Date of Approval: November 16, 2016

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-443

onsior™

robenacoxib

injection

dogs

For the control of postoperative pain and inflammation associated with soft tissue surgery in dogs ≥ 4 months of age; for up to a **maximum of 3 days**.

Sponsored by:

Elanco US Inc

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I. GENERAL INFORMATION

A. File Number

NADA 141-443

B. Sponsor

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

Drug Labeler Code: 058198

C. Proprietary Name

onsior™

D. Product 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 dogs ≥ 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.

The first dose should be administered approximately 45 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 dogs ≥ 5.5 lbs **and** ≥ 4 months of age, for a maximum of 3 total onsior™ doses over 3 days, not to exceed one dose per day. If subsequent doses

are given by subcutaneous injection, different sites for each injection should be used.

K. Route of Administration

Subcutaneous injection

L. Species/Class

Dogs

M. Indication

onsior™ (robenacoxib) injection is indicated for the control of postoperative pain and inflammation associated with soft tissue surgery in dogs ≥ 4 months of age; for up to a **maximum of 3 days**.

N. Effect of Supplement

This supplement provides for the use of onsior™ (robenacoxib) injection, and the interchangeable use of onsior™ (robenacoxib) injection and onsior™ (robenacoxib) tablets, for the control of postoperative pain and inflammation associated with soft tissue surgery in dogs ≥ 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) robenacoxib administered by subcutaneous (SC) injection, once daily for up to three days was selected based on the results of the following studies.

A masked, vehicle and positive controlled dose titration study using an acute synovitis model was conducted in 8 adult Beagles of both sexes. Synovitis was induced by intra-articular injection of uric acid crystals into the stifle joint. Dogs were administered robenacoxib once by SC injection at doses ranging from 0.25 mg/kg - 4 mg/kg. The control groups received vehicle (formulation minus active ingredient) or a positive control, both by SC injection. The primary endpoint (peak vertical force exerted on the force plate) and the secondary endpoint (weight bearing, pain on palpation, and swelling) were monitored daily. The effectiveness of robenacoxib was positively correlated with doses from 1 - 2 mg/kg.

In samples collected at 1 and 2 hours after test article administration, the 1 and 2 mg/kg doses of robenacoxib significantly inhibited *ex vivo* prostaglandin E_2 (PGE_2) production, but robenacoxib had no significant effect on *ex vivo* serum thromboxane B2 (TxB2) production. The clinical relevance of this data has not been shown.

To further assess the optimal dose, robenacoxib administered by SC injection at doses of 0.5, 1, and 2 mg/kg was compared to a positive control in a parallel-group field study in 80 dogs undergoing surgery. Pain was assessed using visual analogue scales, the Glasgow Composite Measure Pain Scale (CMPS-SF), and a numerical rating scale for overall pain control. There were no statistically

significant differences between groups. However, for pain on palpation and overall pain, the effectiveness of robenacoxib was dose related with 2 mg/kg producing similar effectiveness as the positive control, and the 0.5 and 1 mg/kg doses being inferior.

Two relative bioavailability studies were conducted to bridge the non-final formulation (1%: 10 mg/mL) used in the two studies above to the final formulation (2%: 20 mg/mL). The first study bridged the 1% formulation to a preliminary 2% formulation, and the second study bridged this formulation to the final 2% formulation. In both studies, the equivalence of the formulations was based on the pivotal parameter AUC(0-inf) (area under the time concentration curve extrapolated to infinity).

The effectiveness and safety of onsior™ (robenacoxib) injection at a SC dose of 2 mg/kg for up to three days for the control of postoperative pain and inflammation associated with soft tissue surgery was evaluated in a pilot field study. The final formulation was used in this 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 pre-operatively and then daily for two additional days. Enrolled dogs were administered robenacoxib, a positive control, or placebo prior to anesthetic induction, approximately 45 min prior to surgery.

