor the condition of the cats. At any time, if an animal was determined to be in discomfort, rescue pain medication could be administered. Cats receiving postoperative rescue pain treatment were considered treatment failures and withdrawn from the study. However, all cats continued to be monitored for a minimum of 24 hours post-intervention and all observations were recorded.

Posture: This variable assessed the cat's overall mobility in the cage, standing or resting, and any preferential or unequal weight distribution of the limbs, hunched or retracted posture, position

of the head, and any forelimb shifting. The investigator assessed posture as one of the following:

1. Normal
2. Mildly abnormal (ambulates with slightly noticeable weight shifting behavior)
3. Moderately abnormal (Able to ambulate. Noticeable weight shifting behavior but still places affected limbs);
4. Severely abnormal (barely or unable to ambulate. Significant weight shifts or non-weight bearing behavior.)

Behavior: This variable assessed the cat's overall comfort, response to social interaction with the investigator or hospital staff, level of aggression, level of vocalization, and ease of handling as viewed from a distance and following social interaction. The investigator assessed behavior from a distance and following social interaction.

The investigator assessed *Behavior from a distance* as one of the following:

1. Appears comfortable
2. Questionable comfort
3. Distressed cat

The investigator assessed *Behavior following social interaction* as one of the following:

1. Normal
2. Mildly abnormal (slight reduction in level of social behavior but does not overtly object to examination or palpation);
3. Moderately abnormal (May try to avoid examination or palpation. May attempt to bite when affected areas are examined)
4. Severely abnormal (Refuses to be examined and may display aggression without provocation).

Pain elicited on palpation: This variable assessed the cat's level of response to a gradual increase in pressure applied to areas adjacent to the surgical sites. The endpoint of this assessment was the amount of pressure that elicited any level of pain response from the cat (e.g. withdrawal of paw, discomfort or vocalization).

Assessing the paws
Prior to surgery, the paw to be evaluated was determined and the same paw was assessed throughout the study.

The amount of pressure was measured via a palpometer, a pressure-sensing device. Based on the audio feedback, the investigator assessed this variable as one of the following:

1. 5 beeps (greatest recorded pressure) of pressure — equals 800 gf/cm^2
2. 4 beeps — equals 600 gf/cm^2
3. 3 beeps — equals 450 gf/cm^2
4. 2 beeps — equals 300 gf/cm^2
5. 1 beep (lightest recorded pressure) — equals 200 gf/cm^2

Assessing the soft tissue incision sites
The investigator was instructed not to use the palpometer or palpate directly over the incision site. An area immediately adjacent to the incision site was located and slowly digital pressure was applied. The area could be assessed several times and the veterinarian noted the severity of the cat's reaction in response to pressure. Applied pressure was stopped once the cat gave any indication of discomfort.

Based on a subjective evaluation, the investigator assessed this variable by indicating the cat responded to one of the following:

1. Significant pressure (response to a level of pressure that visually distorts the skin of the surgical area and was to a level that was nearly equivalent to what could be applied in a cat that had not undergone surgery).
2. Moderate pressure (response to a level of pressure that visually distorts the skin of the surgical area but does not approach the level of what could be normally accomplished had the cat not had surgery).
3. Slight pressure (response to any level of physical contact to the surgical area/field).

Overall pain control: This variable was a subjective assessment of the examiner's overall impression of pain control based on their assessment of posture, behavior and pain on palpation. The investigator assessed this variable as one of the following:

1. Well controlled (cat is clearly comfortable);
2. Moderately controlled (cat is generally comfortable with only slight indications of discomfort);
3. Poorly controlled (cat is clearly uncomfortable with overt signs of pain).

For each cat rescued due to poor pain control, investigators marked descriptors/reasons for intervention. Investigators were instructed to check all that applied from the following list.

- Difficult or violent post-anesthetic recovery. The patient may be thrashing violently in such a manner that may threaten their safety. Depending on the pre-anesthetic cocktail used, some post-anesthetic dysphoria may be encountered so clinical judgment should be used when determining the origin of such a recovery.
- Patient's posture is reflective of a purposeful avoidance of painful stimulus. The patient may exhibit purposeful forelimb shifting behavior or may be limping in order to alleviate pain caused by weight bearing. Care must be taken when such a behavior is exhibited in cats that have bandaged forelimbs.
- Patient has a hunched posture or any other positions where there is an obvious intent to avoid or move away from painful stimulus or surgical sites.
- Patient appears agitated or cannot find a comfortable position within the cage.
- Patient has poor or unkept appearance that may be reflective of poor grooming behaviors.
- Patient exhibits trembling or shaking that is not part of the dysphoria associated with the immediate anesthetic recovery and may be indicative of painful stimulus.
- Patient exhibits moderate to severe chewing, licking or biting of the surgical sites.
- Patient vocalizes in response to discomfort or pain.
- Patient demonstrates little or no social response to pain assessor or caregiver, prefers to be alone, and has little to no desire for social interaction.
- Patient demonstrates aggression or other defensive/guarding behaviors that are reflective of any discomfort associated with the surgical sites.
- Patient has moderate to severe tenderness of the surgical sites.
- Patient has moderate to severe tachycardia or tachypnea.
- Patient has dilated pupils.
- Other:

