onsior™ (robenacoxib)

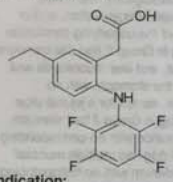
10 mg, 20 mg and 40 mg Tablets for Dogs

For Oral Use in Dogs Only

Do not use in cats. Cats cannot be accurately dosed with the tablet sizes intended to be used in dogs.

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

Description:
ONSIOR (robenacoxib) is a non-narcotic, non-steroidal anti-inflammatory drug (NSAID) of the coxib class. Tablets are round, beige to brown in color, not scored, flavored and contain robenacoxib. The molecular weight of robenacoxib is 327.28. The empirical formula is $C_{16}H_{13}F_4NO_5$. Robenacoxib is [5-Ethyl-2-(2,3,5,6-tetrafluoro-phenylamino)-phenyl]-acetic acid. The structural formula is:



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**.

Dosage and Administration:
Always provide "Information for Dog Owners" Sheet with prescription. Carefully consider the potential benefits and risk of ONSIOR tablets and other treatment options before deciding to use ONSIOR tablets. Use the lowest effective dose for the shortest duration consistent with individual response.

The dose of ONSIOR tablets is 0.91 mg/lb (2 mg/kg) orally once daily, for a **maximum of 3 days**. **(See Warnings, Precautions and Adverse Reactions).**

Dosage Directions: For oral use in dogs ≥ 5.5 lbs **and** ≥ 4 months of age; for up to a **maximum of 3 days**. Tablets are not scored and should not be broken. The calculated dosage should be provided using a combination of whole tablet sizes.

Do not use in dogs weighing less than 5.5 lbs (2.5 kg), as dogs less than 5.5 lbs (2.5 kg) cannot be accurately dosed. **Do not use in cats. Cats cannot be accurately dosed with the tablet sizes intended to be used in dogs.**

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 the oral tablet or interchanged with subcutaneous injection for a maximum of 3 total ONSIOR doses over 3 days, not to exceed one dose per day (**see Animal Safety** and the ONSIOR injection package insert).

ONSIOR tablets may be given with or without food.
If a second and third dose is dispensed to the client to administer at home, doses should be dispensed in the dispensing envelope with the attached Information for Dog Owners Sheet intact. **Do not remove Information for Dog Owners Sheet.**

Contraindications:
ONSIOR should not be used in dogs that have a hypersensitivity to robenacoxib or known intolerance to NSAIDs.

Warnings:
Not for use in humans. Keep this and all medications out of reach of children and pets. Consult a physician in case of accidental ingestion by humans. **For oral use in dogs only.** Store ONSIOR out of reach of dogs and other pets in a secure location in order to prevent accidental ingestion or overdose. **Do not use in cats. Cats cannot be accurately dosed with the tablet sizes intended to be used in dogs.**

Do not use for more than 3 days. Do not administer ONSIOR tablets or injection in conjunction with any other oral or injectable NSAID or corticosteroid. Serious adverse events have been reported, including hepatopathy, with the long term use (28 day study) of robenacoxib in dogs (See Adverse Reactions). Safety not demonstrated for longer than 3 days.

All dogs should undergo a thorough history and physical examination before the initiation of NSAID therapy. Appropriate laboratory tests should be conducted to establish hematological and serum biochemical baseline data prior to administration of an NSAID. **Owners should be advised to observe for signs of potential drug toxicity (see Adverse Reactions and Animal Safety) and be given an "Information for Dog Owners" sheet about ONSIOR tablets.**

Precautions:
Stop administration of ONSIOR if the dog experiences inappetence, vomiting or lethargy.

The safe use of ONSIOR has not been evaluated in dogs younger than 4 months of age, dogs used for breeding, or in pregnant or lactating dogs. Dogs receiving ONSIOR should weigh at least 5.5 lbs.