Pain was evaluated at pre-determined times using the short form of the Glasgow Composite Measure Pain Scale (CMPS-SF). Dogs scoring ≥6 on the CMPS-SF or showing obvious discomfort were removed from the study (rescued) and monitored for an additional 24 hours after rescue. Rescued dogs were considered treatment failures. Treatment success was considered the primary endpoint. A total of 62 dogs were enrolled and 61 were evaluated for effectiveness (22 in the placebo group, 19 in the positive control group, and 20 in the onsior™ injection group). The onsior™ group showed significantly better overall scores in the CMPS-SF behavior categories of Total Pain, Mobility, and Response to Touch on the first day of treatment compared to the placebo group. When comparing results of the primary effectiveness variable, the onsior™ and positive control groups showed better response rates compared to the placebo group. Reduction in the number of rescues in the onsior™ group compared to the placebo group was not statistically significant. The results from this study indicate that SC administration of robenacoxib at a dose of 2 mg/kg approximately 45 minutes prior to surgery should be effective for controlling postoperative pain and inflammation associated with soft tissue surgery in dogs.

B. Substantial Evidence

The effectiveness of onsior™ (robenacoxib) injection for the control of postoperative pain and inflammation associated with soft tissue surgery in dogs was evaluated at twelve (12) veterinary clinics throughout various geographic regions within the U.S. Results of the study demonstrate that onsior™ (robenacoxib) injection is safe and effective when administered at a dose of 0.91 mg/lb (2 mg/kg) of body weight once daily for up to 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 (injection) 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.

Study Dates: March 30, 2015 – September 10, 2015

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

Decatur, IL
Battle Creek, MI
Zachary, LA
Junction City, KS
Quakertown, PA
Farragut, TN
Harleysville, PA
Fort Collins, CO (2 Investigators)
Springfield, MO
Manakin-Sabot, VA
Wichita Falls, TX

Study Design: This was a masked, randomized, multi-center, field study comparing onsior™ (robenacoxib) injection to a placebo (saline). 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) injection, at a subcutaneous 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) injection approximately 45 minutes prior to surgery and once daily for two additional days postoperatively. Placebo dogs received a saline injection at the same time points.

Study Animals: There were 317 (220 females and 97 males) dogs of various breeds included in this study. onsior™-treated dogs were between 6 months - 15 years of age and weighed between 2.5 and 53.8 kg. The average age of the onsior™-treated group was 5.7 years and the average age of the placebo group was 5.9 years. Fifty-seven of the 317 dogs were less than 1 year of age.

Treatment Groups: Dogs were randomized into two treatment groups in a 1:1 ratio, and received onsior™ (robenacoxib) injection or placebo (0.9% NaCl). onsior™ (robenacoxib) injection was administered SC at 2 mg/kg (0.9 mg/lb) 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) injection. The placebo group received an injectable saline solution (0.9% sodium chloride). All dogs received the first injection 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 on the CMPS-SF, 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
2. attention to wound area
3. mobility
4. response to touch
5. demeanor
6. posture and activity

[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.

Hematology, serum chemistry and urine samples were obtained prior to study initiation and at study exit. Injection sites on the day of surgery (Day 0) were evaluated prior to dosing and 24 and 48 hours later. Day 1 injection sites were evaluated prior to dosing and 24 hours later. Day 2 injection sites were evaluated prior to dosing. All injection sites were evaluated at study exit. All owners received a follow-up phone call 3-10 days post-study to assess for any adverse events.

Statistical Methods: Dogs that received rescue pain medication, had a CMPS score $\geq$ 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™ group to the placebo group. A generalized linear mixed model was utilized, which included 'Treatment' as a fixed effect and 'Site' and 'Treatment by Site' as random effects.

For secondary effectiveness variables, a repeated measures analysis of covariance was used including Treatment, Time and Treatment-by-Time as fixed effects, and Site, Site-by-Time, and Treatment-by-Site-by-Time as random effects. Pre-treatment Total Pain Score was also included in the model as a fixed covariate.

Results: Effectiveness was evaluated in 303 dogs and field safety was evaluated in 317 dogs. A statistically significant difference (p = 0.0055) was observed in the proportion of treatment successes in the onsior™ injection group (73.7%) compared to the placebo group (58.1%) (Table 1).

Table 1. Results by Treatment Group[a]

Treatment Group	Number of Treatment Successes‡	Number of Treatment Failures†	Total Number of Evaluable Cases
onsior™ (robenacoxib) injection	108 (73.7%)	43 (26.3%[b])	151
Placebo (saline injection)	85 (58.1%)	67 (41.9%)	152

[a] p-value = 0.0055
[b] Proportions were the least squares means based on the generalized linear mixed model described in Statistical Methods.
† Failure = withdrawn
‡ Success = completed

Forty-three (43) out of 151 onsior™ cases (26.3%) and 67 out of 152 placebo cases (41.9%) were treatment failures. For Total Pain Scores, the Treatment-by-Time interaction was not statistically significant (p=0.1203), nor was the overall effect of Treatment statistically significant (p=0.0863). Statistically significant differences in reductions in Response to Touch scores (p=0.0013) and Posture/Activity (p=0.0466) were observed in the onsior™ injection group relative to the placebo group. Other secondary variables did not indicate a statistically significant difference due to treatment.