6) Statistical Methods: Summary tables (number of observations, means and standard deviations or median and frequency counts, and minimum and maximum values) were presented for all variables.

Effectiveness Variable

Animals that received rescue pain medication or were removed due to adverse events were considered treatment failures. The effectiveness variable was treatment success or failure. The pivotal test for effectiveness compared treatment success rates in the

ONSIOR tablet group to the placebo group. A generalized linear mixed model (using GLIMMIX in SAS) was utilized, assuming a binomial distribution and a logit link function. The statistical model included 'Treatment' as a fixed effect and 'Site' and 'Site x Treatment' as random effects.

Individual Variables

The above noted individual variables of posture, behavior (viewed from a distance and following social interaction), pain elicited on palpation (paws and incision site) and overall pain control were assessed. Data from the day of surgery (extubation to hour 8), with Last Observation Carried Forward (LOCF) utilized on any animal that required rescue therapy on the day of surgery, was analyzed using generalized linear mixed models. The covariance was modeled using the AR(1) structure and the Kenward-Rogers adjustment was used to compute the denominator degrees of freedom for the test of the fixed effect.

d. Results:

Effectiveness was evaluated in 244 cats and field safety was evaluated in 249 cats. A statistically significant difference (p-value = 0.0476) in the proportion of treatment successes in the ONSIOR tablets treatment group compared to the placebo control group was observed (Table 2).

Table 2. Results of the Effectiveness Analysis.

Treatment Group	N	Treatment Outcome (%)		P-value[a]
		Success	Failure	
ONSIOR	164	137 (83.5%)	27 (16.5%)	0.0476
Placebo	80	43 (53.8%)	37 (46.2%)	

[a] Treatment contrast based on generalized linear mixed model with logit link, using 'Treatment' as a fixed effect and 'Site' and 'Site x Treatment' as random effects.

Twenty-seven out of 164 robenacoxib cases (16.5%) and 37 out of 80 placebo cases (46.2%) were treatment failures. Of the 64 treatment failures, 49 cases (76.5% of the failures) were rescued/withdrawn by 24 hours post-surgery. Fourteen of the failures were rescued/withdrawn between 24 and 48 hours post-surgery (22%

of failures). The remaining 1 case (1.5 %) was withdrawn after 48 hours post-surgery.

The most common descriptors checked by investigators for rescue were tenderness of surgical sites, aggressive/guarding behavior, vocalizing, and agitated, purposeful avoidance of painful stimulus, hunched position, trembling/shaking, little or no social response, and tachycardia/tachypnea.

For the individual variables, the analysis showed that for OVH or castration incision site pain, there were statistically significant ($P<0.05$) differences in incision site pain scores at assessment times 5 and 8 hours, indicating less pain in the ONSIOR group; and, in social behavior scores and posture scores at times 3, 5, and 8 hours, indicating less pain in the ONSIOR group. The statistical analysis did not converge for distance behavior score, overall pain control, and paw assessment pain score so no further comparisons were performed for these variables.

Body weight change was similar between both groups. No clinically significant difference existed between the ONSIOR tablets and the placebo group for hematology, serum chemistry or urinalysis results. Concurrent medications used during the field study with ONSIOR tablets included antiparasiticides, anesthetics, pre-anesthetic medications, and antibiotics.

e. Adverse Reactions: The most commonly reported adverse reactions were surgical site bleeding, infected surgery sites, lethargy and inappetance. The adverse reactions and number of cats experiencing each are summarized in Table 3. Some cats experienced more than one adverse reaction during the study.

Table 3. Adverse Reactions Reported in the Field Study.

