Date of Approval: May 17, 2016

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-463

ONSIOR

Robenacoxib

Tablets

Dogs

ONSIOR (robenacoxib) tablets are indicated for the control of postoperative pain and inflammation associated with soft tissue surgery in dogs $\geq$ 5.5 lbs **and** $\geq$ 4 months of age; for up to a **maximum of 3 days**.

Sponsored by:

Elanco US, Inc.

Table of Contents

I. GENERAL INFORMATION

A. File Number

NADA 141-463

B. Sponsor

Elanco US, Inc.
2500 Innovation Way
Greenfield, IN 46140

Drug Labeler Code: 058198

C. Proprietary Name

ONSIOR

D. Product Established Name

Robenacoxib tablets

E. Pharmacological Category

Non-steroidal anti-inflammatory drug (NSAID)

F. Dosage Form

Tablets

G. Amount of Active Ingredient

Tablets contain 10, 20, or 40 mg of robenacoxib

H. How Supplied

ONSIOR tablets are available as 10, 20 and 40 mg round flavored tablets in perforated blisters and are supplied in cards containing 6 tablets. Each carton holds 10 blister cards (60 tablets per carton). The appropriate number of tablets per patient is to be dispensed in an ONSIOR dispensing envelope containing an Information for Dog Owners Sheet.

I. Dispensing Status

Rx

J. Dosage Regimen

The dose of ONSIOR (robenacoxib) tablets is 0.91 mg/lb (2mg/kg) orally once daily, for a maximum of three days.

For oral use in dogs ≥ 5.5 lbs and ≥ 4 months of age. Tablets are not scored and should not be broken. The calculated dosage should be provided using a combination of whole tablet sizes.

The first dose should be administered approximately 45 minutes prior to surgery, at the same time as the pre-anesthetic agents are given.

Tablets may be given with or without food.

K. Route of Administration

Oral

L. Species/Class

Dogs

M. Indication

ONSIOR tablets are indicated for the control of postoperative pain and inflammation associated with soft tissue surgery in dogs ≥ 5.5 lbs (2.5 kg) **and** ≥ 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 orally, once daily for up to three days was selected based on the results of the following experimental studies.

A masked, placebo and positive controlled dose titration study using an acute synovitis model, induced by intra-articular injection of uric acid crystals into the stifle joint, was conducted in 12 adult Beagles of both sexes. Fasted dogs were administered a single dose of robenacoxib orally as a lactose tablet at doses ranging from 0.5-8.0 mg/kg. The primary endpoint (peak vertical force exerted on the force plate) and the secondary endpoint (weight bearing, pain on palpation and swelling assessed subjectively) were monitored daily. The effectiveness of robenacoxib was positively correlated with doses from 0.5 - 2 mg/kg with an optimal effect achieved at 2 mg/kg.

At all doses, robenacoxib was rapidly absorbed (mean T_{max} = 1.3 hour) and rapidly eliminated (harmonic mean terminal half-lives = 0.60 to 0.91 h) when administered as tablets to fasted dogs. The C_{max} and AUC 0-inf were linear over the tested dosage range (0.5 to 8 mg/kg) and there was no sex effect.

At all doses, robenacoxib significantly inhibited *ex vivo* prostaglandin E2 (PGE2) production at one and two hours after dosing (heparinized whole blood samples incubated with LPS). Up to 4 mg/kg, robenacoxib had no significant effect on *ex vivo* serum thromboxane B2 (TxB2) production (clotted whole blood samples). The clinical relevance of this data has not been shown. Based on the *in vivo* and *in vitro* data from this study, 2 mg/kg was determined to be the optimal effective dose using the acute synovitis model.

The absolute oral and subcutaneous (SC) bioavailability of robenacoxib and the effect of food on oral (PO) bioavailability were further evaluated in a four-phase crossover study following a single oral, SC, or intravenous (IV) dose of approximately 1 mg/kg in 12 Beagle dogs of both sexes. The tablets were

administered in both the fed and fasted states. Results showed that robenacoxib was rapidly absorbed after PO and SC administration (median T_{max} =0.25-0.5 h). Elimination was also shown to be rapid, with mean terminal elimination half-lives (t1/2) of 0.66 hours (IV), 0.82 hours (SC), 0.86 hours (PO, fasted) hours, and 1.15 (PO, fed) hours. Bioavailability was high at 0.84 (PO, fasted), 0.62 (PO, fed) and 0.88 (SC). Food decreased the mean C_{max} and AUC 0-inf by approximately 14% and 30% respectively. No significant differences were found between males and females for any PK parameter. Therefore, this study demonstrated a similarity in absorption, elimination, and bioavailability of robenacoxib administered PO (fasted) and SC.

