Date of Approval: August 5, 2015

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-443

ONSIOR

(robenacoxib)

injection

cats

ONSIOR (robenacoxib) injection is indicated for the control of postoperative pain and inflammation associated with orthopedic surgery, ovariohysterectomy and castration in cats $\geq$ 4 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 141-443

B. Sponsor

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

Drug Labeler Code: 058198

C. Proprietary Name

ONSIOR

D. Established Name

Robenacoxib injection

E. Pharmacological Category

Non-steroidal anti-inflammatory drug (NSAID)

F. Dosage Form

Injection

G. Amount of Active Ingredient

20 mg/mL

H. How Supplied

ONSIOR (robenacoxib) injection is available as a 20 mg/mL solution in a 20 mL multidose vial.

I. Dispensing Status

Rx

J. Dosage Regimen

For cats $\geq$ 4 months: The dose of ONSIOR (robenacoxib) injection is 0.91 mg/lb (2 mg/kg) subcutaneously once daily, for a maximum of 3 days. To ensure accuracy of dosing, the use of a 1 mL graduated syringe is recommended. The first dose should be administered approximately 30 minutes prior to surgery, at the same time as the pre-anesthetic agents are given.

Subsequent doses can be given via subcutaneous injection, or interchanged with the oral tablet in cats $\geq$ 5.5 lbs **and** $\geq$ 4 months of age, for a maximum of 3 total ONSIOR doses over 3 days, not to exceed one dose per day.

Note the dose of ONSIOR tablets and ONSIOR injection are different.

K. Route of Administration

Subcutaneous injection

L. Species/Class

Cats

M. Indication

ONSIOR (robenacoxib) injection is indicated for the control of postoperative pain and inflammation associated with orthopedic surgery, ovariohysterectomy and castration in cats $\geq$ 4 months of age; for up to a maximum of 3 days.

II. EFFECTIVENESS

A. Dosage Characterization

A dose of 0.91 mg/lb (2 mg/kg) administered subcutaneously 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 PD parameters by correlating concentration 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 doses for lameness and locomotion were determined to be 1.5 and 3 mg/kg respectively, after SC administration of robenacoxib in the cat.

The above study indicated that a dose of 2 mg/kg administered SC once daily was an appropriate dose for further investigation. To confirm these results, a pilot study was conducted in client-owned cats to evaluate the effectiveness of robenacoxib injection (final formulation) at a dose of 2 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 injection 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.

Cats were evaluated postoperatively 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 (1/12)

compared to the negative control group (7/12). The difference was statistically significant. 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 2 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 (robenacoxib) injection 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 thirteen (13) veterinary clinics throughout various geographic regions within the U.S. Results of the study demonstrate that ONSIOR (robenacoxib) injection is well-tolerated and effective when administered at a dose of 2 mg/kg of body weight once daily for a maximum of 3 days.

1. Type of Study: Field study

   a. Title: Field effectiveness and safety of ONSIOR (robenacoxib) injection for the control of postoperative pain and inflammation associated with ovariohysterectomy, castration and onychectomy in cats (Study 11-001).

   b. Investigators(s):

Dr. Brooks
Lodi, WI

Dr. Buzhardt
Zachary, LA

Dr. Campaigne
Seguin, TX

Dr. Clekis
Bradenton, FL

Dr. Edwards
Largo, FL

Dr. Jessup
Winston-Salem, NC

Dr. Lukof
Harleysville, PA

Dr. Mays
Farragut, TN

Dr. Robinson
Fort Collins, CO

Dr. Rowland
Lawrence, KS

Dr. Sifferman
Springfield, MO

Dr. Thomas
Junction City, KS

Dr. VanVranken
Battle Creek, MI

c. Study Design: This was a masked, randomized, multi-center field study comparing ONSIOR (robenacoxib) injection to saline.

(1) Objective: The objective of the study was to demonstrate the effectiveness and field safety of ONSIOR (robenacoxib) injection, at a dose of 2 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 (robenacoxib) injection as a pre-operative treatment and continued to receive it once daily for two additional treatments. Control animals received injectable saline at the same time points. All cats were adequately hydrated throughout the surgical procedure.

(2) Study Animals: There were three hundred and forty-nine (162 males and 187 females) healthy, intact cats of various breeds included in this study. ONSIOR treated cats were between 4 months and 7 years of age and weighing between 2.5 and 6.0 kg. The majority of cats were young. Of the 174 cats treated with robenacoxib, 165 (94.8%) were <3 years of age and 145 (83.3%) of these cats were 4 months to 1 year of age.