Adverse Reaction*	ONSIOR 6 mg tablets N = 167	Placebo (vehicle tablets minus robenacoxib) N = 82
Inappetance, weight loss	4	2
Incision site bleeding	7	1
Incision site infection	6	2
Decreased activity, lethargy, hiding	4	1
Cystitis/hematuria	3	0
Hair loss, excoriation, bruising	2	0
Vomiting	4	1
Bloody stool, diarrhea	3	1
Respiratory, cardiac arrest	1	0
Incoordination, weakness	1	1
Death	0	1

*Cats may have experienced more than one type or occurrence of an event during the study.

f. Conclusion(s): Administration of ONSIOR tablets at a dose of 0.45 mg/lb (1 mg/kg) once daily for up to three days, with the first dose administered approximately 30 minutes prior to surgery, was effective and well-tolerated for the control of postoperative pain and inflammation associated with orthopedic surgery, ovariohysterectomy and castration in cats.

III. TARGET ANIMAL SAFETY:

A. Drug Tolerance Study of Robenacoxib Tablets in Cats:

1. Type of Study: Laboratory safety study (GLP)

2. Study Director: Jennifer Bassett, BS
Ricerca Biosciences, LLC
Concord, OH

3. General Design:

a. Purpose: The objective of this laboratory study was to evaluate the safety of robenacoxib tablets following daily oral administration over a 21 day period at 24 mg/kg/day (10X the maximum exposure).

b. Test Animals: Eight month old, healthy male and female domestic shorthair (DSH) cats were used in the study (4/sex/group)

c. Control: Empty gelatin capsules

d. Dosage form: Gelatin capsules containing final market formulation, 6 mg robenacoxib tablets

e. Route of administration: Oral administration with water used to facilitate swallowing

f. Dosages used:

Table 4. Treatment Groups for the Drug Tolerance Study

Group	Dose	Number and Sex of Animals
1	0, empty gelatin capsules	4M, 4F
2	24 mg/kg/day	4M, 4F

g. Test duration: Twenty-one days

h. Variables measured: The following variables were measured prior to study initiation, during, and/or at the end of the study – body weight, food and water consumption, clinical observations, physical and neurologic examinations, body temperature, ophthalmic exams, coagulation and buccal mucosal bleeding times (BMBT), hematology and clinical chemistries, urinalyses, organ weights, and gross pathology and histopathology.

4. Results: All cats survived to termination of the study.

a. Adverse reactions included vomiting and decreased activity. Two cats in the 10X group exhibited abnormal rear limb neurologic function. One of these cats also exhibited a head tilt and nystagmus at the end of the study. Mean food consumption was less in the 10X group.

Table 5. Food Consumption Mean Values

	Pre (g)	**Week 1** (g)	**Week 2** (g)	**Week 3** (g)
Control	103.38	110.14	103.43	93.17
10X	101.56	90.91	88.48	83.98

b. Hematology and clinical chemistry evaluations showed a decrease in the mean calcium value in the 10X group compared to the controls, and mean cholesterol was higher in the 10X group compared to the controls. The mean potassium value was higher in the 10X group compared to the controls. All

mean values remained within the reference range used for this study. The post-study pooled, urine specific gravity in the 10X group was lower compared to the control group; and the pooled urine volume was comparably higher in the 10X group compared to the controls.

c. Pathology findings and organ weights: The mean kidney weights were lower in the 10X group compared to the control group; and the mean thymus weights were also lower in the 10X group compared to the controls. There were some changes in pooled brain, heart, and spleen weights in the 10X group compared to controls. Two cats in the 10X group had either unilateral or bilateral extensive, chronic interstitial nephritis. There was a focal cecal/large intestinal erosion in one 10X cat. One 10X cat and one control cat had periportal, multifocal necrosis in one lobe of the liver. There were four 10X cats and 2 control cats with focal, extensive, unilateral or bilateral, renal tubular degeneration.

5. **Conclusions**: Under the conditions of this study, cats administered 24 mg/kg/day of robenacoxib remained clinically healthy throughout the 21 day duration, except for 2 cats in the 10X group with neurologic signs.

B. Target Animal Safety (TAS) Study of Robenacoxib Tablets Administered Daily to cats for Six Months

1. **Type of Study**: Laboratory safety study (GLP), 1X, 3X, and 5X TAS study

2. **Study Director**: Zac Lloyd, B.S.
MPI Research, Inc.
Mattawan, MI

3. **General Design**:

a. Purpose: The objective of this laboratory study was to evaluate the safety of robenacoxib tablets, when orally administered, once daily to DSH, adult cats at 1X, 3X, and 5X the maximum exposure of 2.4 mg/kg for 6 months compared to placebo (the actual mg/kg dose received depended upon the cat's weight due to the inherent dose band of the non-scored, one-size, 6 mg tablet).

b. Test Animals: There were 3 treatment groups and 1 control group; 4/sex/group. The study used healthy, 8 month old DSH cats ranging in weight from 1.97 – 5.15 kg on the first day of dosing.