A bioequivalence study was conducted to assess the similarities of the lactose tablet formulation utilized in the studies described above to the approved flavor tablet formulation. The study utilized a two-phase crossover design with a wash-out period. Dogs were fasted prior to dosing with the tablets. Each formulation of robenacoxib tablets was administered as a single PO dosage of 1 mg/kg to 16 healthy, adult Beagles (8 male and 8 female). All PK parameters (C_{max}, AUC, T_{max}, and t ½) were similar for the two formulations. The AUCs of both formulations were bioequivalent, but the C_{max} of the flavor tablet was slightly lower. The acceptance of the lower C_{max} was justified because of the inherent variability in C_{max} and the identification of AUC as the pivotal parameter.

The above studies indicated that a dose of 2 mg/kg once daily for three days was an appropriate dose for further investigation. Effectiveness and safety of robenacoxib at a SC dose of 2 mg/kg for up to three days was assessed in a pilot US study. The study was a randomized, masked, placebo and positive-controlled, multi-center field study with a rescue clause. The study investigated the effectiveness and field safety of injectable robenacoxib at a SC dose of 2 mg/kg administered perioperatively, followed by once-daily SC injections for two additional days for the control of postoperative pain and inflammation associated with soft tissue surgery in dogs. Dogs were evaluated postoperatively at predetermined times to assess the overall response to treatment and to monitor their condition. Pain was evaluated using the short form of the Glasgow Composite Measure Pain Scale (CMPS-SF).

Based on the similarity in absorption, elimination, and bioavailability of the PO (fasted) and the SC routes of administration, the results regarding effectiveness of ONSIOR (robenacoxib) injection administered SC for up to three days from this pilot study were extrapolated to the tablet formulation. Enrolled dogs were administered robenacoxib (n= 20), positive control (n= 20), or placebo (n=22) prior to anesthetic induction, approximately 45 min prior to surgery. Sixty-one (61) dogs were evaluated for effectiveness (n= 22 placebo, n= 19 positive control, and n= 20 robenacoxib cases). Robenacoxib was compared to positive control and placebo groups. There were fewer cases needing rescue therapy in the robenacoxib (9 rescued cases) and positive control (9 rescued cases) groups compared to placebo (18 rescued cases). No differences were noted between the robenacoxib and positive control groups. The results from this study indicate that SC administration of robenacoxib at a dose of 2 mg/kg should be effective for controlling postoperative pain and inflammation associated with soft tissue surgery in dogs.

B. Substantial Evidence

The effectiveness of ONSIOR (robenacoxib) tablets for the control of postoperative pain and inflammation associated with soft tissue surgery in dogs was evaluated at eleven (11) veterinary clinics throughout various geographic regions within the U.S. Results of the study demonstrate that ONSIOR (robenacoxib) tablets are well-tolerated and effective when administered at a dose of 0.91 mg/lb (2 mg/kg) of body weight once daily for a maximum of 3 days.

Type of Study: Field Study

Title: A randomized, blinded, placebo controlled pivotal field study to evaluate the effectiveness and safety of robenacoxib (tablets) when administered at a dose of 2 mg/kg once daily for 3 days for the control of postoperative pain and inflammation associated with soft tissue surgery in dogs (14-171).

Study Dates: August 2014 – September 2015

Study Locations: Eleven US veterinary clinics from the following locations participated in this study.

Lake Worth, FL
Zachary, LA
Cedar Park, TX
Leawood, KS
Nolensville, TN
Quakertown, PA
Farragut, TN
Harleysville, PA
Commerce, GA
Springfield, MO
Manakin-Sabot, VA

Study Design: This was a masked, randomized, multi-center, field study comparing ONSIOR (robenacoxib) tablets to a vehicle control. The study was conducted in accordance with Good Clinical Practices (GCP).