Mean body weight change was similar between both groups. No clinically significant differences existed between the onsior™ and the placebo group for hematology, serum chemistry, or urinalysis results. Concurrent medications used

during the field study included anesthetic agents, prophylactic antibiotics, anesthetics, and parasiticides.

Adverse Reactions: The most commonly reported adverse reactions in dogs treated with onsior™ (robenacoxib) injection were pain on injection, diarrhea, and vomiting. 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) injection N = 159	**Placebo** (0.9% NaCl) N = 158
Pain on injection**	18	8
Diarrhea	15	8
Vomiting	10	6
Bradycardia	6	1
Decreased appetite	5	2
Hypotension	2	0
Facial edema, hypersensitivity	1	0
Increased incisional bleeding	1	0

*Dogs may have experienced more than one type or occurrence of an event during the study.
**Most often occurred as a single event.

Conclusion: Subcutaneous administration of onsior™ (robenacoxib) injection 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 safe and effective for the control of postoperative pain and inflammation associated with soft tissue surgery in dogs.

III. TARGET ANIMAL SAFETY

A. Interchangeable Use Safety study

Title: Interchangeable use safety study of onsior™ administered orally and subcutaneously to mongrels.

Study Dates: June 2012 – September 2013

Study Location: Madison, WI

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

Objective: The objective of this laboratory study was to evaluate the safe interchangeable use of onsior™ tablets and onsior™ injection when administered to 4-month-old mongrel dogs at multiples of the oral dose, and at multiples of the

injectable dose. This study was designed to support the safe use of onsior™ tablets at the postoperative pain dose (POP) of 2 mg/kg once a day for a maximum of three days; the safe use of onsior™ injection at a postoperative pain dose of 2 mg/kg once a day subcutaneously for a maximum of 3 days; or any combination use of the tablets or the injectable once daily over 3 days.

Study Animals: Thirty-two healthy, 4-month old mongrel dogs, ranging in weight from 11.9 to 19.3 kg at the start of the study were included in the 4 treatment groups (4/sex/group).

Control: Control treatments were empty gelatin capsules during the oral dosing period or saline (0.9% Sodium Chloride for Injection, USP) injection during the subcutaneous dosing period.

Dosage form: onsior™ injection (20 mg/mL of robenacoxib) and onsior™ tablets (20 and 40 mg of robenacoxib); final market formulations

Route of administration: Tablets were administered orally. Injections were administered subcutaneously, in the dorsal thoracic region. For the purpose of masking the investigator, robenacoxib tablets were placed in one or two gelatin capsules.

Doses used: Three 20-day oral and subcutaneous treatments (separated by a 14-day washout) were alternated over 88-days according to a schedule of 7 days of tablet administration at a lower dose, 3 days of tablet at a higher dose for 3 days maximum-use for postoperative pain, 3 days subcutaneous injection, and then 7 days of tablet administration at a lower dose. Each dosing cycle consisted of the following groups:

- 7 days of an oral tablet at 2 mg/kg/day (0.5X), 4 mg/kg/day (1X), or 6 (1.5X) mg/kg/day on Days 1-7, 35-41, 69-75, and on Days 14-20, 48-54, and 82-88.
- 3 days of oral tablets at multiples of the postoperative pain dose of 4 mg/kg (1X), 8 mg/kg (2X), or 12 mg/kg/day (3X) on Days 8-10, 42-44, and 76-78.
- 3 days of a subcutaneous injection at doses of 4 mg/kg (2X), 8 mg/kg (4X), or 12 mg/kg (6X) on Days 11-13, 45-47, and 79-81.
- And a 14-day washout period (no control or test articles administered) between cycles (during Days 21-34 and 55-68).

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 number of capsules used was equivalent to the 3X dose group and saline volume used was equivalent to the 6X dose group.

On the days of dosing, food was administered 2-3 hours post-dose, except on the days of toxicokinetic blood collection when food was provided after the 5 hour post-dose blood collection.

Table 3. Dosing Schematic - 3 Cycles of the Following Schedule Repeated Over the 88-Day Study.