(3) Treatment Groups: The cats were randomized into two treatment groups in a 1:1 ratio of ONSIOR (robenacoxib) injection and saline, respectively.

Table 1: Treatment Groups

ONSIOR (robenacoxib) injection	2 mg/kg (0.1 mL/kg; 0.9 mg/lb) SC* once daily for 3 days
Placebo control (saline)	0.1 mL/kg (0.45 mL/lb) SC once daily for 3 days

*SC - subcutaneous

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. All cats received butorphanol subcutaneously as a pre-anesthetic medication and a metacarpal four-point ring block.

Onychectomy: Three types of procedures were 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 (robenacoxib) injection at 0.9 mg/lb (2 mg/kg) as a subcutaneous injection. The control group received saline as a subcutaneous injection. ONSIOR (robenacoxib) injection or saline was administered approximately 30 minutes prior to surgery at the time of administration of pre-anesthetic medication and once daily for 2 more treatments (total of 3 injections).

(5) Measurements and Observations: A baseline assessment of behavior was made upon study enrollment and 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. Injection site evaluations were performed for each site prior to injection and at various time points post injection. 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 time points, 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 a cat 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.

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)	equals 800 gf/cm^2 of pressure
2.	4 beeps	equals 600 gf/cm2
3.	3 beeps	equals 450 gf/cm2
4.	2 beeps	equals 300 gf/cm2
5.	1 beep (lightest recorded pressure)	equals 200 gf/cm2

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 unkempt 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: Investigator could record other indicators of pain.

(6) Statistical Methods: 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 group to the control 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 'Treatment by Site' as random effects. Estimated success rates were back-transformed from the GLIMMIX least squares estimates.

The 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 also 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 CS structure and the Kenward-Rogers adjustment was used to compute the denominator degrees of freedom for the test of the fixed effect.

Body weight change, pain on injection, and clinical pathology variables were analyzed for safety evaluation.

d. Results: Effectiveness was evaluated in 348 cats and field safety was evaluated in 349 cats. In the ONSIOR (robenacoxib) injection group, 139 of 173 cats were treatment successes. In the control group, 102 of 175 cats were treatment successes. Based on the statistical analysis, the estimate least squares mean success rates are 83.5% and 61.9% for the ONSIOR (robenacoxib) injection and saline group, respectively. A statistically significant difference (p-value = 0.0370) in the proportion of treatment successes in the ONSIOR group compared to the control group was observed (Table 2).

Table 2: Treatment Success Rates and P-Value.

ONSIOR (robenacoxib) injection	**Placebo control**	**P-value***
83.5%	61.9%	0.0370

* P-value and estimated success rate are based on back-transformed mean estimates from the statistical analysis.

Thirty-four out of 173 ONSIOR (robenacoxib) injection cases and 73 out of 175 placebo cases were treatment failures. Of the 107 treatment failures (robenacoxib and control), 91 cases (85.0% of the failures) were rescued/withdrawn by 24 hours post-surgery. Sixteen of the failures were rescued/withdrawn between 24 and 28 hours post-surgery (15.0 % of failures). No cases were withdrawn after 32 hours post-surgery.

The most common pain descriptors checked by investigators for rescue were tenderness of surgical sites, agitated, aggressive/guarding behavior,

hunched posture, vocalizing, purposeful avoidance of painful stimulus, chewing/licking/biting of surgical sites, little or no social response, dilated pupils, trembling/shaking, and tachycardia/tachypnea.

For the individual variables, the analysis showed statistically significant ($P<0.05$) differences for OVH or castration incision site pain, overall pain and behavior (from a distance and following social interaction) scores at assessment times 1, 3, 5 and 8 hours; and pain in the paws and posture scores at assessment times 3, 5 and 8 hours, indicating less pain in the ONSIOR (robenacoxib) injection group.

Body weight change was similar between both groups. No clinically significant differences existed between the ONSIOR (robenacoxib) injection and the control group for hematology, serum chemistry or urinalysis results or for injection site evaluation. Concurrent medications used during the field study with ONSIOR injectable included parasiticides, anesthetics, pre-anesthetic medications, and antibiotics.

e. Adverse Reactions: The most commonly reported adverse reactions in cats treated with ONSIOR (robenacoxib) injection were infected incision sites, increased incision site bleeding, vomiting, inappetence, and lethargy. The adverse reactions and number of cats experiencing each reaction 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 (robenacoxib) injection N = 174****	**Placebo Control (saline) N = 175**
Incision site infection, dehiscence	9	0
Increased incision site bleeding	6	4
Vomiting	5	0
Decreased appetite	4	3
Lethargy (after day of surgery)	4	2
UTI	2	0
Coughing	1	0
Fever	1	0
Semiconscious***	1	0
Soft stool, diarrhea	0	2