Objective: The objective of this study was to demonstrate the effectiveness and field safety of ONSIOR (robenacoxib) tablets, at an oral dose of 2 mg/kg of body weight, for the control of postoperative pain and inflammation associated with soft tissue surgery in dogs. In addition to the pre-anesthetic medication, treated dogs received ONSIOR (robenacoxib) tablets approximately 45 minutes prior to surgery and once daily for two additional days postoperatively. Control animals received a vehicle control at the same time points.

Study Animals: There were 239 (143 females and 96 males) dogs of various breeds included in this study. ONSIOR treated dogs were between 6 months - 14 years of age and weighed between 2.7 and 55 kg. The average age of the ONSIOR treated group was 6.2 years and the average age of the control group was 5.5 years. Thirty-nine of the 239 dogs were less than 1 year of age.

Treatment Groups: Dogs were randomized into two treatment groups in a 1:1 ratio, and received whole tablets of ONSIOR (robenacoxib) tablets or vehicle control. ONSIOR (robenacoxib) tablets were dosed at 2 mg/kg (0.9 mg/lb) orally once daily for 3 days.

Surgical procedures: All dogs received perioperative fluids and butorphanol as a pre-anesthetic medication. Dogs of any gender or breed > 6 months of age at the time of enrollment and weighing at least 2.5 kg were enrolled. Soft tissue surgeries included ovariohysterectomy, cryptorchidectomy, cystotomy, gastropexy, and major external surgeries, such as mastectomy or skin tumor removal >8 cm in size.

Drug Administration: The ONSIOR group received the final market formulation of ONSIOR (robenacoxib) tablets as 10 mg, 20 mg, or 40 mg non-scored tablets. The control group received 20 mg or 40 mg vehicle tablets of identical appearance to ONSIOR tablets. All dogs received the first treatment approximately 45 minutes prior to surgery, and the two subsequent daily doses approximately 24 hours and 48 hours later.

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 at any time, and scheduled pain evaluations using the short form of the Glasgow Composite Measure Pain Scale (CMPS-SF)[1].

Scheduled evaluations and the determination of the need for rescue pain medication were conducted at 1.5 hours (post-extubation), 3 hours, 5 hours, and 8 hours following surgery on Day 0. On Day 1, evaluations were performed 24 hours after the pre-surgery test article administration and at 2 and 8 hours after test article administration on Day 1. On Day 2, evaluations were performed prior to administration of the third dose of the test article and at 2 and 4 hours after the third dose. Although these were the scheduled evaluation time points, rescue pain medication could be given any time at the veterinarian's discretion.

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

Pain was evaluated using the short form of the Glasgow Composite Measuring Pain Scale (CMPS-SF). Dogs could be rescued with non-NSAID or non-corticosteroid analgesic medications. Dogs that had a total pain score $\geq$ 6, or received rescue pain medication, or were removed due to adverse events were considered treatment failures.

The following six CMPS-SF categories were assessed as secondary variables along with the total CMPS-SF score:

1. vocalization

[1] Reid J, Nolan AM, Hughes JML, et. al. Development of the short form Glasgow Composite Measure Pain Scale (CMPS-SF) and derivation of an analgesic intervention score. *Animal Welfare*. 2007; 16(S):97-104.

2. attention to wound area
3. mobility
4. response to touch
5. demeanor
6. posture and activity

Hematology, serum chemistry and urine samples were obtained prior to study initiation and at study exit. In addition, all owners received a follow-up phone call 3-10 days post-study.

Statistical Methods: Dogs that received rescue pain medication, had a CMPS score > 6, or were removed due to adverse events were considered treatment failures. The primary effectiveness variable was treatment success or failure. The pivotal test for effectiveness compared treatment success rates in the ONSIOR tablet group to the control group. A random effects generalized linear mixed model was utilized (using PROC GLIMMIX in SAS). The statistical model included 'Treatment' as a fixed effect and 'Site' and 'Treatment by Site' as random effects.

Results: Effectiveness was evaluated in 231 dogs and field safety was evaluated in 239 dogs. A statistically significant difference (p-value = 0.0188) in the proportion of treatment successes in the ONSIOR tablets group (76.72%) compared to the control group (64.35%) was observed (Table 1).