Low dose	**POP dose** (oral)	**POP dose** (Injectable)	**Low dose**	**Washout**
Oral tablet	Oral tablet	Subcutaneous injection	Oral tablet	No treatment
7 day dosing	3 day dosing	3 day dosing	7 day dosing	14 days

Table 4. Treatment Groups for Interchangeable Use Study.

Group	**Dose**	**Number and Sex of Animals**
1	Control, 0 mg/kg Empty gelatin capsule or saline injection	4 M, 4 F
2	0.5X and 1X oral; 2X injectable (2 and 4 mg/kg oral; 4 mg/kg injectable)	4 M, 4 F
3	1X and 2X oral; 4X injectable (4 and 8 mg/kg oral; 8 mg/kg injectable)	4 M, 4 F
4	1.5X and 3X oral; 6X injectable (6, 12 mg/kg oral; 12 mg/kg injectable)	4 M, 4 F

Because of the inherent dose band, when considering the available tablet sizes and a dog's weight, it is possible that the administered dose (based on tablet sizes) to some dogs for postoperative pain could result in those dogs receiving up to a 4 mg/kg dose. Thus, in this safety study the high end of the inherent dose band (4 mg/kg) was tested as the 1X oral dose.

Test duration: Eighty-eight days

Measurements and Observations: The following variables were measured prior to study initiation, during, and/or at the end of the study – clinical observations and injection site evaluations, physical, ophthalmic, electrocardiographic and neurological examinations, body weight, food consumption, heart rate, body temperature, coagulation and buccal mucosal bleeding time (BMBT), hematology and clinical chemistries, urinalyses, organ weights, gross pathology and histopathology. Blood samples were also collected for toxicokinetic analysis.

Statistical Methods: Continuous outcomes measured only once during the study were analyzed using an analysis of variance (ANOVA) model with treatment, sex and sex-by-treatment terms as fixed effects. Continuous outcomes measured only once during the study and with a baseline covariate were analyzed using analysis

of covariance (ANCOVA) model with treatment, sex and sex-by-treatment terms as fixed effects.

Ordinal outcomes measured multiple times during the study were analyzed using a generalized linear mixed model (GLIMMIX) model with a multinomial distribution and cumulative logit link. Continuous outcomes measured multiple times during the study and with a baseline covariate (such as body weight, food consumption, hematology, coagulation, urinalysis and clinical chemistry) were analyzed using a mixed models procedure in SAS for Repeated Measures Analysis of Covariance (RMANCOVA). Both RMANCOVA and GLIMMIX models contained treatment, sex, time, treatment-by-sex, sex-by-time, treatment-by-time, and treatment-by-sex-by-time terms as fixed effects. The random effect of room was also included in the model. Animal was identified as the subject for the repeated measurements. For each variable the pre-treatment value closest to dosing was included as a covariate in the RMANCOVA model.

Toxicokinetic evaluation: Blood was collected for toxicokinetic evaluations on Days 1, 14, 69, and 82 at pre-dose (within 30 minutes prior to dosing) and approximately 1 and 5 hours post-dose. On Days 6, 8, 11, 74, 76, and 79 blood was collected approximately 1 and 5 hours post-dose. Robenacoxib concentrations in whole blood were determined using a validated LC-MS/MS method.

Results:

All dogs survived to termination of the study.

Injection sites: There was a greater number of injection sites with edema at 8 hours post-injection and with erythema at 24, 48, and 72 hours post-injection in 4X and 6X dogs compared to the 2X injection group and control dogs. In some instances the erythema continued as skin thickening and/or an ulcer/cyst developed followed by granulation. Ulcers or fluid-filled cysts occurred in one control dog, 2 dogs in the 2X injection group, 4 dogs in the 4X injection group, and in 4 dogs in the 6X injection group. Ulcers tended to have a delayed occurrence, happening 6-8 days after injection out to 10-14 days after injection.

Clinical Pathology: The mean WBC values mildly decreased from pre-study to Day 21 in all groups administered robenacoxib, and increased thereafter.