*Cats may have experienced more than one type or occurrence of an event during the study.
**One cat in the ONSIOR (robenacoxib) injection group suffered an anesthetic-related death.
***Semiconscious cat fully recovered.

f. Conclusion(s): Administration of ONSIOR (robenacoxib) injection at a dose of 0.9 mg/lb (2 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. 3-Day Injection Site Tolerance Study

1. Study Title: Acute injection site tolerance of robenacoxib injectable in cats.

2. Type of Study: Laboratory target animal safety study

3. Location:

   Novartis Centre de Recherche Santé Animale SA
   St-Aubin, Switzerland

4. General Design:

   a. Purpose of Study: To evaluate the safety of ONSIOR (robenacoxib) injection when subcutaneously administered once a day over three consecutive days at 5X the dose for the injection.

   b. Description of Test Animals: Twelve castrated male and 12 non-pregnant, intact female domestic shorthair cats, ranging in age from 1.5 to 3 years of age, weighing 2.3 to 4.8 kg on the day before first dose administered.

   c. Control and Treatment Groups: Control group cats received 0.9% sodium chloride (saline) for injection (Table 4).

Table 4: Treatment Groups

Group	**Dose**	**Number and Gender of Animals**
1	0 mg/kg (saline negative control)	4 M / 4 F
2	10 mg/kg robenacoxib (5X)	8 M / 8 F

   d. Drug Administration:

      (1) Dosage amount, frequency, and duration: Animals were dosed once daily over three consecutive days. Control animals received 0.5 mL/kg of 0.9% sodium chloride once daily at an equivalent volume to the 5X dose. Treated cats received 0.5 mL/kg of ONSIOR (robenacoxib) injection once daily.

      (2) Route of administration: Subcutaneous injections were administered over the scapular area using different sites during the course of the study.

   e. Variables Measured:

      (1) Animal observations: Cageside technician assessments, veterinary physical examinations, and injection site evaluations were obtained.

(2) Clinical pathology: Hematology, clinical chemistry, urinalysis, and coagulation parameters (PT, aPTT) were assessed.

(3) Histopathology: Each injection site was biopsied on Study Day 6 (6, 5, and 4 days following the first, second, and third injections, respectively).

5. Results:

a. Animal observations: Transient injection site edema was noted in all treated animals and in one control group animal. Injection site erythema was recorded in one 5X cat, who had an 18-mm diameter area of erythema with skin thickening. This finding was noted 72 hours following injection and remained present until the end of study.

During the dosing period, two treated cats vomited once. Three out of the 16 ONSIOR (robenacoxib) injection-treated cats were found to have soft feces and one cat had soft feces and diarrhea.

b. Clinical pathology: Several treated animals had elevated creatine kinase (CK) levels compared to control group animals.

c. Histopathology: A local skin necrosis with an acute inflammatory reaction was noted at the injection site in one 5X cat. Minimal to slight inflammatory cell infiltration in the subcutaneous tissue underlying the injection site was noted in most treated and two control cats.

Minimal to moderate, locally extensive subcutaneous muscle necrosis with myophagocytosis and signs of muscle regeneration was seen in 35/37 (95% of evaluated samples) of 5X group biopsies and in 0/20 of control cat biopsies.

6. Conclusions: Subcutaneous administration of ONSIOR (robenacoxib) injection at a dose of 10 mg/kg once daily for three days was associated with gastrointestinal (vomiting, soft feces) effects, elevated creatine kinase levels, and local effects at injection sites. Histologically, injection site changes were characterized by transient edema, and minimal subcutaneous inflammation and regenerative muscle necrosis.

B. 37-Day Interchangeable Use Study

1. Study Title: Robenacoxib: Interchangeable use target animal safety study in 4-month old cats.

2. Type of Study: Laboratory target animal safety study

3. Location:

MPI Research, Inc.
Mattawan, Michigan

4. General Design

   a. Purpose of Study: To evaluate the safe interchangeable use of robenacoxib when administered orally as a 6 mg tablet and as a 20 mg/mL subcutaneous injection at zero (0x), one (1X), two (2X), and three (3X) times the upper limit of the inherent dose band (tablets) and the recommended daily dose (injection). The 1X dose was 2.4 mg/kg orally and 2 mg/kg subcutaneously.

   b. Description of Test Animals: Seventeen healthy intact male and 17 intact female domestic short hair cats. At the time of the first dose, cats were 120 to 124 days old, weighing 1.7 – 3.0 kg.

   c. Control and Treatment Groups: Oral and subcutaneous treatments were alternated over a 37-day period according to the following schedule: 7 days tablet/3 days subcutaneous injection/7 days tablet/3 days subcutaneous injection/7 days tablet/3 days subcutaneous injection/7 days tablet. Dose groups are illustrated in Table 5.