As a class, cyclo-oxygenase inhibitory NSAIDs may be associated with gastrointestinal, renal, and hepatic toxicity. Sensitivity to drug-associated adverse events varies with the individual patient. Dogs that have experienced adverse reactions from one NSAID may experience adverse reactions from another NSAID. Patients at greatest risk for adverse events are those that are dehydrated, on concomitant diuretic therapy, or those with existing renal, cardiovascular, and/or hepatic dysfunction. Anesthetic drugs may affect renal perfusion; approach concomitant use of anesthetics and NSAIDs cautiously. Appropriate monitoring procedures (including ECG, blood pressure, and temperature regulation) should be employed during all surgical procedures. The use of parenteral fluids during surgery is recommended to decrease potential renal complications when using NSAIDs perioperatively.

If additional pain medication is needed after a daily dose of ONSIOR, a non-NSAID/non- corticosteroid class of analgesic may be necessary. Concurrent administration of potentially nephrotoxic drugs should be carefully approached and monitored. NSAIDs may inhibit prostaglandins which maintain normal homeostatic function. Such anti-prostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease that has not been previously diagnosed. NSAIDs possess the potential to produce gastrointestinal ulcerations and/or gastrointestinal perforations. Do not use ONSIOR concomitantly with other anti-inflammatory drugs, such as NSAIDs or corticosteroids. Consider appropriate washout times when switching from one NSAID to another or when switching from corticosteroid use to NSAID use. ONSIOR injection and ONSIOR tablets are safe to use interchangeably when given once a day for a **maximum of 3 days** in dogs ≥ 4 months of age **and** ≥ 5.5 lbs.

The use of concomitantly protein-bound drugs with ONSIOR has not been studied in dogs. Commonly used protein-bound drugs include cardiac, anticonvulsant, and behavioral medications. The influence of concomitant drugs that may inhibit metabolism of ONSIOR has not been evaluated. Drug compatibility should be monitored in patients requiring adjunctive therapy.

It is unknown whether dogs with a history of hypersensitivity to ß lactam drugs will exhibit hypersensitivity to ONSIOR. Robenacoxib is poorly soluble in water and in acid solutions readily degrades to form γ-lactam. In dogs, lactam is a minor metabolite of robenacoxib. Additionally, lactam is a degradation product that increases over the shelf life of the tablets. Neurologic signs have been associated with the use of ß lactam drugs; it is unknown if the lactam produced by robenacoxib may cause similar neurologic signs (**See Animal Safety**).

Adverse Reactions:
In a controlled field study, a total of 239 male and female dogs representing 35 breeds were included in the field safety analysis. ONSIOR-treated dogs ranged in age from 6 months to 14 years and weighed 5.9 to 121 lbs (2.7 to 55 kgs). The following table shows the number of dogs exhibiting each observation.

Adverse reactions 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 occurence of an event during the study.

The most commonly reported adverse reactions were diarrhea, vomiting, and decreased appetite. Changes in the clinical pathology values were not considered clinically significant.

Occurrences of hepatopathy, ataxia, skin lesions/urticaria, and anaphylaxis have been associated with the use of ONSIOR. In a US month-long pilot study, 3 dogs that received ONSIOR developed hepatic toxicity. Two of these dogs were euthanzied and a third dog recovered after prolonged hospitalization and supportive therapy. In foreign market experience, elevated liver enzymes, hepatic necrosis and death have been associated with the long term use of robenacoxib in dogs. Occurrences of liver failure, hepatitis, and cholangiohepatitis have been reported.

For technical assistance or to report suspected adverse drug events, contact Elanco US Inc. at 1-888-545-5973. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/AnimalVeterinary/SafetyHealth.

Information for Dog Owners:
ONSIOR, like other drugs of its class, is not free from adverse reactions. Owners should be advised of the potential for adverse reactions and be informed of the clinical signs associated with drug intolerance. Adverse reactions may include vomiting, diarrhea, decreased appetite, dark or tarry stools, increased water consumption, increased urination, anemia, yellowing of gums, skin or whites of the eye due to jaundice, lethargy, incoordination, seizure, or behavioral changes. **Serious adverse reactions associated with this drug class can occur without warning and in some cases result in death (see Warnings and Adverse Reactions). Owners should be advised to discontinue ONSIOR therapy and contact their veterinarian immediately if signs of intolerance are observed.** The vast majority of patients with drug related adverse reactions have recovered when the signs are recognized, the drug is withdrawn, and veterinary care, if appropriate, is initiated.

Clinical Pharmacology:
Robenacoxib is a non-steroidal anti-inflammatory drug (NSAID) of the coxib class. Repeated subcutaneous administration showed no evidence of robenacoxib bioaccumulation. Although the bioaccumulation of robenacoxib metabolites has not been tested, radiolabeled studies suggest that the various unidentified metabolites are associated with markedly longer elimination half-lives (approximately 22 hrs) as compared to that of the parent molecule. The activity of these metabolites has not been evaluated. The pharmacokinetics of robenacoxib injection does not differ between male and female dogs, and is linear over the range of 0.25-4 mg/kg in dogs. The pharmacokinetics of robenacoxib tablets are linear over the range of 0.5 - 8 mg/kg.

Absorption
After oral administration of robenacoxib flavored tablets at 1 mg/kg without food, mean whole peak blood concentrations are attained rapidly with Tmax values generally occurring within 0.5 to 1 hr following oral administration. The systemic bioavailability of robenacoxib flavored tablets in dogs was 62% with food and 84% without food. Robenacoxib pharmacokinetics is characterized by extensive within and between subject variability, particularly as it pertains to Cmax (as high as 75% coefficient of variation). With fasted administration, there may be times where the Cmax value is greater than the AUC_{0-inf} value. While this rarely occurs, it is attributable to a very early and high peak with very rapid post-absorption clearance.

Distribution
Robenacoxib has a relatively small volume of distribution (Vss of 174 to 336 mL/kg, average = 240 mL/kg), which is consistent with a drug that is extensively bound to plasma proteins. Based upon *in vitro* canine plasma samples, robenacoxib is approximately 98% bound to plasma proteins when at concentrations ranging from 200 – 2000 ng/mL. The corresponding canine *in vitro* whole blood-plasma ratio in artificially spiked blood was 0.44. Robenacoxib persists longer at the site of inflammation than in the blood (Silber *et al*, 2010). The clinical relevance of this data has not been shown.

Biotransformation
Robenacoxib is extensively metabolized by the liver in dogs. Apart from one γ-lactam metabolite, the identities of other metabolites are not known in dogs. Robenacoxib is excreted predominately via the biliary route in dogs (approximately 65%); therefore, the majority of the absorbed dose (parent drug and metabolite) is eliminated in the feces. The remainder of the administered dose is eliminated in urine, via the kidneys.

Elimination
After intravenous administration to normal healthy dogs, robenacoxib is rapidly cleared from blood (CL of 0.61 to 1.13 L/kg/hr, average = 0.81 L/kg/hr) with an elimination half-life ranging from 0.41 to 1.07 hrs. After subcutaneous administration to normal healthy dogs, the terminal half-life from blood was within 1 – 4 hrs. The mean elimination half-life estimated after oral administration of 1 mg/kg is 0.86 hours (fasted) and 1.15 hours (fed).

Animal Safety:
6-Month Oral Margin of Safety Study:
ONSIOR tablets (5, 10, 20, and 40 mg) were administered orally to 6- to 7-month old healthy Beagles (4/sex/group) at 0, 0.5 (2 mg/kg), 1.5 (6 mg/kg), and 2.5 (10 mg/kg) times the maximum exposure dose based on the tablets sizes, once daily for 6 months. The following variables were evaluated: clinical observations, body weights, food and water consumption, veterinary physical examinations (including neurological assessment), ophthalmoscopic examinations, electrocardiographic examinations, fecal observation with flotation analysis, evaluation of coagulation and buccal mucosal bleeding times, hematology, clinical chemistry, urinalysis, gross pathology (including organ weights), and histopathology.

Findings considered treatment-related include: salivation, soft/mucoid/watery feces, elevated buccal mucosal bleeding times in one 1.5X female and one 2.5X male, gastrointestinal tract lesions on gross necropsy (one 1.5X male had cecal lesions described as red foci, and one 2.5X female had minimal, red mucosal discoloration of the duodenum). The gross lesions did not correspond to any histological changes. In addition, decreased mean ovarian weights in 1.5X and 2.5X females as compared to the controls were observed (there were no gross or histological changes in the ovaries of any study animal).

88-Day Interchangeable Use Study :
In an 88-day laboratory interchangeable use study, 4-month old healthy mongrel dogs (4 sex/dose) were administered three 20 day cycles (separated by a 14-day washout) of alternating regimens of ONSIOR tablets and ONSIOR injection. Each cycle included a schedule of 7 days once daily oral tablet administration (0, 2, 4, or 6 mg/kg/day; Groups 1, 2, 3, and 4, respectively), 3 days of once daily oral administration (0, 4, 8, or 12 mg/kg/day; Groups 1, 2, 3, and 4, respectively), 3 days of once daily subcutaneous injection (0, 4, 8, or 12 mg/kg/day; Groups 1, 2, 3, and 4, respectively), and then 7 days once daily oral administration (0, 2, 4, or 6 mg/kg/day; Groups 1, 2, 3, and 4, respectively). The negative control group (Group 1) received empty gelatin capsules or saline injection.

All mongrels were in good health through study termination. Injection site reactions, including skin thickening, ulceration, or granulation, occurred in dogs in all groups in a dose-dependent manner, including one control dog. Histologically, there was minimal to severe subcutaneous necrosis, degeneration, and/or fibrosis with occasional myonecrosis of the underlying panniculus muscle. On gross pathology, one dog in Group 2 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 had stomach, duodenal and jejunal mucosal discoloration with no corresponding histopathology findings. One Group 3 dog 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 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 microscopically. This dog vomited on 3 study days. Microscopic cecal inflammation was noted in one Group 4 dog. There were no gastrointestinal findings noted in the control group. Treated male dogs exhibited an increased number and severity of lymphocyte depletion within the thymus compared to the controls.

Effectiveness:
Effectiveness was demonstrated using ONSIOR tablets in a masked, vehicle controlled, multi-site field study involving client owned dogs. In this study, 239 dogs presenting for soft tissue surgery were randomly administered ONSIOR tablets or vehicle control. Drug was administered approximately 45 minutes prior to surgery along with pre-anesthetic medications and continued once daily for two additional treatments. All dogs received fluids perioperatively. Effectiveness was evaluated in 231 dogs and field safety was evaluated in 239 dogs. A statistically significant difference in the proportion of treatment successes in the ONSIOR tablets treatment group (89/116; 76.72%) compared to the vehicle control group (74/115; 64.35%) was observed. Twenty seven of the 116 dogs in the robenacoxib group and 41 out of 115 control dogs were treatment failures. On the day of surgery, significant improvement in the total pain scores at various post-surgical time points, and overall significant improvement in response to touch and posture/activity were observed. The results of the field study demonstrate that ONSIOR tablets, when administered for a maximum of 3 days, are effective and well-tolerated for the control of postoperative pain associated with soft tissue surgery in dogs.

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.

Storage Conditions:
Store at controlled room temperature, between 59° - 77°F (15° - 25°C).

Manufactured for:
Elanco US Inc.
Greenfield, IN 46140

References:

1. Silber H.E., Burgener C., Letellier I.M., Peyrou M., Jung M., King J.N., Gruet P. and Giraudel J.M. (2010) Population pharmacokinetic analysis of blood and joint synovial fluid concentrations of robenacoxib from healthy dogs and dogs with osteoarthritis. Pharmaceutical Research, 27: 2633-2645.

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