Pathology findings: Microscopic findings at dorsoscapular injection sites included minimal to severe subcutaneous necrosis, degeneration, and/or fibrosis with occasional involvement of the underlying panniculus muscle in dogs given ≥ 2X doses. Minimal to moderate acanthosis/hyperkeratosis of the overlying skin was observed in dogs given ≥ 2X doses. Minimal or slight acanthosis/hyperkeratosis in two 4X dogs and one 6X dog, and minimal to moderate ulceration of the skin in dogs given ≥ 4X doses were also observed. Slight infiltrates of macrophages and an infiltrate of lipid within the axillary lymph nodes were noted in one control dog and all dogs injected with onsior™.

On gross pathology, one dog in Group 2 (0.5X and 1X oral; 2X injectable) had discoloration throughout the entire duodenal, jejunal, and ileal mucosa, as well as multiple mucosal discolorations in the stomach, with no corresponding histopathology findings, except for a jejunal ulcer with minimal inflammation.

Another dog in Group 2 (0.5X and 1X oral; 2X injectable) had stomach, duodenal, and jejunal mucosal discoloration with no corresponding histopathology findings. One dog in Group 3 (1X and 2X oral; 4X injectable) had multiple mucosal discoloration in the stomach and duodenum with no histopathology findings, and microscopic minimal cecal hemorrhage with microscopic cecal inflammation. This dog also vomited on 2 days. Another dog in Group 3 (1X and 2X oral; 4X injectable) had discoloration grossly along the entire duodenal and jejunal mucosa with no correlating histopathology findings, a single mucosal discoloration in the stomach with no histopathology findings, and slight duodenal congestion on histopathology. This dog vomited on 3 study days. Microscopic cecal inflammation was noted in one dog in Group 4 (1.5X and 3X oral; 6X injectable). There were no gastrointestinal findings noted in the control group.

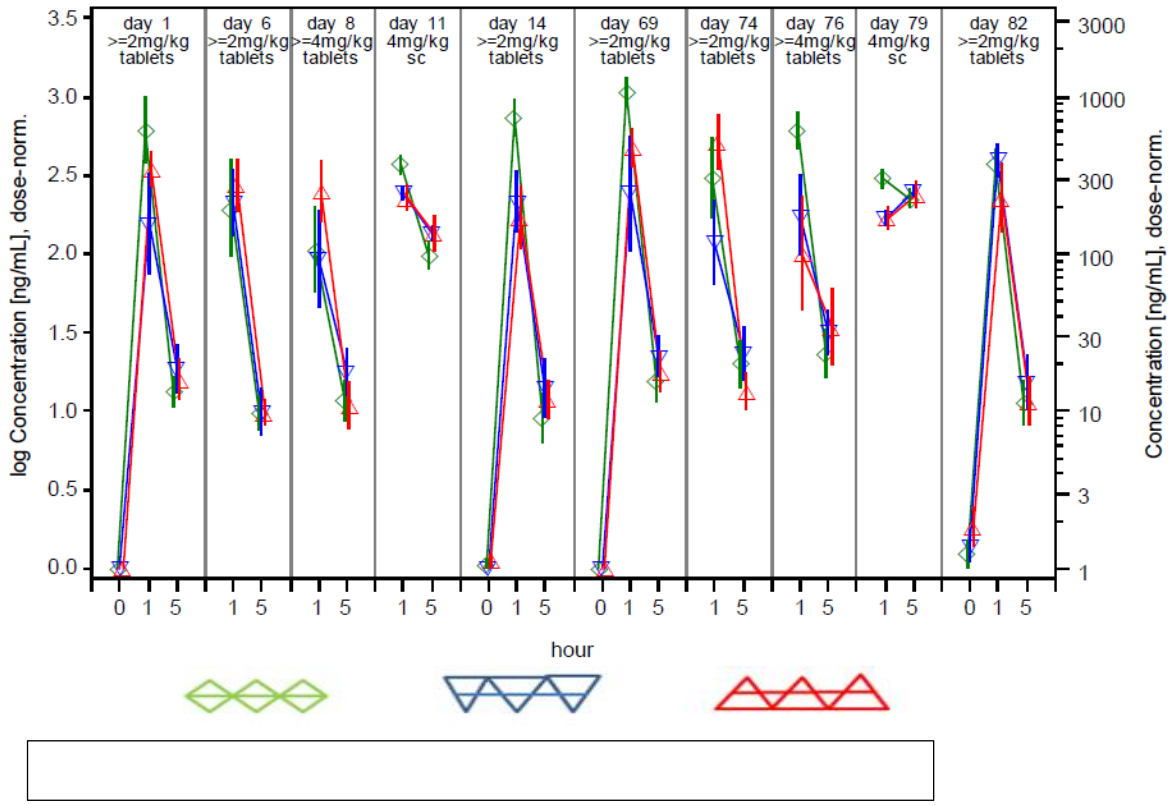
One dog in Group 4 (1.5X and 3X oral; 6X injectable) had moderate bilateral eosinophilic and histiocytic inflammation of the adrenal cortex of unknown clinical relevance. There was a significant increase in kidney-to-body weight ratios in the groups administered robenacoxib compared to the controls. Male dogs in the groups administered robenacoxib exhibited an increased number and severity of lymphocyte depletion within the thymus compared to the controls.