c. Control: Empty gelatin capsules

d. Dosage form: Gelatin capsules containing final market formulation, 6 mg robenacoxib tablets

e. Route of administration: Oral administration with water used to facilitate swallowing

f. Dosages used:

Table 6. Treatment Groups for the 6 month TAS Study

Group	Dose	Number and Sex of Animals
1	0, empty gelatin capsules	4M, 4F
2	1X, 2. 4 mg/kg	4M, 4F
3	3X, 7.2 mg/kg	4M, 4F
4	5X, 12.0 mg/kg	4M, 4F

g. Test duration: Six months

h. Variables measured: The following variables were measured prior to study initiation, during, and/or at the end of the study – body weight, food and water consumption, clinical observations, physical and neurologic examinations, body temperature, fecal exams, ophthalmic exams, coagulation and buccal mucosal bleeding times (BMBT), hematology and clinical chemistries, urinalyses, electrocardiography, organ weights, and gross pathology and histopathology. Additionally, blood samples were collected for periodic pharmacokinetic analysis.

4. Results: All cats survived to termination of the study.

a. Abnormal clinical findings included one 5X cat that had clonic seizures on Day 115 and ataxia on Day 175. Another cat in the 5X group had skin cold to the touch on Day 106. One cat in the 1X group experienced urethral obstruction and feline lower urinary tract disease (FLUTD). Vomiting, decreased activity, injected sclera, and soft stools were the most common adverse reactions observed in the treated groups. Soft stools and injected sclera were also observed in the control group.

b. Pharmacokinetics: There was no obvious accumulation in C_{max} or AUC between Days 1, 31 and 171, and there was no apparent difference in parameters between males and females. The following parameters were calculated for the 1X dosage: T_{max} was 0.5 h (median), the dose-normalized mean C_{max} was 668 ng/mL and the dose-normalized mean area under the curve (AUC (0-inf)) was 902 h*ng/mL. Similarly, the following parameters were calculated for the 3X dosage: T_{max} was 0.5 h (median), the dose-

normalized mean C_{max} was 1019 ng/mL and the dose-normalized mean area under the curve (AUC(0-inf)) was 1394 h*ng/mL. For the 5X dosage the following parameters were calculated: T_{max} was 1.0 h (median), the dose-normalized mean C_{max} was 1198 ng/mL and the dose-normalized mean area under the curve (AUC(0-inf)) was 1884 h*ng/mL. A post hoc analysis of PK parameters revealed that dose normalized C_{max} and AUC were greater than dose proportional.

c. Body Weight: Significant mean body weight differences ($p \leq 0.0587$) were observed between the control group and all treated groups (lower than controls). These lower body weights (compared to the control group) were statistically significant for the 3X group from Day 35 – Day 182 ($p \leq 0.0587$) and statistically significant for the 1X and 5X groups from Day 49 – Day 182 ($p \leq 0.0487$).

d. Echocardiography: There was a clear dose-related and possible time-related increase in the QTc interval at Day 41 and Day 175. It is unknown if the increased QTc interval suggests an elevated risk of cardiac arrhythmias or Torsades de Pointe in cats.

   The control cats showed no increase in QTc intervals. In the 1X group, 1 cat showed an increase in QTc between 30 – 60 msec; and 13 cats showed interval increases of < 30 msec (7 cats on Day 41 and 6 cats on Day 175).

   In the 3X group, 4 cats showed an increase in QTc interval between 30 – 60 msec (1 cat on Day 41 and 3 cats on Day 175) and 9 cats showed increases of less than 30 msec (6 cats on Day 41 and 3 cats on Day 175).

   In the 5X group, there were 3 QTc interval increases > 60 msec (2 cats on Day 41 and 1 cat on Day 174); 3 increases between 30 – 60 msec (1 cat on Day 41 and 2 cats on Day 175), and 6 increases < 30 msec (4 on Day 41 and 2 on Day 175).

   No treatment effect was noted for heart rate, PR or RR intervals, or QRS duration.

e. Hematology and clinical chemistry evaluations: One 5X cat with decreased kidney weight and size also had transient increases in BUN and creatinine (BUN 44 mg/dL and creatinine 2.4 mg/dL on Day 90). This cat had bilateral renal tubular degeneration/regeneration with chronic inflammation. There were transient increases in aspartate aminotransferase (AST), amylase, and alanine aminotransferase (ALT) in the 3X and 5X cats from Day 30 – Day 183. Compared to controls, there was a statistically significant difference in mean amylase in the 3X and 5X groups ($p \leq 0.0168$). The mean GGT values

in the 1X and 3X groups on Day 183 were 40 IU/L and 50 IU/L higher than the Day 149 values, respectively.

f. Pathology findings and organ weights: The mean kidney weights were lower in all robenacoxib-treated groups compared to the control group. There were test article-related histopathology changes noted in the kidneys of two 1X cats and two 5X cats; the two 1X cats and one 5X cat had moderate, tubular degeneration/regeneration of greater severity than seen in any control cats. There was also the additional presence of inflammation, papillary necrosis and papillary mineralization in the kidneys of these treated cats. An additional 5X cat had minimal tubular degeneration/regeneration with minimal chronic inflammation.