Table 5: Treatment Groups

Group	**Dose**	**Number and Gender of Animals**
1	0X Empty gelatin capsules (oral)/ saline (injection)	5 M / 5 F
2	1X 2.4 mg/kg (oral)/ 2 mg/kg (injection)	4 M / 4 F
3	2X 4.8 mg/kg (oral)/ 4 mg/kg (injection)	4 M / 4 F
4	3X 7.2 mg/kg (oral)/ 6.0 mg/kg (injection)	4 M / 4 F

   d. Drug Administration:

      (1) Dosage forms, amount, frequency, and duration: Robenacoxib as a 20 mg/mL solution for injection and 6 mg tablets were used for dosing. Cats were dosed at 1X, 2X, and 3X the upper limit of the inherent dose band (tablets) and the recommended daily dose (injection). One additional group served as the negative control and received empty gelatin capsules during the oral dosing period, or a saline injection during the subcutaneous dosing period. The 1X oral dose was 2.4 mg/kg and the 1X subcutaneous dose was 2 mg/kg (0.1 mL/kg).

      (2) Route of administration: Oral and subcutaneous doses were alternated over a 37-day period. Subcutaneous injections were administrated

over the scapular area using different sites during the course of the study.

e. Variables Measured:

(1) Animal Observations: Cageside technician assessments, veterinary physical and neurological examinations, injection site evaluations, food consumption, body weights, and temperature were recorded.

(2) Electrocardiographic (ECG) evaluation: Animals were sedated with ketamine and acepromazine to facilitate evaluation.

(3) Ophthalmoscopic examination: Indirect ophthalmoscopy following pupil dilation with tropicamide 1% solution was performed by a veterinary board certified ophthalmologist.

(4) Buccal mucosal bleeding time (BMBT)

(5) Clinical pathology evaluations: Hematology, clinical chemistry, urinalysis, and coagulation parameters were evaluated.

(6) Plasma drug concentrations: Samples were collected within 30 minutes prior to dosing and at 0.75 and 4 hours post-dose on Days 1, 4, 7, 10, 17, 30, and 37. Additional samples were collected at 4 hours post-dose on Days 8, 11, 14, 28, 31, and 34.

(7) Gross necropsy and histopathology: A complete gross necropsy was performed at study termination. Histopathology was performed on all animals following gross necropsy.

5. Results

a. Clinical Observations: One 2X male cat vomited once on each of the last two days of the study. Soft stools were noted sporadically in all groups, including the controls, during the treatment period. However, soft stools were seen more frequently in the higher dose groups.

Injection site edema was observed in both control and treated cats at 8 to 48 hours after dosing. However, a significant increase in the number of edema occurrences was observed in the 2X group when compared to the control group in the 8-hour post-dose observation. In the 24 and 48-hour post-dose observations, a significant increase in the number of edema occurrences was observed in the 3X group compared to the control group. Edema persisted in one 2X male and one 3X female for 120 hours following injection before resolving.

b. ECG Evaluations: There was a dose-dependent increase in the QT interval at all 3 dose levels that was statistically significantly different from control group values following treatment. A prolonged PR interval was noted in 1X group females as compared to the controls on Day 36.

c. BMBT Evaluations: One 2X cat had an approximately seven-fold increase in the BMBT value (217 seconds) compared to the pre-treatment value. All other coagulation values for this cat remained within the reference ranges.

d. Clinical Pathology: Both treated and control cats had elevated creatine kinase (CK) levels. The highest elevations were seen in female treated cats during the study.

e. Pharmacokinetics: Dose-normalized area under the curve (AUC) and concentration levels were higher following the oral route than the subcutaneous route. The dose normalized oral robenacoxib exposure (AUC 0-4) was approximately twice that observed with the injectable formulation. Furthermore, a slightly less than dose proportional increase in exposure was observed with an increase in injectable dose (a 2X dose resulted in a 1.4X increase in drug exposure; a 3X increase in dose resulted in a 2.3X increase in drug exposure). There was no significant accumulation following once daily administration.

f. Histopathology: Injection site findings included minimal or mild, subacute/chronic inflammation. Although inflammation was observed in both treated and controls animals, and no increase in severity was associated with increased dosages, this finding was seen more frequently in the higher dose groups than in the control and 1X groups.