Table 1. Results by Treatment Group

Treatment Group	Number of Treatment Successes	Number of Treatment Failures	Total Number of Evaluable Cases
ONSIOR (robenacoxib) tablets	89 (76.72%)	27 (23.28%)	116
Vehicle control	74 (64.35%)	41 (35.65%)	115

p-value = 0.0188

Twenty-seven out of 116 cases (23.28%) in the ONSIOR group and 41 out of 115 cases (35.65%) in the control group were treatment failures.

There were significant differences in the least squares mean of Total Pain scores between the ONSIOR group compared to the control group at 3, 5, and 8 hours post-treatment (p=0.0023, p=0.0072, and p=0.0018, respectively), with the robenacoxib group having lower scores (i.e. experiencing less pain). For the individual variables, the analysis showed an overall significant improvement in Response to Touch and Posture/Activity at post-treatment in the ONSIOR group having lower scores (i.e. experiencing less pain).

Body weight change was similar between both groups. No clinically significant differences existed between the ONSIOR and the control group for hematology, serum chemistry, or urinalysis results. Concurrent medications used during the field study with ONSIOR tablets included anesthetic agents, prophylactic antibiotics, anesthetics, and parasiticides.

Adverse Reactions: The most commonly reported adverse reactions in dogs treated with ONSIOR (robenacoxib) tablets were diarrhea/soft stools, vomiting, and decreased appetite. The adverse reactions and number of dogs experiencing

each are summarized in Table 2. Some dogs experienced more than one adverse reaction during the study.

Table 2. Adverse Reactions Reported in the Soft Tissue Surgery Field Study.

Adverse Reaction*	ONSIOR (robenacoxib) tablets N = 119	Control (vehicle tablets minus robenacoxib) N = 120
Diarrhea	6	3
Vomiting	6	4
Decreased appetite	3	0
Weight loss	1	0
Hypotension	1	0

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

Conclusion: Administration of ONSIOR (robenacoxib) tablets at a dose of 0.91 mg/lb (2 mg/kg) once daily for up to three days, with the first dose administered approximately 45 minutes prior to surgery, was effective and well-tolerated for the control of postoperative pain and inflammation associated with soft tissue surgery in dogs.

III. TARGET ANIMAL SAFETY

A. Six-Month Margin of Safety Study

Title: A Six-Month Oral Margin of Safety Study of Robenacoxib Tablets in Dogs

Study Dates: July 26, 2006 to June 18, 2007

Study Location: Mattawan, MI

Study Design: Laboratory target animal safety study conducted in accordance with Good Laboratory Practices (GLP).

Objective: To evaluate the safety of robenacoxib tablets when administered daily to adult dogs at 0.5, 1.5, and 2.5 times the maximum targeted exposure of 2 mg/kg for 6 months.

Study Animals: Intact male and female healthy Beagles, aged 6 to 7 months and weighing between 6.61 to 13.79 kg at the start of the study.

Control and Treatment Groups: Three treatment groups of four male and four female dogs received the test article at 0.5, 1.5, and 2.5 times the maximum target exposure based on the inherent dose bands of the tablet sizes. One additional group of 4 males and 4 females served as the negative control (sham dosing). The test article or sham dose was administered orally once a day from Day 1 through the day prior to the terminal necropsy (Day 181). Approximately 5 mL of tap water was administered orally to each dog after dosing.

Table 3. Control and Treatment Groups.

Group	**Dose (mg/kg)**	**Number and Gender of Animals**
1	Negative control (0 mg/kg)	4 males/ 4 females
2	0.5X (2 mg/kg)	4 males/ 4 females
3	1.5X (6 mg/kg)	4 males/ 4 females
4	2.5X (10 mg/kg)	4 males/ 4 females

Drug Administration: Dogs in Groups 2-4 received oral robenacoxib tablets once daily from Days 1 to 181 (the day prior to terminal necropsy). The appropriate number of tablets was administered based on the weekly body weight and the dosing table provided in the protocol.

Relationship to feeding: Dogs were fed *ad libitum* for approximately 6 hours a day. After overnight fasting, food was offered at least 1 hour after dosing (Weeks 1 to 13) or at least 2 hours after dosing (Weeks 14 to 26). If vomiting was observed within 10 minutes after dosing, tablets were re-administered.

Measurements and Observations: The following variables were measured prior to study initiation, during the study, and/or at the end of the study:

- Cageside Observations and Veterinary Physical Examinations (including neurological assessment)
- Body Weight
- Food Consumption
- Water Consumption
- Buccal Mucosal Bleeding Time
- Ophthalmoscopic Examinations: Exams were conducted on all animals by a board-certified veterinary ophthalmologist.
- Electrocardiographic Examinations: ECGs were performed and evaluated by a board-certified veterinary cardiologist.
- Clinical Pathology: Hematology, clinical chemistry, urinalysis, and coagulation parameters (PT, APT).
- Toxicokinetic Analysis: Samples were obtained from all animals prior to dosing, and at approximately 0.25, 0.5, 1, 2, 5, 12, and 24 hours post-dose on Days 1, 30, and 150. Robenacoxib concentrations in whole blood were quantified using high performance liquid chromatography with UV and mass selective detection (LC-MS).
- Gross Necropsy
- Organ Weights
- Histopathology

Statistical Methods: Analysis of variance was used to evaluate all continuous variables. Models included treatment, sex and the treatment-by-sex interaction as fixed effects. For variables measured more than once throughout the study, the following fixed effects were also included: time and the interactions treatment-by-time, sex-by-time and treatment-by-sex-by-time. The pre-treatment value closest to dosing was included as a covariate.

Results:

Animal observations: Salivation was noted in all groups, but observed most frequently in the 1.5X group. Similarly, soft/mucoid/watery feces was noted in all groups, but observed more frequently in the treated groups as compared to the control group.

Buccal Mucosal Bleeding Time (BMBT): Increased BMBTs were observed in one 1.5X female and one 2.5X male on Day 178. Both dogs had values within normal limits prior to treatment.

Ophthalmoscopic Examinations: One 2.5X female had a normal ophthalmoscopic exam prior to dosing and unilateral retinal dysplasia noted on Day 177. This abnormality was described as a single retinal fold in the tapetal fundus of the left eye.

Veterinary Physical Examinations, Including Neurological Assessments: On Day 178, abnormal neurological examinations were noted in two 0.5X dogs and two 2.5X dogs. Abnormalities were described as unilateral or bilateral decreased hopping and unilateral decreased conscious proprioception. One of the 0.5X dogs had abnormalities noted on neurological examination prior to receiving the test article.

Electrocardiographic Examinations: A 0.5X male was noted to have 3 ventricular premature complexes (VPCs) on the Day 178 ECG.

Gross Necropsy: One 1.5X male was noted to have cecal lesions described as "red foci." A 2.5X female had "red mucosal discoloration, minimal" of the duodenum. There were no corresponding findings on histological evaluation in either dog.

Organ Weights: Mean ovarian weights (all parameters) were statistically significantly decreased in 1.5X and 2.5X group females as compared to the controls. There were no gross or histological changes noted in the ovaries of any study dog.

Toxicokinetics: Despite large inter-animal variation in robenacoxib blood concentrations, the average first dose C_{max} and $AUC_{0\text{-}inf}$ (estimated from hour zero to time infinity) values increased in a dose-proportional manner and did not significantly change as a function of duration of administration. On average, peak concentrations were observed within1 hour for the three dose levels throughout the duration of the study. Across all dose groups, the intersubject variability in $AUC_{0\text{-}inf}$ values and C_{max} values were 30 – 40% and 50 – 95%, respectively. On average (months 0 – 6), a 2 mg/kg/day dose resulted in AUC 0-inf values of 2003 ng*hr/mL and C_{max} values of 996 ng/mL.

Conclusions: This 6-month laboratory study supports the safe use of ONSIOR (robenacoxib) tablets at a dose of 2 mg/kg/day for the labeled 3 day duration. Treatment-related findings included: abnormal feces, effects on coagulation, retinal changes, neurological abnormalities, ECG changes, gross pathology changes, and organ weight changes.

Additional Field Safety: In a month-long pilot study, 3 dogs that received ONSIOR developed hepatic toxicity. Dogs received a daily ONSIOR dose of 1 or 2 mg/kg. Two of these dogs were euthanized and a third dog recovered after prolonged hospitalization and supportive therapy.

IV. HUMAN FOOD SAFETY

This drug is intended for use in dogs. 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 (robenacoxib) tablets:

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.

VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR part 514. The data demonstrate that ONSIOR (robenacoxib) tablets when used according to the label, is safe and effective for the control of postoperative pain and inflammation associated with soft tissue surgery in dogs $\geq$ 5.5 lbs and $\geq$ 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.