Clinical observations included vomiting in 2 dogs in Group 2 (0.5X and 1X oral; 2X injectable), in 3 dogs in Group 3 (1X and 2X oral; 4X injectable), and in 2 dogs in Group 4 (1.5X and 3X oral; 6X injectable). Diarrhea and soft stools occurred in all study groups.

Toxicokinetics: Marked within and between subject variability was observed across all treatment groups (See Figure 1). However, there were no trends observed that would indicate that the sequential uses of doses/routes altered the rate and extent of robenacoxib exposure.

Although the use of gelatin capsules increased the variability and delayed the *in vitro* release of robenacoxib from the tablets, the *in vivo* Cmax values were consistent with those observed in other canine robenacoxib pharmacokinetic investigations. Therefore, it was determined that the current study is acceptable for confirming that the exposure associated with low oral doses of robenacoxib administration is not affected by the sequential use of the high oral doses or subcutaneous administration of robenacoxib (and vice versa).

Figure 1: Mean profile plot of dose-normalized (parameter/dose) robenacoxib concentrations as a function of dosing day and hour after treatment administration.



The left axis describes log concentrations (ng/mL) of robenacoxib and the right axis is the actual concentrations but plotted on a logarithmic (rather than linear) scale. On the X axis are the sampling times (pre-dose and 1 and 5 hours post-dose). Each column provides information as a function of treatment and dosing day. Within each column, the plots represent the mean robenacoxib concentration ± standard deviation as a function of time for each treatment group. The results show that regardless of the administered dose, route of administration, or dosing day, log transformed values of the peak concentrations were approximately 2.5 to 3.0 ng/mL. These results support the lack of significant accumulation of robenacoxib and the similarity of robenacoxib toxicokinetics across dose and route of administration.

Conclusions: This interchangeable use study supports the safe use of onsior™ injectable for 3 days, and the safe interchangeable use for onsior™ tablets and onsior™ injectable (at 2 mg/kg subcutaneously for up to 3 days) in dogs ≥ 4 months of age. Significant findings included injection site reactions and mild gross pathology and histopathology changes.

B. Injection Site Tolerance Study

Title: Acute injection site tolerance of robenacoxib injectable in dogs

Study Dates: May 30, 2006 through June 12, 2006

Study Location: St-Aubin, Switzerland

Study Design: Laboratory target animal safety study conducted in accordance with OECD Good Laboratory Practices.

Objective: The objective of this laboratory study was to evaluate the injection site tolerance of once a day subcutaneous (SC) injections of onsior™ (robenacoxib) injection at 0, 2 (1X), and 10 mg/kg (5X) doses.

Study Animals: Healthy Beagles, 5 to 7.5 year old, ranging in weight from 9.4-14.2 kg, were used in the study (4/sex/group).

Control and Treatment Groups: In the control group, 0.9% sodium chloride for injection, USP was used at a volume equivalent to the 10 mg/kg/day dose group. onsior™ (robenacoxib) injection, 20 mg/mL of robenacoxib was used in the onsior™ groups.

Table 5. Treatment Groups for Injection Site Tolerance Study.

Treatment Group	Dose	Number and Sex of Animals
1	0 mg/kg/day (saline)	4M, 4F
2	2 mg/kg/day (1X) onsior™ injection	4M, 4F
3	10 mg/kg/day (5X) onsior™ injection	4M, 4F

Route of administration: dorsothoracic subcutaneous injections, once daily for 3 days

Test duration: Three days

Measurements and Observations: The following variables were measured prior to study initiation, during, and/or at the end of the study – clinical observations and injection site observations, physical examinations, body weights (prior to initiation of the study), food consumption, hematology, coagulation, clinical chemistries, urinalyses, and microscopic evaluations of biopsied injection sites (4 to 6 days after injection).

Results:

All dogs survived to termination of the study.

Injection sites: Transient, fluid-filled swellings (6 of 8 saline and all onsior™-injected dogs) which disappeared over a period of 72 hours.

Hematology and clinical chemistry evaluations: There were increases in platelet and white blood cell counts, and blood urea nitrogen concentrations in 2 mg/kg and 10 mg/kg dogs.

Pathology: Subcutaneous inflammatory cell infiltration at injection sites was minimal to slight and decreased over time. Minimal to mild acute myonecrosis with concomitant signs of regeneration (6 days after injections) were observed in 8/13 and 11/17 injection sites containing muscle tissue from 2 mg/kg and 10 mg/kg dogs, respectively.

Conclusions: The acute injection site study supports the safe use of onsior™ injectable for 3 days. This study demonstrated injection site reactions including transient swelling and minimal subcutaneous inflammation with minimal myonecrosis and muscular regeneration on histopathology.

C. Telemetry Study

Title: Telemetry cardiovascular assessment of onsior™ injectable in conscious dogs

Study Dates: November – December 2010

Study Location: Baugy, France

Study Design: Laboratory safety study conducted in accordance to OECD Good Laboratory practices.

Objective: The objective of this laboratory study was to evaluate the cardiovascular safety of onsior™ (robenacoxib) injection in healthy Beagles.

Study Animals: Healthy Beagles, 18 to 40 months old, ranging in weight from 11.5 to 14.8 kg, were used in the study (4/sex).

Control and Treatment Group: The placebo used was 0.9% sodium chloride for injection, USP at a volume equivalent to the 2X dose group. onsior™ (robenacoxib) injection, 20 mg/mL was used at various doses in a cross-over design. Each dog was administrated placebo or onsior™ (robenacoxib) injection in a randomized crossover design with a minimum washout period of 72 hours between the doses of robenacoxib: 0 (IV), 2 mg/kg (1X; SC and IV), and 4 mg/kg (2X; IV).

Table 6. Treatment Groups for Telemetry Study.

Group	**Dose** (Crossover Design)	**Number and Sex of Animals**
1	0 mg/kg, saline, IV; 72-hour washout 2 mg/kg/day onsior™ SC; 72-hour washout 2 mg/kg/day onsior™ IV; 72-hour washout 4 mg/kg/day onsior™ IV	4M, 4F

Route of administration: Subcutaneous (SC) and intravenous (IV) injections

Test duration: Sixteen days

Measurements and Observations: The following variables were measured prior to study initiation, during, and/or at the end of the study – clinical observations, physical examinations, body weight, food consumption, coagulation, buccal mucosal bleeding times (BMBT), hematology and clinical chemistries, and urinalyses. A cardiovascular telemetry assessment (i.e., systolic and diastolic arterial blood pressure; heart rate; duration of PR, PQ, QT and QRS intervals; and body temperature) was performed on 2 conscious dogs per sex. Telemetric measurements started approximately 2 hours before and continued for 8 hours after each administration.

Results:
All dogs survived to termination of the study. There was no effect on arterial blood pressure, heart rate, or cardiac conduction times for a period of 8 hours post-dosing. No arrhythmia attributable to the test article was observed. Abnormal clinical findings included two dogs that vomited after IV administration of the 4 mg/kg dose.

Conclusions: There were no cardiovascular telemetry effects in dogs when onsior™ injectable was administered IV at 2 mg/kg and 4 mg/kg, or subcutaneously at 2 mg/kg.

D. Field Safety

In two other field studies, bradycardia, 2nd degree heart block in 4 dogs, and ventricular arrhythmia in one dog were noted in anesthetized dogs treated with onsior™ injection.

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) injection:

Not for use in humans. Keep this and all medications out of reach of children. Consult a physician in case of accidental exposure to humans.

The safety data sheet (SDS) contains more detailed occupational safety information. To report adverse reactions in users or to obtain a copy of the SDS for this product call 1-888-545-5973.

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) injection 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 $\geq$ 4 months of age; for 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

This supplemental approval for onsior™ qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the FD&C Act because the supplemental application included safety and effectiveness studies. This exclusivity begins as of the date of our approval letter and only applies to use of onsior™ (robenacoxib) injection in dogs.

C. Supplemental Applications

This supplemental NADA required a reevaluation of the safety and effectiveness data in the original NADA (21 CFR 514.106(b)(2)).

D. Patent Information:

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