   Two treated cats were noted to have decreased myeloid:erythroid ratios. One 1X cat had a mild, transient anemia and a moderately decreased M:E ratio with a moderate increase in lymphoid cells at the end of the study. One 2X cat had a mild decrease in the M:E ratio with a moderate decrease in lymphoid cells.

   One 3X cat was noted to have focal, minimal mineralization of the left ventricular papillary muscle.

   One 1X cat had a histologic observation of a minimal erosion/ulcer on the tongue.

6. Conclusions: This 37-day laboratory study supports the safe interchangeable use of ONSIOR (robenacoxib) injection at a dose of 2 mg/kg/day with ONSIOR (robenacoxib) tablets at a dose of 1 mg/kg/day, for a maximum of 3 days. Treatment-related findings include: injection site changes (transient edema with minimal or mild, subacute/chronic inflammation histologically); vomiting/soft feces, prolongation of the QT interval on ECG evaluation, and oral ulceration.

C. Comparative Injection Site Tolerance Study

1. Study Title: Comparative injection site tolerance of robenacoxib injectable in cats.

2. Type of Study: Laboratory target animal safety study

3. Location:

   Novartis Centre de Recherche Santé Animal SA
   St Aubin, Switzerland

4. General Design:

   a. Purpose of Study: To evaluate the injection site tolerance in cats administered ONSIOR (robenacoxib) injection subcutaneously at 1X and 2X the dose for the injection. ONSIOR (robenacoxib) injection was qualitatively compared to meloxicam injectable (METACAM, Boehringer Ingelheim).

   b. Description of Test Animals: Intact male and female (non-pregnant, nulliparous) domestic short haired, 8- to 10-month old healthy cats, weighing 2.4 – 4.0 kg 3 days before first dose was administered.

   c. Control and Treatment Groups: Negative control group cats received sodium chloride (saline) for injection at an equivalent volume to the Group 3 (2X) dose. The positive control, meloxicam injectable, was administered at the labeled dose. ONSIOR-treated cats received up to two times the labeled dose (Table 6).

Table 6: Treatment Groups

Group	**Dose**	**Number and Gender of Animals**
1	Saline (0 mg/kg)	2 M / 2 F
2	1X ONSIOR (robenacoxib) injection (2 mg/kg)	2 M / 2 F
3	2X ONSIOR (robenacoxib) injection (4 mg/kg)	2 M / 2F
4	Meloxicam (0.3 mg/kg)	2 M / 2 F

d. Drug Administration:

(1) Dosage amount, frequency, and duration: Cats were dosed once daily for two consecutive days.

(2) Route of administration: Subcutaneous injection was administrated over the scapular area using different sites during the course of the study.

e. Variables Measured:

(1) Animal Observations: Cageside technician assessments, veterinary physical examinations, and injection site evaluations (pre-dose, 1, 6, 24, 48, and 72 hours following dosing) were recorded.

(2) Clinical pathology: Hematology and clinical chemistry evaluations were performed.

(3) Injection site biopsies: A biopsy sample was obtained from one injection site of each animal 7 days after the first injection and from another injection site of each animal 14 days following the second injection.

5. Results:

a. Animal observations: Edema was noted at the injection site in 1X and 2X ONSIOR (robenacoxib) injection cats at 1 hour and 6 hours following injection.

b. Clinical pathology: A 1X ONSIOR (robenacoxib) injection female cat had elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) values on Day 4. This cat had markedly elevated ALT values and normal AST values pre-treatment. Post-treatment, AST values rose above the reference range, while ALT values remained above the reference range.

c. Histopathology: The 7-day post-dose biopsy revealed minimal diffuse inflammatory cell infiltration in the subcutaneous tissue (subcutis) of 1X (2 mg/kg) and 2X (4 mg/kg) ONSIOR (robenacoxib) injection cats. Minimal to slight, locally extensive muscle necrosis with myophagocytosis and muscular regeneration was observed in both 2X ONSIOR (robenacoxib) injection male cats at the 7 days post-dose biopsy sample. Muscle necrosis was not seen in the 14 day post-dose biopsy.

6. Conclusion: This study supports the safe subcutaneous use of ONSIOR (robenacoxib) injection. Two consecutively administered subcutaneous injections of ONSIOR (robenacoxib) injection at 2 or 4 mg/kg/day resulted in transient injection site edema. Seven days post-dose, minimal subcutaneous inflammation was seen at the injection site of 1X and 2X treated cats. Muscle necrosis with myophagocytosis and muscular regeneration was observed histologically at the injection site in 2X treated cats.

D. Single Intravenous Injection Study

1. Study Title: Safety evaluation of a single intravenous administration of ONSIOR injectable to anesthetized cats.

2. Type of Study: Laboratory target animal safety study

3. Location:

   Novartis Centre de Recherche Santé Animale SA
   St. Aubin, Switzerland

4. General Design:

   a. Purpose of Study: To assess the safety of ONSIOR (robenacoxib) injection when administered to anesthetized cats either subcutaneously at 1X, or intravenously at 1X and 2X the recommended therapeutic dose.

   b. Description of Test Animals: Sixteen intact male and 16 intact, non-pregnant, nulliparous female, 7- to 17-month old healthy European shorthair cats, weighing 2.6 – 4.6 kg on the day before the dose was administered.

   c. Control and Treatment Groups: Cats were randomly assigned to either the negative control group or one of the three ONSIOR (robenacoxib) injection treatment groups (Table 7).

   Table 7: Treatment Groups

Group	**Dose**	**Number and Gender of Animals**
1	Saline (0 mg/kg) IV∗	4 M / 4 F
2	1X ONSIOR (robenacoxib) injection SC ° (2 mg/kg)	4 M / 4 F
3	1X ONSIOR (robenacoxib) injection IV (2 mg/kg)	4 M / 4 F
4	2X ONSIOR (robenacoxib) injection IV (4 mg/kg)	4 M / 4 F

   ° SC= subcutaneous; ∗IV= intravenous

   d. Drug Administration:

      (1) Dosage amount, frequency, and duration: All cats were anesthetized prior to dosing. Cats in Groups 1 and 2 received saline or ONSIOR (robenacoxib) injection once on Day 0, and cats in Groups 3 and 4 received ONSIOR (robenacoxib) injection once on Day 1.

      (2) Route of administration: Subcutaneous injection (Group 2) and intravenous injection (Groups 1, 3 and 4).

e. Variables Measured:

(1) Animal Observations: Cageside technician assessments and veterinary physical examinations were performed.

(2) Electrocardiogram (ECG) Evaluation: An ECG was performed once either 5 minutes post-dosing (Groups 1, 3, and 4) or 60 minutes post-dosing (Group 2).

(3) Clinical Pathology: Hematology, clinical chemistry, and coagulation parameters were obtained.

5. Results

a. Animal observations: Vomiting was noted in one 2 mg/kg and two 4 mg/kg ONSIOR-treated cats following intravenous dosing.

b. ECG evaluation: One ONSIOR-treated female cat (2 mg/kg IV) was noted to have several instances of supraventricular premature complexes and escape rhythms 5 minutes following intravenous dosing.

6. Conclusions: Intravenous administration of ONSIOR (robenacoxib) injection to anesthetized cats was associated with vomiting and supraventricular premature complexes and escape rhythms on ECG evaluation.

E. Preliminary Interchangeable Use Study

1. Study Title: Pilot tolerance study of robenacoxib injectable and tablets in >4 month old kittens.

2. Type of Study: Laboratory target animal safety study

3. Location:

Liberty Research, Inc.
Waverly, New York

4. General Design:

a. Purpose of Study: To evaluate the tolerance of the interchangeable use of robenacoxib when administered orally as a 6 mg tablet and as a 20 mg/mL subcutaneous injection at zero (0X), one (1X), and five (5X) times the upper limit of the inherent dose band (tablets) and the recommended daily dose (injection) for 37 days.

b. Description of Test Animals: Thirteen male and 13 female healthy domestic shorthair cats, aged 127- to 132-days old.

c. Control and Treatment Groups: Treatments were alternated over a 37-day period according to the following schedule: 7 days tablet/3 days subcutaneous injection/7 days tablet/3 days subcutaneous injection/7 days tablet/3 days subcutaneous injection/7 days tablet. Dose groups are illustrated in Table 8.

Table 8: Treatment Groups

Group	**Dose**	**Number and Gender of Animals**
1	0X (0 mg/kg, empty gelatin capsules oral/saline injection, negative control)	5 M / 5 F
2	1X (2.4 mg/kg tablet, 2 mg/kg injection)	4 M / 4 F
3	5X (12 mg/kg tablet, 10 mg/kg injection)	4 M / 4 F

d. Drug Administration:

(1) Dosage forms, amount, frequency, and duration: ONSIOR (robenacoxib) injection and ONSIOR tablets were used for dosing. 1X cats received an oral dose of 2.4 mg/kg/day robenacoxib, and a subcutaneous dose of 2 mg/kg/day robenacoxib. 5X cats received an oral dose of 12 mg/kg/day robenacoxib, and a subcutaneous dose of 10 mg/kg/day robenacoxib. Negative control cats received empty gelatin capsules during the oral dosing period, and sterile saline during the subcutaneous dosing period.

(2) Route of administration: Oral (tablet phase) and subcutaneous injection (injection phase). In each cat, injections were administered in the scapular area using the same site over the course of the study.

e. Variables Measured

(1) Animal observations: Cageside technician assessments, injection site evaluations, and veterinary physical (heart and respiratory rates and body temperature) and neurological examinations, body weight, and food consumption were performed.

(2) Electrocardiogram (ECG) evaluation: Cats were sedated with acepromazine and ketamine to facilitate the evaluation.

(3) Buccal mucosal bleeding time (BMBT) evaluation

(4) Clinical pathology: Hematology, clinical chemistry, urinalysis, and coagulation parameters were evaluated.

(5) Gross necropsy: All study animals were euthanized on Day 37. Post mortem evaluations included examination of the abdominal and thoracic cavities for gross lesions, with particular attention paid to the liver, kidneys, and gastrointestinal tract. Tissues from select organs (colon, duodenum, stomach, ileum, jejunum, kidneys, liver, injection sites, untreated skin, and thymus) were evaluated histologically.

5. Results:

   a. Animal observations: Scabs and sores were observed at the injection sites of one 1X female and two 5X females. Dose-dependent increases in the incidence of injection site edema and sporadic heat or erythema were observed in treated cats. Edema was sporadically observed in control cats following injection. However, prolonged edema as well as heat and erythema were only seen in treated cats.

      One 5X cat had a brief episode of ataxia and lethargy on Day 16. This cat was subsequently noted to be dehydrated and constipated, requiring veterinary intervention with subcutaneous fluid therapy and nutritional supplementation. This cat had the smallest body weight gain during the acclimation and treatment periods and the greatest QT interval increase on ECG evaluation. On gross necropsy, this cat was noted to have red discoloration of the lung lobes, correlating histologically with moderate congestion, mild acute alveolar inflammation, and mild perivascular infiltrate. Mild mucosa infiltrate of the stomach cardia was also documented.

      All cats gained weight over the course of the study. However, the mean body weights on Day 35 were approximately 6% and 9% lower in 1X and 5X ONSIOR treated cats, respectively, compared to the controls.

   b. Clinical pathology: Creatinine was significantly increased in 5X cats compared to the controls.

      Alanine aminotransferase (ALT) was elevated in one 1X cat. This cat was also noted to have moderate granulomatous inflammation of the injection site, and minimal bilateral regeneration of the proximal tubules.

   c. Histopathology

      (1) Oral ulceration: A 1X cat had bilateral red depressed areas on the upper lip grossly, corresponding microscopically with mild chronic inflammation. A 5X cat had a red depressed area on the upper lip, corresponding microscopically with a minimal ulcer.

      (2) Injection site changes: Injection sites in 1X and 5X cats had minimal to moderate granulomatous inflammation, minimal chronic inflammation, and minimal to moderate fibroplasia/fibrosis. Minimal myofiber regeneration was observed in the underlying skeletal muscle in three out of four 5X males. A 1X cat had moderate necrosis of a blood vessel within the granulomatous inflammation.

      (3) Renal changes: Bilateral or unilateral minimal to moderate vacuolation and bilateral or unilateral minimal to mild degeneration of proximal tubules were observed in three 5X male cats. The affected proximal tubules were lined by swollen, vacuolated epithelial cells with pyknotic nuclei. Renal vacuolation and degeneration of proximal tubules correlated with increases in serum creatinine in 5X male cats. Two 5X

males had unilateral, minimal mineralized foci in the epithelium covering the papilla.

(4) Hepatic changes: Minimal pigmented macrophages (Kupffer cells) were observed in one 5X cat. This cat was also noted to have bilateral mild vacuolation and minimal to mild degeneration of the renal proximal tubules, and minimal focal mineralization of the epithelium of the renal papilla.

d. ECG evaluation: 5X cats had significantly decreased heart rates, increased respiratory rates, and increased QT (uncorrected for heart rate changes) intervals compared to the controls.

6. Conclusions: The study results support the interchangeable use of ONSIOR (robenacoxib) tablets and ONSIOR (robenacoxib) injection. Microscopic tissue examination revealed minimal to moderate changes in the renal proximal tubules, as well as mineralization of the renal papillary epithelium in 5X cats. Renal vacuolation and degeneration of proximal tubules correlated with increases in serum creatinine in 5X male cats. Injection site edema and sporadic heat or mild erythema was noted more often in treated animals. Microscopically, injection site changes included acute and chronic inflammation, granulomatous changes, and fibrosis. ECG evaluation revealed a treatment-related QT prolongation (uncorrected for heart rate).

F. Field Safety:

Field effectiveness and safety of ONSIOR (robenacoxib) injection for the control of postoperative pain and inflammation associated with ovariohysterectomy, castration and onychectomy in cats (Study 06-0024).

Study 06-0024 was conducted in client-owned animals to evaluate ONSIOR (robenacoxib) injection at a dose of 2 mg/kg administered subcutaneously, once daily (maximum of three days) for the control of postoperative pain and inflammation associated with an onychectomy (forelimbs only) and ovariohysterectomy (OVH) or castration. This study was a masked, negative controlled, multi-center field study. This field study provided relevant field safety information in support of the target animal safety of ONSIOR (robenacoxib) injection.

1. Study Animals: There were one hundred and eighty-seven (73 males and 114 females) healthy, intact cats of various breeds, between 6 months and 7 years of age and weighing between 2.5 and 6.4 kg.

2. Treatment Groups: The animals were randomized into two treatment groups in a 2:1 ratio of ONSIOR (robenacoxib) injection and control (0.9% physiologic saline), respectively.

Table 9: Treatment Groups

ONSIOR (robenacoxib) injection	2 mg/kg (0.1 mL/kg; 0.9 mg/lb) SC, once daily for 3 days
Control (saline)	0.1 mL/kg (0.45 mL/lb) SC, once daily for 3 days

Cats were evaluated postoperatively at predetermined times to assess the overall response to treatment and to monitor their condition. The study used the same measurements and observations as described for the field study in the Effectiveness section above (Study 11-001).

3. Safety Results: There were no deaths in the study. Minimal changes in body weight from baseline were noted similarly across the two treatment groups. There were no gross lesions associated with the administration of ONSIOR (robenacoxib) injection. In addition, there were no differences in the injection site parameters evaluated (visual, palpation, presence of erythema) between ONSIOR (robenacoxib) injection and the control.

    a. Hematology: The mean WBC count in the ONSIOR (robenacoxib) injection group was 13.8 + 5.64 103/µL (ranging from 4.4 – 36.8) and the mean white blood cell (WBC) count in the control group was 12.7 + 5.41 103/µL (with values ranging from 2.9 – 30.1). There were 6 ONSIOR (robenacoxib) injection cats with elevated alanine aminotransferase (ALT) post-treatment compared to 1 control case. There were 4 ONSIOR (robenacoxib) injection cases with elevated aspartate aminotransferase (AST) post-treatment compared to 1 control case.

    b. Adverse Reactions: The most commonly reported adverse reactions in cats treated with ONSIOR (robenacoxib) injection were increased incision site bleeding, leukocytosis, fever, inappetence, infected incision sites, vomiting, and lethargy. The adverse reactions and number of cats experiencing each reaction are summarized in Table 5. Some cats experienced more than one adverse reaction during the study.

Table 10: Adverse Reactions from Field Study 6-0024

Adverse Reaction*	**ONSIOR (robenacoxib) injection N = 127**	**Control (0.9% physiologic saline) N = 60**
Surgical or venipuncture site bleeding	9	3
Leukocytosis	9	2
Fever	8	11
Lethargy (after day of surgery)	7	0
Vomiting	6	0
Anorexia/decreased appetite	6	3
Infected/drainage surgical site(s), infection	5	2
Dehiscence	1	0
Diarrhea	1	3
Bloody stool	1	0
Hypersalivation	1	2
Urinary Tract Infection (UTI)	0	1

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

4. Effectiveness Results: There was a reduction in the proportion of rescues in the robenacoxib group compared to the control group and a difference in the success between the ONSIOR (robenacoxib) injection (79.4%) and control groups (62.7%); however the differences were not statistically significant. The failure to demonstrate statistical significance may have been due to the use of a 2:1 allocation ratio, inclusion of sites with a small number of subjects, or the overall sample size in this study.

5. Conclusion(s): Administration of ONSIOR (robenacoxib) injection at a dose of 0.91 mg/lb (2 mg/kg) subcutaneously, once daily for up to three days, with the first dose administered approximately 30 minutes prior to surgery, was well-tolerated for the control of postoperative pain and inflammation associated with orthopedic surgery, ovariohysterectomy, and castration in cats.

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:

> "Not for human use. Keep this and all medications out of the reach of children. Consult a physician in case of accidental ingestion or injection by humans. **For subcutaneous 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 $\geq$ 4 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

ONSIOR, as approved in our approval letter, qualifies for THREE years of marketing exclusivity beginning as of the date of our approval letter. This drug qualifies for exclusivity under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act because the sponsor submitted an original NADA that contains new studies that demonstrate the safety and effectiveness of ONSIOR.

C. Patent Information:

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