All treated cats had increased Kupffer cell pigmentation in the liver. In the treated cats, Kupffer cells were prominent with abundant brownish-tinged cytoplasm. There were no clinical signs noted, and the origin of the pigment is unknown.

One 5X cat had focal, minimal degeneration/necrosis of the mucosal epithelial cells of the gastric fundus (peptic and parietal cells). In another safety study, a duodenal ulcer was also noted after 28 days in a cat administered 10 mg/kg robenacoxib per day.

5. **Conclusions**: All cats survived the 6 month study. Test article effects were noted on body weight, food consumption, QTc interval, and kidney and liver pathology. One treated cat had seizures and ataxia. An adequate safety margin was demonstrated for ONSIOR tablets when administered under the conditions of this study to support the use of the tablets for the control of postoperative pain and inflammation associated with orthopedic surgery, ovariohysterectomy and castration in cats for a maximum of 3 days.

C. Target Animal Safety Study of Robenacoxib 6 mg Tablets Administered Orally, Twice Daily to Cats for 42 Days

1. **Type of Study**: Laboratory safety study (GLP)

2. **Study Director**: Rolf Hotz, DVM
Novartis Centre de Recherche Sante Animale SA
Switzerland

3. **General Design**:

a. Purpose: The objective of this laboratory study was to evaluate the safety of robenacoxib tablets administered orally, twice daily to adult cats 2 mg/kg (0.8X), 6 mg/kg (2.5X), and 10 mg/kg (4X) for 42 days.

b. Test Animals: Thirty-two healthy, DSH cats, 7.5 to 8 month of age were included in the 4 treatment groups (4/sex/group).

c. Control: Empty gelatin capsules

d. Dosage form: Gelatin capsules containing final market formulation robenacoxib tablets

e. Route of administration: Oral administration with water used to facilitate swallowing

f. Dosages used:

Table 7. Treatment Groups for the 42 Day TAS Study

Group	Dose	Number and Sex of Animals
1	0	4 M, 4 F
2	0.8X, 2 mg/kg BID	4 M, 4 F
3	2.5X, 6 mg/kg BID	4 M, 4 F
4	4X, 10 mg/kg BID	4 M, 4 F

g. Test duration: Forty-two days

h. Variables measured: The following variables were measured prior to study initiation, during, and/or at the end of the study – body weight, food and water consumption, clinical observations, physical examinations, hematology and clinical chemistries, urinalyses, organ weights, and gross pathology and histopathology.

4. Results: All cats survived to termination of the study.

a. Clinical pathology: There was a mild increase in creatinine in the 0.8X group and a transient increase in BUN in the 2.5X group.

b. Pathology findings: Thymus weights were lower in all treated groups (atrophic changes were noted). There was a decrease in the kidney weights in the 4X group compared to the controls.

c. Adverse reactions: Vomiting was the most common adverse reaction noted in the treated cats. Other adverse reactions reported in other supportive safety studies included vomiting, diarrhea and lacrimation.

5. **Conclusions:** An adequate safety margin was demonstrated for ONSIOR tablets when administered under the conditions of this 42 day study.

IV. HUMAN FOOD 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, 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 ONSIOR tablets:

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. Consult a physician in case of accidental ingestion by humans. **For use in cats only."**

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 ONSIOR, when used according to the label, is safe and effective for the control of postoperative pain and inflammation associated with orthopedic surgery, ovariohysterectomy and castration in cats $\geq$ 5.5 lbs (2.5 kg) and $\geq$ 6 months of age; for up to a maximum of 3 days.

A. Marketing Status:

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. Furthermore, the veterinarian monitors patients for possible adverse effects of the drug.

B. Exclusivity:

Under section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of the approval because no active ingredient of the new animal drug has previously been approved.

C. Patent Information:

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

U.S. Patent Number	Date of Expiration
6,291,523	September 18, 2018
6,310,099	August 25, 2018
7,115,662	August 25, 2018

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

VII. ATTACHMENTS: